PD-1 inhibitor shows some antitumor activity

With additional follow-up of approximately 10 months, monotherapy with the PD-1 inhibitor pembrolizumab (Keytruda) continued to show antitumor activity in men with metastatic castration-resistant prostate cancer. However, monotherapy alone is likely not a sufficient treatment in this patient population, according to Emmanuel Antonarakis, MBBCh, of Johns Hopkins University in Baltimore, Maryland. In this interview, Antonarakis discusses updated results with additional follow-up in this population, the study’s take-home messages, and the possible future role of combination therapy in men with castration-resistant disease.
IT’S A TOUGHS TIME TO BE A STONE.

This changes everything.
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A treat this issue of Urology Times® went to press, multiple states had begun the process of reopening following the COVID-19-prompted shutdown. As various business and services test the waters of this process, urologists must consider not only how to resume their practices, but what their practices will be like in the “new normal” the pandemic has presented everyone.

Telemedicine, in particular, has seen an exponential increase in use in recent times, a necessary consequence of the circumstances thrust upon providers and patients. It’s becoming apparent that rather than a short-term solution, telemedicine will remain a significant part of the urology practice, which was explored in 2 recent webinars from Urology Times®. In these informative and insightful programs, “Coding and Reimbursement” columnist Jonathan Rubenstein, MD, moderated discussion among urologists John Gore, MD, MS; Aaron Spitz, MD; and Eugene Rhee, MD, covering everything urologists need to know about successfully implementing—and getting reimbursed for—telemedicine services. To view the webinars, visit www.urologytimes.com.

Along those same lines, for this month’s cover feature, Steven A. Kaplan, MD, and Alexis E. Te, MD, 2 urologists in the US COVID-19 epicenter of New York City, outline a plan for urologists to resume their practices. In doing so, they not only discuss recommended screening and prevention measures, but also consider the opportunities the post-COVID-19 world presents for the specialty. “This pandemic will create a new paradigm of how we provide care and are compensated for the delivery of more efficient health care. Resource utilization and cost-effective care will become more valuable, and those who operate more efficiently will be better placed than those who simply do more, in terms of quality—versus quantity—based reimbursement,” Kaplan and Te write. Given its reputation for innovation and exploration of new frontiers, the specialty appears well-positioned to thrive in this health care landscape.

In a similar vein, Robert A. Dowling, MD, dedicates this month’s “Practice Matters” column to 4 lessons urology practices can take away from the pandemic (page 40), and for “Money Matters,” Jeff Witz, CFP, breaks down the CARES Act and the ways it benefits clinicians (page 45). In prostate cancer, look for a report on the KEYNOTE-199 study evaluating mono-therapy with pembrolizumab (Keytruda) in men with metastatic castration-resistant prostate cancer (page 18). In addition, we include coverage of real-world studies of radium-223 (Xofio) and enzalutamide (Xandi) (pages 19 and 28).

In benign conditions, we highlight results from a study evaluating a digital intervention that was found to improve fluid intake in patients with kidney stones (page 29), report on a recent study of the role of ultrasound in determining the underlying cause of erectile dysfunction in some men (page 30), and report on the benefits of holmium laser enucleation of the prostate with MOSES-enabled pulsed modulation for lower urinary tract symptoms related to benign prostatic hyperplasia (page 32).

We wrap up this month’s clinical topics with “Speak Out,” in which 3 urologists discuss how the FDA’s mesh guidance has affected their treatment of pelvic organ prolapse (page 17). Finally, I’d like to acknowledge and thank all of you for your efforts during these unprecedented times. Whether it is through rapid implementation of telemedicine or working in intensive care units to care for patients with COVID-19, all of us at MJH Life Sciences® are grateful for your dedication, diligence, and professionalism. Thank you and stay safe.
From the Board

Checkpoint inhibition plus CRT: Rationale is strong

NEAL D. SHORE, MD
Shore, a member of the Urology Times® Clinical Practice Board, is medical director, Carolina Urologic Research Center, Myrtle Beach, South Carolina.

Urothelial carcinoma encompasses a range of tumors that arise from the urothelial endothelium and is the predominant histologic type of bladder cancer in the United States and Western Europe. According to Surveillance, Epidemiology, and End Results estimates, there were over 91,000 new cases of bladder cancer in the United States alone in 2018 and more than 17,000 associated deaths in 2018.

Bladder cancer can be categorized as non–muscle-invasive bladder cancer (NMIBC), which represents 75% of primary diagnoses, or MIBC, which represents the other 25%. MIBC is a heterogeneous disease ranging from T2 tumors that invade the muscularis propria to T4 tumors that invade the prostate, uterus, vagina, bowel, or abdominal wall. Up to 50% or more of patients with high-risk NMIBC can progress to invasive disease.

The management of T2-T4aN0M0 MIBC, according to the National Comprehensive Cancer Network and European Association of Urology, includes 2 options: radical cystectomy (RC) and concurrent chemoradiation therapy (CRT). Both are category 1 options. Careful discussions between the patient and bladder cancer management team, including the urologist, radiation oncologist, and medical oncologist, allow for determining the best options for patients.

Recently, studies using immune checkpoint inhibitors (ICIs) have potentially added to improvements in disease control in neoadjuvant therapy and could have a similar outcome for improvements in disease control in neoadjuvant therapy techniques and careful monitoring.

Phase 3 studies are ongoing to determine whether the addition of ICIs will improve the efficacy of CRT while maintaining safety. The clinical need for improved therapy in MIBC and the evidence of clinical activity in metastatic UC, NMIBC, and as neoadjuvant therapy provide a robust rationale for investigating the addition of ICI therapy to CRT for bladder-sparing therapy. Thus, it is critical that urologic oncologists understand and participate in the delivery of immunologic therapies.
Bladder Cancer / CLINICAL UPDATES

High-grade NMIBC linked with disease progression after bladder-sparing therapy

Data indicate high unmet need for novel bladder-sparing treatments

Wayne Kuznar
UT Correspondent

High-grade nonmuscle-invasive bladder cancer (NMIBC) is characterized by high rates of disease progression following introduction of bladder preservation therapy after treatment with Bacillus Calmette-Guérin (BCG).

Among patients identified with high-grade NMIBC from the SEER-Medicare database, only 8.8% received bladder preservation therapy within 6 months of BCG induction. Among this subset, the rate of progression-free survival (PFS) was only 52.3% at year 5, reported Min Yang, MD, PhD, at the 2020 Genitourinary Cancers Symposium in San Francisco.

“What these data are calling for is better treatment. It’s needed for this population.”

MIN YANG, MD, PhD

“Over the 5-year time frame, what we saw is a high rate of disease progression,” said Yang, vice president of Analysis Group, Inc, in Boston, Massachusetts. “Even in year 1, 19% of patients progress. By year 3, more than one-third, and by year 5, it’s close to half of the patients. Available treatments are not doing a fair job in terms of slowing progression. What these data are calling for is better treatment. It’s needed for this population.”

The data indicate a high unmet need for novel bladder-sparing therapies to improve outcomes in this difficult-to-treat population.

Cystectomy is the recommended treatment following failure of BCG but many patients are hesitant to undergo cystectomy and instead choose bladder preservation therapy, according to Yang.

“We wanted to know what happens after BCG failure,” she said.

The SEER-Medicare database was used to identify 7,074 patients with high-grade NMIBC between 2008 and 2015 who received at least one course of BCG induction (defined as ≥5 weekly instillations). Of these, 620 received bladder preservation therapy within 6 months of the last consecutive BCG instillation. The most common therapy was mitomycin C, used in 60.0% of patients, followed by BCG plus interferon alpha (22.9%), valrubicin (Valstar) (4.0%), doxorubicin (Adriamycin) (2.9%), and gemcitabine (Gemzar) (2.1%). Others could include docetaxel (Taxotere), epirubicin (Ellence), nab-paclitaxel (Abraxane), thiota (Tepadin), gemcitabine plus docetaxel, and gemcitabine plus mitomycin C.

Half (50.5%) of the patients had a high-grade T1 tumor at diagnosis, 31.1% had high-grade Ta, and 18.4% had carcinoma in situ. The mean number of transurethral resections of bladder tumor prior to the index date was 2.5. Patients received a median of 5.9 BCG instillations, and 85.1% received 5 or more.

The mean Charlson Comorbidity index (CCI) was 1.4. CCI comorbidities included diabetes in 37.9% of patients, chronic pulmonary disease in 31.0%, peripheral vascular disease in 25.8%, congestive heart failure in 19.4%, and renal disease in 17.7%. Other common comorbidities were hypertension (86.0%), dyslipidemia (78.9%), urinary tract infection (78.2%), other malignancies (33.5%), anxiety/depression (32.7%), and Alzheimer’s disease (29%).

52.3% PFS observed at 5 years

The rate of PFS at 1, 3, and 5 years was 80.9%, 61.8%, and 52.3%, respectively. Time to progression (TTP) was defined as time from bladder preservation therapy initiation to progression event. In TTP analysis, disease progression occurred in 18.7%, 36.4%, and 45.4% of patients at 1, 3, and 5 years, respectively. Disease progression was predominantly identified by metastases, which accounted for 40.5%, 50.0%, and 50.2% of progression events within 1, 3, and 5 years of bladder preservation therapy, respectively.

At 1, 3, and 5 years, 9.5%, 24.8%, and 32.6% of patients, respectively, had metastases. Progression events as identified by radical cystectomy occurred in 35.1% of progressors during year 1, 30.1% of progressors during year 3, and 30.0% of progressors during year 5. Muscle-invasive bladder cancer accounted for 24.3% of progression events in year 1, 19.9% in year 3, and 19.8% in year 5.

Disclosure: Ferring Pharmaceuticals, Inc provided funding for the study. Yang has received institutional funding from Ferring Pharmaceuticals, Inc. For full disclosures, see bit.ly/453disclosures.

FDA GRANTS EXPEDITED APPROVAL FOR LOW-GRADE UPPER TRACT UROTHELIAL CANCER TREATMENT

The FDA granted expedited approval for mitomycin (Jelmyto) for pyelocalyceal solution, a first-in-class treatment indicated for adults with low-grade upper tract urothelial cancer (LG UTUC), UroGen Pharma Ltd reported.

Jelmyto consists of mitomycin, an established chemotherapy, and sterile hydrogel, using UroGen’s proprietary sustained release RTGel technology. It has been designed to enable longer exposure of urinary tract tissue to mitomycin, thereby enabling the treatment of tumors by nonsurgical means.

“Jelmyto offers a new, non-surgical treatment approach for patients who otherwise may require treatment by radical nephroureterectomy, which is associated with declining kidney function and other complications,” said Seth Lerner, MD, professor of urology at Baylor College of Medicine in Houston, Texas, and principal investigator of the OLYMPUS trial.

“This novel, minimally invasive, kidney-sparing treatment has the potential to transform the way low-grade upper tract urothelial cancer is treated and help patients avoid long-term complications associated with surgery and the loss of their kidney.”

The FDA approval is based on results from the phase 3 OLYMPUS trial showing Jelmyto achieved clinically significant disease eradication in adults with LG UTUC. The study yielded a complete response (CR) of 58% in the intent-to-treat population and in the subpopulation of patients who were deemed not capable of surgical removal at diagnosis. At the 12-month time point for assessment of durability, 19 patients remained in CR. 7 had experienced recurrence of disease, and 9 patients continued to be followed for the 12-month duration of response.

The most commonly reported adverse events (≥20%) were ureteric obstruction, flank pain, urinary tract infection, hematuria, renal dysfunction, fatigue, nausea, abdominal pain, dysuria, and vomiting. Most adverse events were mild to moderate and manageable using well-established treatments. No treatment-related deaths occurred.
Enfortumab plus pembrolizumab encouraging in urothelial cancer

Combination yields 73% objective response rate in patients with advanced disease

Gina Columbus
Managing Editor, OncologyLive®

Enfortumab vedotin-ejfv (Padcev) combined with pembrolizumab (Keytruda) led to an objective response rate (ORR) of 73% in previously untreated patients with locally advanced or metastatic urothelial cancer who were ineligible for cisplatin-based chemotherapy, according to updated results of the phase Ib/2 EV-103 trial (NCT03288545) that were presented during the 2020 Genitourinary Cancers Symposium in San Francisco.

Additionally, 45 patients were treated with the combination and were also evaluable for safety and efficacy. At a median follow-up of 11.5 months (range, 0.7-19.2 months), results showed that the 73% ORR (95% CI, 58.1-85.4) included a 15.6% complete response (CR) rate and a 57.8% partial response (PR) rate. The median duration of response (DOR) has not yet been reached (range, 1.2-12.9+ months).

“Cisplatin-based chemotherapy is the standard treatment for first-line advanced urothelial cancer; however, it isn’t an option for many patients,” Jonathan E. Rosenberg, MD, medical oncologist and chief, Genitourinary Medical Oncology Service at Memorial Sloan Kettering Cancer Center, New York, said in a press release. “I’m encouraged by these interim results, including a median progression-free survival of a year for patients who received the platinum-free combination of Padcev and pembrolizumab in the first-line setting.”

In the ongoing, multicohort, open-label, multi-center, phase Ib/2 EV-103 trial, investigators evaluated the efficacy and safety of enfortumab vedotin alone or in combination with pembrolizumab in patients with muscle-invasive, locally advanced, and first- and second-line metastatic urothelial cancer. In the dose-escalation and dose-expansion phases of cohort A, patients enrolled had locally advanced or metastatic urothelial cancer and were ineligible for cisplatin-based chemotherapy.

In cohort A, patients received enfortumab vedotin intravenously (IV) on days 1 and 8 and pembrolizumab on day 1 in a 21-day cycle. At the time of the initial analysis, 45 patients (dose-escalation, n = 5; dose-expansion, n = 40) with locally advanced and/or metastatic urothelial cancer were treated with enfortumab vedotin at 1.25 mg/kg plus pembrolizumab in the frontline setting.

The primary end point in the analysis is safety; key secondary endpoints, related to efficacy, include ORR, disease control rate (DCR), DOR, progression-free survival (PFS), and overall survival (OS).

The median age was 69 years, and men accounted for 80% (n = 36) of the study population. The primary tumor location was lower tract in 69% (n = 31), and metastatic sites consisted of lymph nodes only in 4 patients, and also of visceral disease in the remaining 41 patients, including liver metastases (n = 15). PD-L1 expression status by combined compositive score was <10 in 19 patients, ≥10 in 13, and was not evaluable or not available in 13 patients. The DOR, PFS, and OS are immature. Further findings showed that 35% of the 33 responses were ongoing at the time of the analysis, with 83.9% of responses lasting 26 months and 53.7% of responses lasting ≥12 months, according to Kaplan-Meier estimates. The median PFS was 12.3 months, and the median OS has not been reached. However, the 1-year OS rate was 81.6% (95% CI, 62%-91.8%).

Initial results of this cohort of EV-103 were presented at the 2019 ESMO Congress. Here, the combination of enfortumab vedotin and pembrolizumab led to an ORR of 71%, including a 13% CR rate. Moreover, the stable disease rate was 22%, leading to a clinical benefit rate of 93%. All but 3 evalable patients had some degree of tumor shrinkage.

Additional urothelial cancer cohorts of EV-103 will evaluate enfortumab vedotin: alone or in combination with pembrolizumab or a platinum-based chemotherapy in the first-line setting for patients with metastatic disease; plus pembrolizumab and carboplatin or cisplatin in first-line metastatic disease; alone or in combination with pembrolizumab in muscle-invasive disease; in combination with pembrolizumab in second-line metastatic disease; and plus gemcitabine in first- or second-line metastatic disease.

In December 2019, the FDA granted an approved acceleration to enfortumab vedotin for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have received prior treatment with a PD-1/PD-L1 inhibitor and platinum-containing chemotherapy.

Disclosure: Seattle Genetics, Inc. provided funding for the study. For full disclosures from Rosenberg and study co-authors, see https://bit.ly/2xthWxS. \( \text{UI} \)

SUPPLEMENTAL BLA IS SUBMITTED FOR AVELUMAB AS FIRST-LINE MAINTENANCE TX FOR UROTHELIAL CA

EMD Serono announced completion of the submission of a supplemental biologics license application (sBLA) to the FDA for avelumab (Bavencio) for first-line maintenance treatment of patients with locally advanced or metastatic urothelial carcinoma.

The FDA granted breakthrough therapy designation to avelumab for this indication, and the sBLA is being reviewed by the FDA under its Real-Time Oncology Review pilot program.

The application is based on positive results from an interim analysis of the phase III JAVELIN Bladder 100 trial, which met its primary end point of overall survival. In this study, avelumab plus best supportive care (BSC) as first-line maintenance therapy significantly extended the survival of patients with previously untreated locally advanced or metastatic urothelial carcinoma whose disease did not progress on induction chemotherapy, compared with BSC only. A statistically significant improvement was demonstrated in both co-primary populations: all randomized patients and patients with PD-L1-positive tumors.

The safety profile for avelumab in the trial was consistent with that in the JAVELIN monotherapy clinical development program. Detailed results from the JAVELIN Bladder 100 trial will be presented at an upcoming medical congress.

SINGLE-USE CYSTOSCOPE RECEIVES FDA 510(K) CLEARANCE, READY FOR NORTH AMERICAN LAUNCH

The Ambu aScope Cysto has received 510(k) clearance from the FDA and is now ready for launch in North America, Ambu announced. The aScope Cysto is designed for single use and is also portable.

“For a urologist, it is crucial to be able to maneuver and navigate the scope smoothly in the urethra and bladder. Therefore we have designed the aScope Cysto for high bending angles of up to 210 degrees, and it is possible to advance and completely retroflex the cystoscope to inspect the bladder neck— with or without forceps inserted,” said Greg Swanson, senior vice president of marketing at Ambu.

The aScope Cysto will be launched together with Ambu’s latest monitor platform, Ambu aView 2 Advance.
Urothelial cancers are sensitive to platinum-based chemotherapy, but due to the low incidence of upper tract urothelial cancer (UTUC) and difficulty in conducting clinical trials, strong evidence supporting the use of chemotherapy has been lacking. However, recently published results of a multi-institutional, randomized, phase 3 trial from the United Kingdom demonstrate significant benefit of adjuvant chemotherapy after nephroureterectomy (Lancet 2020; 395:1268-77).

The investigators carried out the POUT (Peri-Operative Chemotherapy Versus Surveillance in Upper Tract Urothelial Cancer) trial to assess the efficacy of systemic platinum-based chemotherapy in patients with UTUC. The eligible patients included those with UTUC after nephroureterectomy, stages pT2-T4 or N1-3, without distant metastasis. Before randomization, patients underwent imaging studies and those with residual lymphadenopathy were excluded.

Between June 2012 and November 2017, 261 patients were recruited from 57 of the 71 open sites. The number of patients assigned to receive 4 cycles of platinum-based chemotherapy was 132, and 129 patients were assigned to undergo initial surveillance, with the option to undergo chemotherapy in case of disease progression. Cisplatin was the agent of choice to be used with gemcitabine, but patients with low glomerular filtration rate (GFR; 30-50 ml/min) could be treated with carboplatin. The primary end point of the study was disease-free survival. Cisplatin use is born of necessity in patients with low GFR, although from data previously conducted trials endorse the superiority of cisplatin against urothelial cancers. Further, there are some barriers to using cisplatin chemotherapy before a nephroureterectomy when renal function is still preserved. The main hurdle appears to be the difficulty in proper staging to identify stage T2 or higher, due to the limitations posed by the anatomy and available instruments. Thus, there is a valid concern about overtreatment of nearly 40% to 50% of patients with UTUC.

This important trial supports the use of adjuvant chemotherapy after nephroureterectomy for stage T2 or higher cases. Studies are ongoing to assess the feasibility of adjuvant vs neoadjuvant platinum-based chemotherapy for UTUC. As the quality of imaging and instrumentation improves, using a combination of antegrade, retrograde, and percutaneous techniques, it will help to identify candidates who may benefit from upfront chemotherapy. 

**Some questions remain unanswered**

Although the use of adjuvant chemotheraphy using platinum-based agents following nephroureterectomy is not a new concept, it had been based primarily on heterogeneous data showing mixed results. The POUT trial represents the largest study in this patient population assessing the benefit of adjuvant chemotherapy. Due to the rarity of this disease, it is difficult to recruit patients, which is further underscored that it took over 5 years, 71 centers, and the weight of a national health system to recruit 261 patients. With those inherent constraints, some questions remain unanswered.

As acknowledged by the authors, disease-free survival may not be a proven surrogate for overall survival but it may be the best we can achieve for some rare conditions. Adjuvant chemotherapy is suggested as the new standard of care after nephroureterectomy in those who are fit enough to qualify. However, the denominator is not provided which may be instructive; ie, how many patients underwent nephroureterectomy at these 71 centers who met the inclusion criteria but did not enroll in the study? Due to small numbers in the subset analysis, it is difficult to ascertain whether the benefit of adjuvant chemotherapy was noted primarily in organ-confined disease or in patients with positive margins or nodal disease.

Carboplatin use is born of necessity in many patients with low GFR, although from data previously conducted trials endorse the superiority of cisplatin against urothelial cancers. Further, there are some barriers to using cisplatin chemotherapy before a nephroureterectomy when renal function is still preserved. The main hurdle appears to be the difficulty in proper staging to identify stage T2 or higher, due to the limitations posed by the anatomy and available instruments. Thus, there is a valid concern about overtreatment of nearly 40% to 50% of patients with UTUC.
PD-1 inhibitor shows some antitumor activity in prostate cancer

Pembrolizumab alone yields 4%-5% objective response rate; combination therapy may be key

Gina Columbus
Managing Editor, OncologyLive®

With additional follow-up of approximately 10 months, monotherapy with the PD-1 inhibitor pembrolizumab (Keytruda) continued to show antitumor activity in men with metastatic castration-resistant prostate cancer (mCRPC). However, monotherapy alone is likely not a sufficient treatment in this patient population, according to Emmanuel Antonarakis, MBBC, professor of oncology at Johns Hopkins University in Baltimore, Maryland.

Antonarakis presented findings on cohorts 1 to 3 of the multicohort KEYNOTE-199 study (NCT02787005) at the Genitourinary Cancers Symposium in San Francisco. A previous analysis showed that pembrolizumab alone has antitumor activity and acceptable safety in patients with mCRPC who were previously treated with a next-generation hormonal agent and docetaxel.

In this interview by Urology Times® sister publication OncologyLive®, Antonarakis discusses updated results with additional follow-up in this population.

Q: Can you give a little background on KEYNOTE-199 and the rationale for this study?
A: What we presented this year at the 2020 Genitourinary Cancers Symposium was an updated analysis of the KEYNOTE-199 pembrolizumab study in advanced prostate cancer. This is a study of single-agent pembrolizumab in 5 different cohorts. The first 3 cohorts were without the use of enzalutamide [Xandi]. Then cohorts 4 and 5, which were presented at the symposium by Julie Graff, MD [Oregon Health & Science University], were looking at the patients progressing on enzalutamide where the pembrolizumab was added in conjunction with enzalutamide. This was sort of an encore presentation; we have previously published results in the Journal of Clinical Oncology of the first 3 cohorts of the study.

Q: What were the key findings?
A: The first 3 cohorts were people who were receiving pembrolizumab as a monotherapy in 1 of 3 groups. First were patients who had soft tissue disease and were PD-L1 positive by immunohistochemistry. The second group consisted of patients with soft tissue disease who were PD-L1 negative. And the third group consisted of patients who had bone-predominant or bone-only metastases.

The punchline of the encore abstract is that it’s very consistent with the original data from the Journal of Clinical Oncology publication. We have an additional 10 or 11 months of median follow-up, so we have more mature follow-up, but the message is fairly consistent. We’re seeing about a 4% or 5% objective response rate in these patients with pembrolizumab monotherapy. Again, this is a CRPC [castration-resistant prostate cancer] population, and we’re seeing approximately a 10% PSA [prostate specific antigen] response rate.

The safety seems consistent. There doesn’t seem to be any extra or negative safety signal for our patients to be concerned about, with the main side effect being fatigue. The risk of autoimmune conditions when pembrolizumab is used as a monotherapy in prostate cancer is quite low, so we don’t have to worry too much about that.

Overall, this suggests that there is some activity with pembrolizumab as a monotherapy, but we need to do better. This leads to the next phase of the development of this drug, which will be in combination with either enzalutamide, and there’s an ongoing phase 3 study; or in combination with docetaxel, and there’s another ongoing phase 3 study for that; or in combination with the PARP inhibitor olaparib, and there’s also a phase 3 study with that. So, I think as a monotherapy, it’s been encouraging but probably not enough on its own. And now we need to figure out what’s the best combination partner and there might be more than 1.

“Overall, this suggests that there is some activity with pembrolizumab as a monotherapy, but we need to do better.”

EMMANUEL ANTONARAKIS, MBBC+

Q: What other take-home messages from these data do you have for clinicians?
A: In a biomarker-unselected population, any PD-1 or PD-L1 inhibitor by itself is probably not going to be enough. Now, there are some patients [for whom] even as a monotherapy, a PD-1 or a PD-L1 inhibitor might be beneficial, for example, the small subset of patients who have mismatch repair deficiency or microsatellite instability high genotypes. The second population [for whom] these drugs might work as monotherapy could be those patients who have CDRK12 mutations.

And then there are some preliminary data that have not yet been confirmed [indicating] that perhaps patients…with BRCA1 and BRCA2 mutations may also be slightly enriched for a response to single-agent PD-1 blockers.

Disclosure: Merck provided funding for the study. For full disclosures from Antonarakis and study co-authors, see https://bit.ly/2yhWzK.

**FIRST PATIENT DOSED IN PHASE 3 TRIAL OF PROSTATE CANCER IMAGING AGENT**

Blue Earth Diagnostics announced that the first patient has been dosed in its phase III LIGHTHOUSE clinical trial of rPSMA-7.3 (18F), an investigational Prostate Specific Membrane Antigen-targeted radiolabeled positron emission tomography imaging agent.

The LIGHTHOUSE study is a phase III, multi-center, single-arm imaging study being conducted in the United States and Europe to evaluate the safety and diagnostic performance of rPSMA-7.3 (18F) PET imaging in men with newly diagnosed prostate cancer (NCT04186819). The primary objectives of the LIGHTHOUSE study are to assess the sensitivity and specificity of rPSMA-7.3 (18F) PET for detecting pelvic lymph node metastases compared to surgical pathology on a patient level. Secondary end points will assess the safety of rPSMA-7.3 (18F) in patients and determine inter- and intra-reader agreement of rPSMA-7.3 (18F) scan interpretations by blinded independent readers.

The first patient in the LIGHTHOUSE study was dosed in Los Angeles, California at RadNet’s Liberty Pacific Advanced Imaging Center in conjunction with Tower Urology.
Prechemotherapy radium-223 does not affect chemo regimens

Patients are more likely to complete full treatment when radium is administered first.

Gina Columbus
Managing Editor, OncologyLive®

In a study presented at the 2020 Genitourinary Cancers Symposium, researchers examined real-world outcomes for patients with metastatic castration-resistant prostate cancer treated with radium-223 (Xofigo). Study author Rana R. McKay, MD, assistant professor of medicine at UC San Diego Health, discusses this study and its significance in the castration-resistant prostate cancer landscape.

Q: Please discuss the rationale for this study.
A: Radium-223 is a liquid radiopharmaceutical that has been shown to improve survival in patients with advanced prostate cancer. It’s specifically used for patients who have bone metastases, may have symptomatic bone pain, and don’t have visceral metastases. Results from the ALSYMPCA trial demonstrated the improvement of overall survival with this agent.

However, there’s not really been a lot of real-world data documenting how this agent is used in the changing landscape for metastatic castration-resistant prostate cancer. Since the ALSYMPCA trial, we’ve seen approvals of several androgen receptor (AR)-targeting agents and potentially PARP inhibition in the future, so placing radium-223 in the context of real-world practice has not really been established.

The rationale for this study was to characterize the utilization of radium-223 within the real world.

Q: What did the results of the study show about the timing of initiating radium-223?
A: In the study, we included a total of 220 patients who had received radium between 2013 and 2017. We wanted to look at the characteristics of those patients who had received radium pre chemotherapy versus post chemotherapy. About half of our patients had received radium pre and half post chemotherapy on average.

We showed that when radium-223 was given prior to chemotherapy, it did not influence the amount of chemotherapy that any individual patient could receive.

“We showed that when radium-223 was given prior to chemotherapy, it did not influence the amount of chemotherapy that any individual patient could receive.”

Rana R. McKay, MD

Q: What were some of the lessons learned from this study?
A: The biggest lesson learned was about placement of radium. This trial was not meant to examine what is the proper sequence of treatment but instead suggests that there is no increased toxicity or increased decline in the amount of chemotherapy that somebody may receive when they’ve received radium first.

The other thing that we did was characterize how radium is used. How many people are getting radium as a monotherapy; how many patients are getting radium in combination with another agent? Looking at real-world practice patterns, about 40% of patients are getting radium-223 in combination with an AR-targeting agent, the majority of which is enzalutamide (Xtandi). That’s not necessarily on-label use of radium, but in real-world practice there is this use of the concurrent AR-targeting agents. Also, with the ERA data, it’s important to stress the importance of using a bisphosphonate or bone-strengthening agent when radium is used and just the risk of fragility fractures. That’s why the 2 are used together.

It was a good study to paint the landscape of how we utilize radium in the real world and provide some instruction to clinicians regarding placement of radium for patients with metastatic CRPC.

Q: Are there any other kinds of real-world analyses that you would like to see conducted with radium-223?
A: That is a good segue to the project that we’re doing. There has been a lot of excitement around the DNA repair pathway in prostate cancer. Given that radium is an alpha particle that induces DNA damage in cells within the bone niche, we began thinking about synergy in the context of those who have homologous recombination deficiency (HRD). For our next project, we’re working from this data set to look at outcomes in HRD-mutated versus nonmutated patients.

Q: Were there any other takeaways from this study for clinicians?
A: When we think about CRPC and we look at the data that’s out there, I think real-world data are important. What we are understanding is that CRPC is probably an undertreated disease. A lot of patients may see first-line therapy for CRPC, but there are a lot of patients who never see second- and third-line treatments. These agents have been shown to improve overall survival; radium-223 demonstrated an OS benefit in a large phase 3 study. I think the first step for any practicing clinician is to actually treat CRPC patients. There may be reasons to not treat somebody, but these drugs are life-prolonging agents, and with a lot of drugs moving into the castration-sensitive space, the treatment options for CRPC are decreasing. Radium-223 is a good agent to use for those patients who have bone metastases and have castration-resistant disease.

Disclosures: Bayer provided funding for the study. McKay is a consultant/adviser for Astellas Medication, Bristol Myers Squibb, Dendreon, Exelixis, Janssen, Novartis, Pfizer, and Tempus. For full disclosures, see bit.ly/223disclosures.

UT0830_019_Clinical Update PCa 223.indd 19

MAY 2020 | Urology Times®| 19
GnRH antagonists show lower odds of cardiac complications in prostate cancer

Caroline Seymour
Assistant Editor, OncologyLive®

Gonadotropin-releasing hormone (GnRH) agonists have a higher risk of cardiac toxicity than GnRH antagonists, most notably myocardial infarction and heart failure, according to findings from a large-scale disproportionality analysis.

Cardiac complications are the leading cause of non–cancer-related mortality among patients with prostate cancer, said lead study author, Eugene B. Cone, MD, who added that although GnRH agonists and antagonists have similar clinical efficacy in prostate cancer, their cardiac risk profiles have not been well studied.

In the analysis, investigators compiled data from the World Health Organization (WHO) on the cardiac events that had been reported with the GnRH antagonist degarelix (Firmagon) and the GnRH agonists leuprolide, goserelin (Zoladex), triptorelin (Trelstar), and histrelin. The cardiac event rate reported with other drugs, such as aspirin and chemotherapy, served as the comparator.

GnRH agonists had a significantly higher risk of cardiac complications versus GnRH antagonists (odds ratio [OR], 1.20; 95% CI, 1.12-1.29), particularly regarding myocardial infarction (OR, 1.76; 95% CI, 1.57-1.97) and heart failure (odds ratio, 2.02; 95% CI, 1.73-2.35).

In an interview with Urology Times sister publication OncologyLive®, Cone, a urologic oncology fellow at Brigham and Women's Hospital and Massachusetts General Hospital in Boston, discussed the advantages of the study, the need for such research, and the potential to broaden these efforts to more novel agents such as abiraterone acetate (Zytiga), enzalutamide (Xtandi), and immune checkpoint inhibitors.

Q: Please provide some background on this trial.
A: It’s a relatively common problem in urology and medical oncology for patients with prostate cancer to develop biochemical recurrence or present with more advanced disease. First-line medications commonly include GnRH agonists such as leuprolide, or GnRH antagonists such as degarelix. [These agents] both have very similar clinical benefits and clinical profiles; however, the cardiac toxicity [associated with these drugs] has not really been [well defined]. As such, we decided to examine [the cardiac toxicities of these drugs] using pharmacovigilance methodology, which has not traditionally been applied in urology. We did this by using VigiBase, a database from WHO. [The database] accumulates reports from more than 130 countries across the globe. [We collected data from the database] to examine whether a higher risk for cardiac events existed with GnRH agonist or antagonist therapy.

Q: What is the benefit of using data from the VigiBase?
A: There are a couple of advantages and disadvantages to the study. One of the biggest advantages is that this is a real-world application of clinical practice with agonist and antagonist therapy. With all these cases, patients were not necessarily screened one way or the other. [We did] include trial data, but we also included data from real-world clinical practice. You don’t need to worry about whether we were gating patients out with preexisting cardiac risk factors or anything along those lines. Another big benefit is that this was a global analysis that aggregated data from many countries with different practice styles and health systems. Some of the more rigid entrance criteria for trials that may have limited the applicability to trial data in this space don’t necessarily apply in this field. The sample size is extremely large. We found almost 1000 individual cardiac events, which is by far the largest series that has been reported to date.

In terms of our work, we took the number of patients who received the drug and reported the number of adverse events (AEs), and used that number as the denominator. Then, we looked at the number of patients who took the drug and had cardiac AEs. That gave us 1 form of an event rate. To calibrate that event rate to determine what the expected count should be, we took everyone who received any other drug in the database, from aspirin to chemotherapy, and experienced any AE. Then, we looked at the number of patients who took any other drug and had a cardiac AE to see what the expected event rate would be. We compared the 2 and determined whether there is a signal or not [with GnRH agonists and antagonists].

Q: What did the analysis show regarding the relative cardiac toxicity between GnRH agonists and antagonists?
A: Our results showed what has long been suspected. Even now, I don’t believe we can say it has truly been proven, but the analysis certainly supports the fact that GnRH agonist therapy has a significantly worse cardiac risk profile versus GnRH antagonist therapy.

Q: What are some of the strategies in place for patients who develop these cardiac events?
A: Call cardiology. At the end of the day, urologists and medical oncologists underwent a lot of training to deal with things that are really germane to this field. We’re very good at dealing with some things, but heart attacks, heart failure, and cardiitis are probably not those things.

Q: How could the results of this analysis impact clinical practice?
A: When it comes to patient care, this underscores the idea that we need a much better understanding of the individual risk profiles of our patients. We have a general understanding that androgen deprivation may be associated with increased cardiac risk. I don’t believe we really have a granular understanding of which medication is better [in terms of less cardiac or neurotoxicities]. We know enzalutamide has some neurological AEs. There are certainly indications that abiraterone is worse for cardiac toxicity, but we need a much more granular understanding [of these toxicities] so we can deliver truly personalized patient care.

This research is certainly hypothesis generating. However, I don’t believe we have fully answered the question. One of the really interesting hypotheses that has come out of this research [came alongside] a similar study we did in which we examined abiraterone or enzalutamide, in which we found that enzalutamide was not associated with a major increase in cardiac toxicity with the exception of hypertension. Conversely, abiraterone had significantly increased cardiac toxicity, especially with regard to myocarditis and heart failure. When we looked at the literature to determine why that might be, we found some preclinical data to suggest that intracellular levels of androgen are lower if a patient is on a GnRH agonist and abiraterone, both of which are expected.

However, interestingly, with enzalutamide, you find higher levels of intracellular androgen. I haven’t come across data on degarelix, the GnRH agonist, but I wouldn’t be surprised if something similar is going on. A real role for intracellular androgen levels could exist when it comes to cardiac toxicity, and that’s certainly an area we’ll explore more in the future.

Disclosure: One co-author on this study receives honoraria from Astellas Pharma, Bayer, and Janssen. [1]

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Data reveal prevalence of advanced prostate cancer states

Substantial variation in homologous recombination repair gene testing is observed

Cheryl Guttmann Krader, BS, Pharm
UT Contributing Editor

Findings from a systematic literature review further our understanding of the prevalence of distinct clinical states of advanced prostate cancer, their association with homologous recombination repair (HRR) gene alterations, and the use of testing methods to identify HRR gene alterations, researchers say. The data provide important background for appropriate patient care decision making.

They are particularly noteworthy given the anticipated shift in the treatment landscape that is ushering in a new era of personalized medicine, said Neal Shore, MD, at the 2020 Genitourinary Cancers Symposium in San Francisco.

The study involved searches of 9 databases for relevant English-language articles published from January 2009 to May 2019 and of conference proceedings from 10 meetings held from 2014 to 2019. Investigators identified more than 4700 papers that exceeded inclusion criteria and underwent detailed review.

Among the main findings, data showed global increases in the incidence and prevalence of metastatic hormone-sensitive prostate cancer (mHSPC), nonmetastatic castrate-resistant prostate cancer (nmCRPC), and metastatic CRPC (mCRPC), a relatively high prevalence of HRR gene alterations in prostate cancer, and substantial variation in HRR gene testing.

“This comprehensive, detailed review and meta-analysis of a decade of reports identified in global databases has provided numerous interesting findings, notwithstanding the caveats of a retrospective analysis and the associated challenges that variability in reporting and definitions created for quantifying and synthesizing the information,” said Shore, medical director at the Carolina Urologic Research Center in Myrtle Beach, South Carolina.

“Understanding current real-world evidence regarding the epidemiology of and practice trends for mHSPC, nmCRPC, and mCRPC and HRR gene alterations is important as we look forward to the availability of therapies, specifically poly [ADP ribose] polymerase [PARP] inhibitors, that have shown benefit for men with mCRPC harboring certain HRR gene alterations, and the spate of clinical trials investigating these drugs in all stages of metastatic PC.”

According to the meta-analysis, approximately 20% of men with mCRPC and 10% to 15% of men with mHSPC have HRR gene alterations, suggesting they could potentially benefit from PARP inhibitor treatment. Of the studies that were reviewed for information on HRR gene alterations, most focused on germline testing. Therefore, limited data were captured on the prevalence of somatic HRR alterations.

*Germline testing, which is done to identify inherited genetic alterations, can be done using a blood or saliva sample. A tumor sample is required now to test for somatic HRR gene alterations that arise de novo in the prostate cancer, but liquid [blood-based] testing for somatic alterations is also forthcoming,” Shore explained.

“The need to test for somatic HRR gene alterations in men who have a negative result by germline testing is highlighted by analyses that doing both types of tests may double the proportion of patients found to have an actionable HRR gene alteration.”

The National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology for prostate cancer recommend performing germline genetic testing in men with prostate cancer with a positive family history as well as in those with high-risk, very high-risk, regional, or metastatic prostate cancer, Ashkenazi Jewish ancestry, or intraductal histology. The guidelines state that somatic tumor testing for HRR gene mutations can be considered in patients with regional or metastatic prostate cancer.

“In addition to providing information that can be relevant for precision care and counseling for some prostate cancer patients, the finding of certain HRR germline mutations has implications for cascade family testing in order to identify cancer risk genes for family members who may be at risk for ovarian, breast, colorectal, and other cancers,” Shore said.

*Disclosure: Merck provided funding for the study. Shore does research/consulting for Merck, AstraZeneca, Clovis Oncology, Myriad, and Incyte. For full disclosures, see bit.ly/229disclosures.*

Analysis yields potential precision medicine path in mHSPC

Danielle Ternyila
Assistant Web Editor, Targeted Oncology™

A correlative study of gene expression profiling data from the phase 3 CHAARTED trial identified varying benefits with different treatment approaches in patients with different subtypes of metastatic hormone-sensitive prostate cancer (mHSPC).

This variance, said the lead investigator of the analysis, Anis Hamid, MBBS, offers the potential to employ a precision medicine approach to treatment selection in mHSPC by tailoring treatment to the patient’s disease subtype.

The phase 3 CHAARTED trial randomized patients with mHSPC to androgen-deprivation therapy (ADT) with or without docetaxel. Hamid and colleagues successfully used gene expression profiling on 160 available specimens of patient biopsies. Of these specimens, the subtypes were classified as luminal B (50%), basal (48%), and luminal A (2%).

There was a significant improvement in overall survival (OS) and time to castration-resistant prostate cancer in patients with the luminal B subtype who received ADT plus docetaxel; however, there was not an OS benefit with ADT plus docetaxel in the group with the basal subtype, Hamid et al reported at the Genitourinary Cancers Symposium in San Francisco. Thus, the researchers concluded that patients with luminal B disease benefit from the addition of docetaxel, while those with basal disease do not seem to have improved outcomes with the additional upfront treatment.

*See mHSPC page 24*
In an interview with OncologyLive®, Hamid, a medical oncologist and genitourinary oncology research fellow at the Dana-Farber Cancer Institute in Boston, discussed the analysis of genomic profiling from the phase 3 CHAARTED trial and the potential of precision medicine in mHSPC.

Q: Please provide some background on the CHAARTED trial.
A: The CHAARTED trial was a phase 3 randomized trial of men with newly diagnosed mHSPC. This trial was reported about 6 years ago, and before that time, the standard of care for men with metastatic disease was androgen deprivation therapy or hormonal therapy. The CHAARTED trial showed that the addition of docetaxel therapy given at the start of diagnosis significantly improved the survival of men with newly diagnosed metastatic prostate cancer.

Since the CHAARTED trial and related trials, such as STAMPEDE and so forth, docetaxel became the standard treatment for men with metastatic prostate cancer. Since that time, a number of different treatments have been introduced in a sim-
ilar setting, including potent hormonal therapies such as abiraterone acetate (Zytiga), enzalutamide (Xtandi), and apalutamide (Erleada).

Q: Please discuss the luminal B subtype.
A: We know a little about luminal and basal subtypes from initial work done in localized nonmetastatic prostate cancer where luminal A, luminal B, and basal subtypes compromised approximately a third each in that population. What we saw with the CHAARTED population in the mHSPC population is that there were few luminal A tumors and most of the tumors were either luminal B or basal.

Luminal B tumors were associated with a shorter survival on hormonal therapy alone. However, that subtype specifically benefited from docetaxel chemotherapy upfront. On the other hand, basal tumors were associated with a relatively better prognosis compared to luminal B tumors, but when we looked at their outcomes with chemotherapy, we didn’t observe a significantly beneficial response to upfront chemotherapy. In this way, it looks like luminal B and basal subtyping not only have prognostic effects but also has a predictive potential.

See mHSPC page 25
Q: What do you think are next steps?
A: This analysis is interesting, and it has generated a lot of hypotheses and excitement. What is critical is that we take the next step and validate it in independent cohorts. When we develop a biomarker to choose or tailor therapies more precisely for our patients. It’s really important we select biomarkers that have been proven and are reproducible independently. We have collaborated with other groups and other clinical trials that have run similar investigations in this exact disease space to perform similar RNA analyses of their trials in order to test this hypothesis again.

We are not quite ready for primetime, but it is giving us some initial insights about the biology. The second part of that question is we want to dig further into the biology here. We have made some classifications about response and these luminal or basal subtypes, but we need to learn a little bit more about other biological programs and other correlations in place that
explain the chemotherapy sensitivity or chemotherapy insensitivity of these disease subtypes.

Q: Are there other therapies that may be showing benefit for the luminal B subtype?
A: We know that the luminal B subtype appears to benefit from docetaxel. One of the important questions is whether these luminal B and basal subtypes respond similarly with potent hormonal therapies that we have in clinical, such as abiraterone, enzalutamide, or apalutamide. Luckily, we are partnered with trials that have tested these drugs in a prospective setting, and hopefully, we will learn once we have more information from the RNA profiling of those studies.

Q: Are there any other unanswered questions that you hope to answer in the near future?
A: In terms of the development of a more precise way of mHSPC, the data we have at this stage is only related to gene expression profiling, which is what was been presented at the symposium. We want to know other ways of biological information, namely what is happening with the tumor genomics, what are the mutational characteristics of these tumors that may be affecting prognosis, or the predictive effects that we hypothesize there are with certain genomic alterations. There are layers of biological information about genomics, such is epigenomics, and how, for example how demethylation might affect treatment response and prognosis. What we are hoping to do is integrate multiple layers of biological information across independent cohorts to get a more multidimensional view of the biomarkers that might guide precision care for these patients.

“Luminal B tumors were associated with a shorter survival on hormonal therapy alone. However, that subtype specifically benefited from docetaxel chemotherapy upfront.”

ANIS HAMID, MBBS

Q: What is it like to see these precision medicine developments make a lot more headway in prostate cancer?
A: It is exciting to see precision medicine being translated to prostate cancer. We have always known that, for example in the case of chemotherapy, there are certain subpopulations of patients that benefit and sub-populations of patients that do not. We have tested this in ways that are more clinically driven, like volume of metastatic disease, but almost certainly there will be biological parameters that can guide our treatment decisions better to hopefully make our decision more precise.

This is the way that oncology is moving across the board. We are refining the way we treat patients and approach different therapies being informed by not only the clinical information we have but also the biological information and drug response information, and [other details]. It is all in the view of getting the best therapies to patients that are going to have a benefit from it and finding better therapies for patients who are not predicted to benefit from those particular drugs.

Disclosure: Decipher Biosciences and the National Institutes of Health provided funding for the study. For full disclosures from Hamid and co-authors, see bit.ly/3d8YzG.
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See mHSPC page 25

Table 1. Adverse Reactions in AFFIRM (cont’d)

<table>
<thead>
<tr>
<th>Common Adverse Reactions</th>
<th>Grade 1-4 (%)</th>
<th>Grade 3-4 (%)</th>
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<tbody>
<tr>
<td>Nausea</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Constipation</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Flat</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Sleep disorders</td>
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<tr>
<td>Gastrointestinal Disorders</td>
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Table 2. Adverse Reactions in PREVAIL (cont’d)

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<tr>
<td>Nausea</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Diarrhea</td>
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</tr>
<tr>
<td>Constipation</td>
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<td>0%</td>
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<tr>
<td>Flat</td>
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<td>0%</td>
</tr>
<tr>
<td>Sleep disorders</td>
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<tr>
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Table 3. Adverse Reactions in TERRAIN

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<td>0%</td>
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<tr>
<td>Diarrhea</td>
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<tr>
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<tr>
<td>Flat</td>
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<tr>
<td>Sleep disorders</td>
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<tr>
<td>Gastrointestinal Disorders</td>
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Table 5. Adverse Reactions in ARCHES

<table>
<thead>
<tr>
<th>Category</th>
<th>XTANDI (n = 574)</th>
<th>Placebo (n = 462)</th>
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<th>Grade 2 (%)</th>
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<td>Metabolism and Nutrition Disorders</td>
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ARCHES randomized 1150 patients with mCSPC, of whom 1146 received at least one dose of study drug. All patients received either a gonadotropin-releasing hormone (GnRH) analogue concurrently or had bilateral orchectomy. Patients received either XTANDI at a dose of 160 mg once daily (n=574) or placebo (n=574). The median duration of treatment was 12.8 months (range: 0.2 to 24.6 months) with XTANDI and 11.6 months (range: 0.2 to 24.6 months) with placebo. Overall, 10 patients (1.7%) receiving XTANDI died from adverse events. The reasons for death in ≥2 patients included heart disease (n=2) and pulmonary embolism (n=2). Eight patients (1.4%) receiving placebo died from adverse events. The reasons for death in ≥2 patients included heart disease (n=2) and sudden death (n=2). Grade 3 or higher adverse events were reported in 34% of patients treated with XTANDI. Permanent discontinuation due to adverse events was reported in 4.5% of XTANDI-treated patients and 3.7% of placebo-treated patients. The most common adverse events leading to permanent discontinuation in placebo-treated patients were asthenia and fatigue, each in 0.3%. The most common adverse events leading to permanent discontinuation in placebo-treated patients were asthenia and fatigue, each in 0.3%.

Table 6. Laboratory Abnormalities

<table>
<thead>
<tr>
<th>Category</th>
<th>XTANDI (n = 574)</th>
<th>Placebo (n = 462)</th>
<th>Grade 1 (N = 930)</th>
<th>Grade 2 (N = 465)</th>
<th>Grade 3 (N = 551)</th>
<th>Grade 4 (N = 393)</th>
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</thead>
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<td>Grade 1 (%)</td>
<td>Grade 2 (%)</td>
<td>Grade 3 (%)</td>
<td>Grade 4 (%)</td>
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<td>Neutrophil count decreased</td>
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<td>0.9</td>
<td>17.0</td>
<td>0.4</td>
<td>13.0</td>
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<td>Hemoglobin</td>
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<td>Platelet count decreased</td>
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<tr>
<td>Metabolism and Glucose Disorders</td>
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<td></td>
<td>Grade 1 (%)</td>
<td>Grade 2 (%)</td>
<td>Grade 3 (%)</td>
<td>Grade 4 (%)</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>3.5</td>
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<td>Hyperphosphatemia</td>
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<td>Hypophosphatemia</td>
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<td>Hypomagnesemia</td>
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**Dietary Interactions**

Drugs that Inhibit CYP2C8

Co-administration of a strong CYP2C8 inhibitor (gemfibrozil) increased the composite area under the plasma concentration-time curve (AUC) of enzalutamide plus fluoxetine enzalutamide by 22%. Co-administration of XTANDI with strong CYP2C9 inhibitors should be avoided if possible. If co-administration of XTANDI with a strong CYP2C8 inhibitor cannot be avoided, reduce the dose of XTANDI.

Drugs that Induce CYP3A4

Co-administration of rifampin (strong CYP3A4 inducer and moderate CYP2C8 inducer) decreased the composite AUC of enzalutamide plus fluoxetine enzalutamide by 37%. Co-administration of strong CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifampin, ritonavir) 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 CYP2C8 and CYP3A4 inhibitor in humans. At steady-state, XTANDI reduced the plasma exposure to midazolam (CYP3A4 substrate), warfarin (CYP2C9 substrate), and verapamil (CYP3A4/3A5 substrate). Concomitant use of XTANDI with narrow therapeutic index drugs that are metabolized by CYP3A4 (e.g., alfentanil, cyclosporine, troleandomycin, testosterone, fentanyl, midazolam, quinidine, simvastatin, and tacrolimus), CYP2C9 (e.g., phenytoin, warfarin) and CYP3A4 (e.g., 5-hydroxytryptophan, cyclazocine) 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 reproduction 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 (MRHD).

**Use in Specific Populations**

**Prognosis**

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**Use in Specific Populations**
explain the chemotherapy sensitivity or chemotherapy insensitivity of these disease subtypes.

**Q:** Are there other therapies that may be showing benefit for the luminal B subtype?

**A:** We know that the luminal B subtype appears to benefit from docetaxel. One of the important questions is whether these luminal B and basal subtypes respond similarly with potent hormonal therapies that we have in clinical, such as abiraterone, enzalutamide, or apalutamide. Luckily, we are partnered with trials that have tested these drugs in a prospective setting, and hopefully, we will learn once we have more information from the RNA profiling of those studies.

**Q:** What is it like to see these precision medicine developments make a lot more headway in prostate cancer?

**A:** It is exciting to see precision medicine being translated to prostate cancer. We have always known that, for example in the case of chemotherapy, there are certain subpopulations of patients that benefit and subpopulations of patients that do not. We have tested this in ways that are more clinically driven, like volume of metastatic disease, but almost certainly there will be biological parameters that can guide our treatment decisions better to hopefully make our decision more precise.

This is the way that oncology is moving across the board. We are refining the way we treat patients and approach different therapies being informed by not only the clinical information we have but also the biological information and drug response information, and [other details]. It is all in the view of getting the best therapies to patients that are going to have a benefit from it and finding better therapies for patients who are not predicted to benefit from those particular drugs.
Real-world analysis confirms enzalutamide efficacy in mCRPC

PSA declines, time to progression is similar in community practices, phase 3 trial

Enzalutamide (Xtandi®) showed comparable rates of prostate-specific antigen (PSA) decline and time to PSA progression in men with metastatic castration-resistant prostate cancer (mCRPC) treated in community practices compared with those in the phase 3 PREVAIL trial, according to data from a real-world analysis of the androgen receptor inhibitor.

The analysis, presented at the Genitourinary Cancers Symposium in San Francisco, included data for men treated with enzalutamide between September 2014 and February 2018, prior to the FDA approval of the agent for use in patients with nonmetastatic CRPC. Those who received prior chemotherapy and/or abiraterone acetate (Zytiga) were excluded from the analysis. Among 931 evaluable men, the majority were ≥60 years old (95%) and diabetic (17%).

The median follow-up period was 12.5 months, during which a median of 4 PSA tests were performed at a median interval of 2 months. PSA declines of ≥50% and ≥90% were reported in 78% and 47% of patients, respectively (N Engl J Med 2014; 371:424-433). The median time to PSA progression was 18.5 months (95% CI, 15.6-23.7).

In the PREVAIL trial, the median time until PSA progression with enzalutamide was 11.2 months, and a PSA decline of ≥50% and ≥90% was reported in 78% and 47% of patients, respectively (N Engl J Med 2014; 371:424-433). The median PSA at baseline was lower in the analysis, which was pretty encouraging. The median PSA decline was about 58% and about 14% of patients reached an undetectable PSA level.

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"What we saw in the clinical trial is, by and large, what we saw in the real-world [setting]."

STEPHEN J. FREEDLAND, MD

Q: Could you provide background on the real-world analysis of enzalutamide in patients with mCRPC?
A: We know from multiple phase III trials that enzalutamide is a novel therapy in prostate cancer, specifically in the metastatic castration-sensitive, nonmetastatic, and metastatic castration-resistant settings. We know from clinical trials that [enzalutamide] suppresses androgen signaling, [reduces] PSA, and slows tumor growth so that patients live longer.

How does enzalutamide work in the real world? The [clinical] trials [examining the use of the agent] are highly selective; they tend to accrue healthy patients who adhere to the medicine. These patients also get their blood tests on time. In the real world, do we see similar efficacy in terms of PSA control and time to progression? We extracted data on nearly 1000 men who had been treated with enzalutamide in urology practices.

Prior to its approval in the nonmetastatic CRPC setting, the only setting in which enzalutamide was approved for use during the time of our analysis was the mCRPC setting. We assumed patients who started on enzalutamide had mCRPC, although it’s hard to [know] that [for sure]. Then, we looked at patients’ PSA before starting enzalutamide, their characteristics, and their outcomes. We examined the [duration of] time patients stayed on treatment before their PSA started to rise, as well as their PSA decline. Compared with the phase 3 PREVAIL trial, [which evaluated enzalutamide in chemotherapy-naive patients], we saw relatively similar results, which was pretty encouraging. The median PSA decline was about 58% and about 14% of patients had an undetectable PSA level.

A subset of patients didn’t respond to the treatment at all, their PSA kept increasing. We know there can be inherent resistance to hormone therapy. The median time to progression in patients with a rising PSA was 18.5 months. The reduction in PSA levels was a little lower perhaps due to [issues with] drug compliance. Perhaps we didn’t check PSA levels as often, so we may not have captured the best PSA decline. The time to PSA rise was a little bit longer. We may not have captured PSA as closely [as in the trials], but by and large, the data are relatively similar to what we saw in the clinical trials. This gives us a lot of hope that patients can take these drugs and experience similar benefits to what we have seen in clinical trials.

Q: What steps can be taken to standardize when PSA testing is done in the real-world setting?
A: We have to ask how much that matters, and I don’t have an answer to that question. If I’m testing PSA every 3 months and someone else is testing PSA every 4 months, and I find out the patient’s PSA is rising 1 month before, does that make a difference? I don’t know. I see this all the time in my patients, where we test PSA and follow up in 6 months with another PSA test. Then, the patient comes back 2 years later. That’s more of a challenge versus whether we test every 3 or 4 months. In clinical trials, there needs to be established time points. In terms of standardization in clinical practice, it’s reasonable to test PSA every 3 or 4 months, or even every 6 weeks. It’s more of the patients who fall through the cracks who worry me.

Q: How do these findings compare with other real-world analyses with enzalutamide?
A: I believe the data are in line with other real-world evidence with enzalutamide. We didn’t see anything too surprising. It’s always a little bit nerve wracking when you look at real-world evidence. [However, the real-world analysis was comparable to what we saw in the clinical trials in terms of drug efficacy]. Enzalutamide is a potent drug and it works well.

Q: What is the key takeaway from this research?
A: We have data reassuring us that men who aren’t classical clinical trial candidates are going to benefit from enzalutamide. We see in the New England Journal Medicine papers, is, by and large, what we can expect to see in our patients.

Disclosure: The study was funded by Astellas and Pfizer. For full disclosures from Freedland and co-authors, see bit.ly/3aVcFfW.
Digital intervention helps improve fluid intake in patients with stones

Intervention aids majority of patients in achieving desired intake

Lisette Hilton

UT Correspondent

A Fitbit Versa watch-connected water bottle (H20Pal) and smartphone app monitors fluid intake for patients with kidney stones and reminds them when they need to drink more. Early research suggests the digital sip® intervention is feasible for increasing these patients’ notoriously low adherence with recommended fluid intake, according to a study presented at the World Congress of Endourology 2019 in Abu Dhabi.

Typically, less than 50% of patients with kidney stones will adhere to the recommended fluid intake to produce 2.5 liters of urine daily. Adherence also tends to be low when urologists recommend patients drink a lot of water to prevent stone recurrence, according to presenting author Necole M. Streeper, MD, a urologist and assistant professor of surgery at Penn State Health, Hershey, Pennsylvania.

“We live in a world in which there’s increasing use of technology to help us with different activities in our day-to-day lives, and the use of digital tools to improve health is becoming increasingly prevalent, so we developed sip® intervention to get our patients [with stones] to drink more fluids and to try and help them prevent their kidney stones,” Streeper said. “We need to be working on technology like this because it’s what patients want and has the potential to improve adherence.”

The sip® intervention uses a Fitbit Versa watch with an accelerometer to detect when users make a drinking motion. A connected water bottle also detects when users drink and keeps track of their fluid volume. The intervention was developed in collaboration with David Conroy, PhD, in the Department of Kinesiology at Penn State University and Edison Thomaz, PhD, in the Department of Electrical and Computer Engineering at The University of Texas at Austin.

“These 2 devices connect with an app that we developed to be able to monitor if patients are drinking fluids throughout the day,” Streeper said.

If the 2 different digital tools detect that users are not drinking enough, the app will send them a reminder that they need to be drinking.

“The app takes that information—pools it every so often—to be able to see if it detects it via the watch or the connected water bottle if patients are drinking,” Streeper said. “If they’re not drinking, they’re going to get a notification telling them to drink, which can be annoying to patients.

But the idea is to try to model their behavior to get them to drink so they’re not getting these messages.”

80% say intervention helps

Investigators enrolled 31 patients with kidney stones in the study. Patients installed the app on their smartphones, wore the Fitbit, and used the water bottle for 1 month. Twenty-seven patients completed the study.

“It was a feasibility trial to test how the system would work in a clinical setting. We also wanted to look at what patients perceived were their barriers to being able to increase fluids at baseline and if those changed after using the intervention,” Streeper said.

More than 80% of patients said they thought the intervention helped them achieve the desired fluid intake, and they’d recommend the sip® intervention to others with a history of kidney stones.

“[Results from] other studies have shown that 2 of the most common barriers that patients have is that they’re not thirsty or they forget to drink throughout the day. We found that using this intervention decreased those 2 common barriers,” she said.

According to Streeper, the sip® is not yet available for use in practice.

“We’re in the beginning stages of research. In the first several studies, we did focus groups to make sure that this would be something patients would even want and we used their input in the design of the technology. This is also our first clinical feasibility study. From here, we’re going to do longer duration and also look to see whether it actually improves urine output. Doing 24-hour urine monitoring is the next step,” Streeper said.

More than 80% of patients said the intervention helped them achieve the desired fluid intake.

CLINICAL UPDATES / Kidney Stones

Rolling submission of NDA complete for primary hyperoxaluria agent

Alnylam Pharmaceuticals, Inc announced the completion of the rolling submission of a New Drug Application to the FDA for lumasiran, an investigational RNAi therapeutic targeting glycolate oxidase, in development for the treatment of primary hyperoxaluria type 1 (PH1).

In the United States, lumasiran has previously received pediatric rare designation, orphan drug designation, and breakthrough therapy designation for the treatment of PH1, based on data showing a substantial reduction in urinary oxalate, the key toxic metabolite responsible for the clinical manifestations of the disease.

Topline data from the pivotal ILLUMINATE-A phase 3 study show that lumasiran met its primary efficacy end point and all tested secondary end points. Specifically, lumasiran met the primary efficacy endpoint of percent change from baseline, relative to placebo, in 24-hour urinary oxalate excretion averaged across months 3 to 6 (P value <.0001).

Epidemiologic data show a strong relationship between urinary oxalate reduction and long-term kidney function loss. The study also achieved statistically significant results for all six tested secondary end points (P value ≤.001), including the proportion of patients achieving a near-normalization or normalization of urinary oxalate, relative to placebo. Lumasiran demonstrated an encouraging safety and tolerability profile consistent with previous reports from earlier studies.

There were no serious or severe adverse events in the study, and results showed that lumasiran was generally well tolerated with an overall safety profile generally consistent with that observed in phase 1/2 and open-label extension studies of the agent. Full ILLUMINATE-A study results will be presented in 2020.
Ultrasound may help identify underlying cause of erectile dysfunction

Can help successfully diagnose three vascular-related causes of ED

**Whitney Palmer**
Senior Editor, Diagnostic Imaging®

Ultrasound of the penis can play a vital role in determining the underlying cause of erectile dysfunction (ED) in men who don’t respond to medication.

Although prescription drugs have significantly—and successfully—changed how providers treat erectile dysfunction (ED), for those men who don’t see improvement, relying on ultrasound can be the key to identifying next steps and possible treatments, according to an article published in the *American Journal of Roentgenology.*

“Penile Doppler sonography is an essential tool for differentiating between vascular and nonvascular causes of ED,” wrote the article’s authors, led by Cristian Gómez Varela, MD, from the radiology department in Complejo Hospitalario Universitario de Pontevedra in Spain.

When used correctly—with a high-frequency linear array (7.5-12 MHz) and full-length images of the penis in both flaccid and erect states—ultrasound can contribute to successfully diagnosing three vascular-related causes of ED, Varela said.

“Penile Doppler sonography is an essential tool for differentiating between vascular and nonvascular causes of ED.”

CRISTIAN GÓMEZ VARELA, MD, AND COLLEAGUES

**Peyronie’s disease:** The penile deformity caused by scar tissue that develops after repeated injury results in painful erections. In most cases, MRI is the preferred modality to assess Peyronie’s disease. However, gray-scale ultrasound can be very helpful in diagnosis and follow-up, assessing size and location of plaques, detecting small nonpalpable lesions or involvement of the penile septum, or evaluating disease progression. In addition, sonoelastography can estimate tissue stiffness, as well as identify plaques that go undetected on gray-scale ultrasound.

**Penile fracture:** Caused by trauma to the penis, usually during sexual intercourse, fracture can cause a rupture in the membrane responsible for trapping blood in the penis to sustain an erection. Ultrasound can make pinpointing any ruptures easier, as fractures are seen as dark breaches in the membrane.

**Priapism:** This condition can occur in two forms: high-flow and low-flow. Low-flow priapism is considered a medical emergency as it can cause tissue death and, if left untreated, permanent ED. Ultrasound can identify tissue thickening and scarring in the arteries of the penis, and Doppler ultrasound can also pinpoint inadequate blood retention.

Given its effectiveness in identifying these vascular-related conditions behind ED, according to Varela and colleagues, ultrasound is the preferred method for initially evaluating the penile anatomy and blood flow. Not only is it readily available, but it is minimally invasive and can be well tolerated by patients, they wrote.

REFERENCE


**MEN WITH ED MAY FACE HIGHER MORTALITY RISK**

Men with erectile dysfunction have a higher risk of death, regardless of their testosterone levels, suggest results from a study by Belgian researchers.

“As both vascular disease and low testosterone levels can influence erectile function, sexual symptoms can be an early sign for increased cardiovascular risk and mortality,” said lead researcher Leen Antonio, MD, PhD, of KU Leuven-University Hospitals in Belgium.

The study was accepted for presentation at ENDO 2020, the Endocrine Society’s annual meeting (subsequently relaunched as ENDO Online 2020, a virtual meeting).

Low testosterone levels have been linked to a higher risk of death in middle-aged and older men, but results from large studies are inconsistent, Antonio said. Study results have also linked sexual dysfunction with mortality in older men.

The new study used data from the European Male Ageing Study, a large observational study designed to investigate age-related hormonal changes and a broad range of health outcomes in elderly men. The investigators analyzed data from 1913 participants in 5 medical centers. They analyzed the relationship between their hormone measurements and sexual function at the beginning of the study and whether they were still alive more than 12 years later.

During the average follow-up period of 12.4 years, 483 men—25%—died. In men with normal total testosterone levels, the presence of sexual symptoms, particularly erectile dysfunction, increased the risk of death by 51% compared with men without these symptoms.

Men with low total testosterone levels and sexual symptoms had a higher risk of death than men with normal testosterone levels and no sexual symptoms.

Men with erectile dysfunction, poor morning erections, and low libido had a higher mortality risk than men with no sexual symptoms. In men with these 3 sexual symptoms, the risk of dying was almost 1.8 times higher compared to men without symptoms. In men with erectile dysfunction alone, the risk of dying was 1.4 times higher compared with men without erectile dysfunction.

Levels of free testosterone were lower in those who died. Men who had the lowest levels of free testosterone had a higher risk of death than men who had the highest levels.

**PAIN-FREE SOLUTION FOR MALE URINARY INCONTINENCE LAUNCHED**

Pacey MedTech Ltd. has launched the Pacey Cuff Power Sleeve, a protective sleeve to be worn between the skin and the Pacey Cuff urinary control device (UCD) to increase the overall comfort of the Pacey Cuff. The company said the Pacey Cuff reduces or eliminates male urinary incontinence by compressing the urethra and blocking unwanted urine flow while still protecting the blood circulation in the topside of the penis to eliminate possible blood supply restriction pain and damage to the penis.

The Pacey Cuff Power Sleeve is made from a durable, thin neoprene fabric and when worn under the Pacey Cuff ensures a pain-free and odor-free solution to men living with urinary incontinence, allowing them to comfortably and discreetly wear the Pacey Cuff all day and engage in their regular daily activities, Pacey MedTech said in a statement.
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MOSES-enabled pulsed laser allows same-day discharge without catheter

Investigator says benefits justify its consideration as gold standard for BPH-related LUTS

Cheryl Guttman Krader, BS Pharm
UT Contributing Editor

The benefits of holmium laser enucleation of the prostate with MOSES-enabled pulsed laser modulation justify its consideration as the gold standard surgical treatment for lower urinary tract symptoms related to benign prostatic hyperplasia (BPH), according to Amy E. Krambeck, MD.

Krambeck said that after learning holmium laser enucleation of the prostate (HoLEP) in 2008 during her endourology fellowship training, she relied on it exclusively for surgical treatment of BPH after joining the urology department at Mayo Clinic in Rochester, Minnesota, in 2009. In late 2018, Krambeck had the opportunity to trial HoLEP with the MOSES laser platform. She told Urology Times® that she was immediately impressed by its better hemostasis during the enucleation phase, which translated into enhanced visualization, decreased operative time, and reduced postoperative patient care.

“So I was impressed by it immediately. I started using it in parallel with HoLEP, and I found that I started doing it exclusively,” Krambeck said.

“Compared with other surgical techniques for symptomatic BPH, HoLEP was associated with less bleeding, shorter catheter times, decreased operative time, and reduced postoperative patient care. Because it has better hemostasis, MoLEP eliminates the need for overnight bladder irrigation and for checking lab values the next day,” Krambeck observed.

After just 10 cases, Krambeck adopted MOSES laser enucleation of the prostate (MoLEP) as her sole technique for surgical BPH treatment. Based on outcomes observed during accumulating experience, Krambeck and her 2 partners are now performing MoLEP as an outpatient procedure, and they are even discharging patients home without a catheter if they are operated on early in the day.

“Because it has better hemostasis, MoLEP eliminates the need for overnight bladder irrigation and for checking lab values the next day.”

AMY E. KRAMBECK, MD

Although MoLEP involves introducing slightly larger instruments into the bladder and adding more steps, Krambeck said that the procedure is still relatively quick with significantly faster patient recovery. According to Krambeck, patients are sent home the same day.

“Because it is relatively new, and I am not aware of reports about its outcomes from any other centers. The best way to assess new technology outcomes is to assess experience and outcomes at multiple institutions. I encourage others performing the MoLEP procedure to analyze their own results,” she said.

Krambeck is a clinical consultant for Boston Scientific and Lumenis. She is also the chair of the Data Safety Monitoring Board for Sonomotion.

Same-day catheter removal for the first 2 cases of the day was implemented in December 2019 and has been successful in about 90% of attempts. Men operated on later in the day go home with their catheter. Depending on their circumstances, men may be allowed to remove the catheter at home the next day, and if they reported they are doing well during a telephone follow-up, they are next seen 3 months later.

Some men will experience burning when they urinate, but it is easily managed with an anti-inflammatory medication and only affects about 5% of patients, she said.

Krambeck and colleagues had planned to present their experience with outpatient MoLEP at the now-cancelled AUA annual meeting as well as the World Congress of Endourology. They are writing up the manuscript for a paper that reviews outcomes from 112 MoLEP patients compared to standard HoLEP that will be submitted to the Journal of Endourology.

“MoLEP is relatively new, and I am not aware of reports about its outcomes from any other centers. The best way to assess new technology outcomes is to assess experience and outcomes at multiple institutions. I encourage others performing the MoLEP procedure to analyze their own results,” she said.

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FDA GRANTS DE NOVO CLASSIFICATION FOR BENIGN HYPERSTATIC HYPERPLASIA DEVICE

Olympus announced the FDA de Novo classification of the iTind device, a nonsurgical device for the minimally invasive treatment of benign prostatic hyperplasia (BPH).

The iTind device was developed by the Israeli-based medical device manufacturer Medi-Tate. Through an investment in Medi-Tate, Olympus holds the exclusive right to distribute Medi-Tate products, including the iTind device, in the United States.

Treatment with the iTind device is straightforward and avoids complications associated with prescription medications, surgery, or permanent implants, according to Olympus. The flexible 3-strut nitinol device, which can be placed during an in-office procedure, gently expands over 5 days to create channels that allow urine to flow and reshape the prostate, the company said.

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“Most patients tell me that they are next seen 3 months later.

“Most patients tell me that they had no pain at all postoperatively.

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Krambeck and colleagues had planned to present their experience with outpatient MoLEP at the now-cancelled AUA annual meeting as well as the World Congress of Endourology. They are writing up the manuscript for a paper that reviews outcomes from 112 MoLEP patients compared to standard HoLEP that will be submitted to the Journal of Endourology.

“MoLEP is relatively new, and I am not aware of reports about its outcomes from any other centers. The best way to assess new technology outcomes is to assess experience and outcomes at multiple institutions. I encourage others performing the MoLEP procedure to analyze their own results,” she said.

Krambeck is a clinical consultant for Boston Scientific and Lumenis. She is also the chair of the Data Safety Monitoring Board for Sonomotion.

READER RespondS TO BPH GUIDELINES ARTICLE

The March 2020 issue of Urology Times® featured an article discussing updated AUA guidelines on BPH (“Updated AUA BPH guidelines: What you need to know about pre-procedure evaluation, novel surgical enhancements,” page 1) and a related From the Board article (“Alternatives to TURP: Consider these variables,” page 5). A Urology Times® reader, Gregg Eure, MD, responded to both articles with a letter to the editor, for which space was not available in this issue. For the full text of the letter, visit urologytimes.com/bphletter.
INDICATION
ERLEADA® (apalutamide) is an androgen receptor inhibitor indicated for the treatment of patients with:
- Metastatic castration-sensitive prostate cancer (mCSPC)
- Non-metastatic castration-resistant prostate cancer (nmCRPC)

IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS
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) of patients with mCSPC, ischemic cardiovascular events occurred in 4% of patients treated with ERLEADA® and 2% of patients treated with placebo. Across the SPARTAN and TITAN studies, 6 patients (0.5%) treated with ERLEADA® and 2 patients (0.2%) treated with placebo died from an ischemic cardiovascular event. Patients with current evidence of unstable angina, myocardial infarction, or congestive heart failure within 6 months of randomization were excluded from the SPARTAN and TITAN studies.

Ischemic cardiovascular events, including events leading to death, occurred in patients receiving ERLEADA®. Monitor for signs and symptoms of ischemic heart disease. 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 nmCRPC, fractures occurred in 9% 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 full risk.

Seizure—In 2 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 females with male 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 (TITAN and SPARTAN) were fatigue, anorexia, rash, decreased appetite, fall, weight decreased, hypotension, 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 SPARTAN study; anemia ERLEADA® 20% (0.4%), placebo 16% (0.5%), leukopenia ERLEADA® 47% (0.3%), placebo 29% (0.6%), lymphopenia ERLEADA® 41% (2%), placebo 21% (2%).

- Chemistry—In the TITAN study; hyperglycemia ERLEADA® 19% (1%), placebo 12% (0.6%). In the SPARTAN study; hypercalcemia ERLEADA® 70% (0.1%), placebo 46% (0.6%), hyperkalemia ERLEADA® 70% (0.2%), placebo 59% (0.2%), hyperuricemia ERLEADA® 67% (2%), placebo 49% (0.8%), hypercholesterolemia ERLEADA® 32% (2%), placebo 22% (0.5%).

- Rash—In 2 randomized studies, 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%).

- Hypothyroidism—In 2 randomized studies, hypothyroidism was reported in 1% 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 moieties. No initial dose adjustment is necessary; however, reduce the ERLEADA® dose based on tolerability [see Dosage and Administration (2.2)].

Effect of ERLEADA® on Other Drugs—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 CYP2C33 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.

- P-gp, BCRP, or OATP1B1 Substrates—Apalutamide is a weak inducer of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptide 1B1 (OATP1B1) clinically. Concomitant use of ERLEADA® with medications that are substrates of P-gp, BCRP, or OATP1B1 must be co-administered with ERLEADA® and evaluate for loss of activity if medication is continued.

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


Janssen Biotech, Inc. © Janssen Biotech, Inc. 2020 02/20 cp-94389v2
ERLEADA® (apalutamide) tablets

adverse reactions occurred in 26% 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>Laboratory Abnormality</th>
<th>ERLEADA</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>398</td>
<td>398</td>
</tr>
<tr>
<td>Grade 3</td>
<td>121</td>
<td>59</td>
</tr>
<tr>
<td>Grade 4</td>
<td>68</td>
<td>26</td>
</tr>
</tbody>
</table>

Table 2: Laboratory Abnormalities Occurring in ≥5% of ERLEADA-Treated Patients and at a Greater Frequency Than Placebo (Between Arm Difference ≥5% All Grades) in TITAN (mCSPC)

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>All Grades</td>
<td>398</td>
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</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>17</td>
<td>3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>Hot flush</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10</td>
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</tr>
</tbody>
</table>

Fractures

Fractures occurred in patients receiving ERLEADA. Evaluate patients for fracture risk. Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone-targeted therapies.

In a randomized study (SPARTAN) of patients with non-metastatic castration-sensitive prostate cancer, fractures occurred in 12% of patients treated with ERLEADA and 7% of patients treated with placebo. Grade 3-4 fractures occurred in 3% of patients treated with ERLEADA and 2% of patients treated with placebo. Across the SPARTAN and TITAN studies, 6% (0.5%) treated with ERLEADA and 2% (0.2%) treated with placebo died from an ischemic cardiovascular event. Patients with a history of ischemic heart disease, including those with prior myocardial infarction or congestive heart failure within six months of randomization were excluded from the SPARTAN and TITAN studies.

ERLEADA is indicated for the treatment of patients with:

- Metastatic Castration-sensitive Prostate Cancer (mCSPC)
- Metastatic Castration-resistant Prostate Cancer (mCRPC)

Additional clinically significant adverse reactions occurring in 2% or more of patients treated with ERLEADA included hypothyroidism (8% with current use of medication) and heart failure (2.2% versus 1% on placebo).

Table 3: Adverse Reactions in mCSPC

<table>
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Additional clinically significant adverse reactions occurring in 2% or more of patients treated with ERLEADA included hypothyroidism (8% with current use of medication) and heart failure (2.2% versus 1% on placebo).

In the combined data of two randomized, placebo-controlled clinical studies, rash associated with ERLEADA was most commonly described as macular or maculopapular. Adverse reactions of rash were more frequent in 28% of patients treated with ERLEADA and 8% of patients treated with placebo. Grade 3 rashes (defined as covering >30% body surface area) were reported with ERLEADA (8% versus placebo 0.5%). The onset of rash occurred at a median of 83 days of ERLEADA treatment. Rash commonly started on day 21 of treatment. In 78% of patients treated with ERLEADA, rash was managed with oral antihistamines, topical corticosteroids, and 19% of patients received systemic corticosteroids. Dose reduction or dose interruption occurred in 14% and 26% of patients, respectively. Of the patients who had dose interruption, 39% experienced recurrence of rash upon reintroduction of ERLEADA.

Rash

In the combined data of two randomized, placebo-controlled clinical studies, rash associated with ERLEADA was most commonly described as macular or maculopapular. Adverse reactions of rash were more frequent in 28% of patients treated with ERLEADA and 8% of patients treated with placebo. Grade 3 rashes (defined as covering >30% body surface area) were reported with ERLEADA (8% versus placebo 0.5%). The onset of rash occurred at a median of 83 days of ERLEADA treatment. Rash commonly started on day 21 of treatment. In 78% of patients treated with ERLEADA, rash was managed with oral antihistamines, topical corticosteroids, and 19% of patients received systemic corticosteroids. Dose reduction or dose interruption occurred in 14% and 26% of patients, respectively. Of the patients who had dose interruption, 39% experienced recurrence of rash upon reintroduction of ERLEADA.

Table 4: Laboratory Abnormalities Occurring in ≥5% of TITAN-Treated Patients and at a Higher Frequency Than Placebo (Between Arm Difference ≥5% All Grades) in SPARTAN (mCSPC)

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ERLEADA is a weak inducer of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP) and organic anion transporters (OATP1B1). ERLEADA is a weak inhibitor of CYP3A4, and weak transporter of ABCB1 (P-gp), ABCC2 (MRP2), and ABCC11 (BCRP). Concomitant use of ERLEADA with medications that are primarily metabolized by CYP3A4 or P-gp is expected to result in lower exposure to these medications. Substitution for these medications is recommended when possible. Dose adjustment for loss of activity if medication is continued. Concomitant administration of ERLEADA with medications that are substrates of UDP-glucuronosyl transferase (UGT) can result in decreased exposure. Use caution if substrate of UGT must be co-administered with ERLEADA and evaluate for loss of activity (see Clinical Pharmacology (12.3) in full Prescribing Information).

P-gp, BCRP or OATP1B1 Substrates

Table 5: Adverse Reactions in mCSPC

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In the combined data of two randomized, placebo-controlled clinical studies, rash associated with ERLEADA was most commonly described as macular or maculopapular. Adverse reactions of rash were more frequent in 28% of patients treated with ERLEADA and 8% of patients treated with placebo. Grade 3 rashes (defined as covering >30% body surface area) were reported with ERLEADA (8% versus placebo 0.5%). The onset of rash occurred at a median of 83 days of ERLEADA treatment. Rash commonly started on day 21 of treatment. In 78% of patients treated with ERLEADA, rash was managed with oral antihistamines, topical corticosteroids, and 19% of patients received systemic corticosteroids. Dose reduction or dose interruption occurred in 14% and 26% of patients, respectively. Of the patients who had dose interruption, 39% experienced recurrence of rash upon reintroduction of ERLEADA.

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</table>
USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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 [see Clinical Pharmacology (12.1) in full Prescribing Information]. There are no human data on the use of ERLEADA in pregnant women. ERLEADA is not indicated for use in females, so animal embryo-fetal developmental toxicity studies were not conducted with apalutamide.

Lactation

Risk Summary

The safety and efficacy of ERLEADA have not been established in females. There are no data on the presence of apalutamide or its metabolites in human milk, the effect on the breastfed child, or the effect on milk production.

Females and Males of Reproductive Potential

Contraception

Males

Based on the mechanism of action and findings in an animal reproduction study, advise male patients 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].

Infertility

Males

Based on animal studies, ERLEADA may impair fertility in males of reproductive potential [see Nonclinical Toxicology (13.1) in full Prescribing Information].

Pediatric Use

Safety and effectiveness of ERLEADA in pediatric patients have not been established.

Geriatric Use

Of the 1327 patients who received ERLEADA in clinical studies, 19% of patients were less than 65 years, 41% of patients were 65 years to 74 years, and 40% were 75 years and over. No overall differences in effectiveness were observed between older and younger patients. Of patients treated with ERLEADA (n=1073), Grade 3-4 adverse reactions occurred in 39% of patients younger than 65 years, 41% of patients 65-74 years, and 49% of patients 75 years or older.

OVERDOSAGE

There is no known specific antidote for apalutamide overdose. In the event of an overdose, stop ERLEADA, undertake general supportive measures until clinical toxicity has been diminished or resolved.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Ischemic Cardiovascular Events

- Inform patients that ERLEADA has been associated with ischemic cardiovascular events. Advise patients to seek immediate medical attention if any symptoms suggestive of a cardiovascular event occur [see Warnings and Precautions].

Falls and Fractures

- Inform patients that ERLEADA is associated with an increased incidence of falls and fractures [see Warnings and Precautions].

Seizures

- Inform patients that ERLEADA has been associated with an increased risk of seizure. Discuss conditions that may predispose to seizures and medications that may lower the seizure threshold. Advise patients of the risk of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others. Inform patients to contact their healthcare provider right away if they experience a seizure [see Warnings and Precautions].

Rash

- Inform patients that ERLEADA is associated with rashes and to inform their healthcare provider if they develop a rash [see Adverse Reactions].

Dosage and Administration

- Inform patients receiving concomitant gonadotropin-releasing hormone (GnRH) analog therapy that they need to maintain this treatment during the course of treatment with ERLEADA.
- Inform patients to take their dose at the same time each day (once daily). ERLEADA can be taken with or without food. Each tablet should be swallowed whole.
- Inform patients that in the event of a missed daily dose of ERLEADA, they should take their normal dose as soon as possible on the same day with a return to the normal schedule on the following day. The patient should not take extra tablets to make up the missed dose [see Dosage and Administration (2.1) in full Prescribing Information].

Embryo-Fetal Toxicity

- Inform patients that ERLEADA can be harmful to a developing fetus. Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of ERLEADA. Advise male patients to use a condom if having sex with a pregnant woman [see Warnings and Precautions].

Infertility

- Advise male patients that ERLEADA may impair fertility and not to donate sperm during therapy and for 3 months following the last dose of ERLEADA [see Use in Specific Populations].

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Gurabo, PR 00778

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Study adds to evidence linking anticholinergics and dementia

Dementia more prevalent in patients taking anticholinergic vs beta-3 agonist, data indicate

Cheryl Guttmann Krader, BS Pharm  
UT Contributing Editor

Patients using anticholinergic medications for the management of overactive bladder (OAB) are at increased risk of new-onset dementia compared with individuals treated with the beta-3 agonist mirabegron (Myrbetriq), according to findings of a new population-based, retrospective study published online March 13, 2020, in BJU International.

The research, which was conducted by Blayne Welk, MD, MSc, and Eric McArthur, MSc, both of Western University in London, Ontario, Canada, compared matched cohorts of patients who were newly prescribed an anticholinergic agent or mirabegron for OAB. By Cox proportional-hazards modeling, the investigators found a statistically significant, 1.23-fold increased risk of new-onset dementia in the anticholinergic-treated group. The difference in the event rate between the 2 groups was 1 case per 137 person-years.

Welk, an associate professor of surgery (urology) at Western University, told Urology Times®, “The increase in the absolute risk of dementia associated with the anticholinergic agents appears small. Nevertheless, it may be a consideration when selecting medications for treating OAB, particularly in patients concerned about cognitive changes.”

Welk observed that previous studies have raised concern about an association between anticholinergic medication use and dementia. Protopathic bias, however, may be a limitation of those studies because their methods do not rule out that patients were using anticholinergic agents to manage urinary symptoms that were prodromal of dementia.

“Well, our study is unique because it specifically looks at anticholinergic medications that are commonly used by urologists to treat OAB, and we believe it is the first to study the risk of dementia with anticholinergic medications by using a comparator group treated with a nonanticholinergic medication,” Welk said.

Patients included in the study were identified via linked administrative databases that were searched for new users of an anticholinergic agent or mirabegron to treat OAB. A propensity score was created to match the anticholinergic and mirabegron users, taking into account 75 baseline characteristics, which included demographic features, medical comorbidities, other medications, and prior health care utilization.

“We believe it is the first to study the risk of dementia with anticholinergic medications by using a comparator group treated with a nonanticholinergic medication.”

BLAYNE WELK, MD, MSc

A total of 47,324 patients prescribed oxybutynin ( Ditropan), tolerodine (Detrol), solifenacin (VESIcare), darifenacin (Enablex), fesoterodine (Toviaz), or trospium (Sanctura) for OAB were matched to 23,662 new users of mirabegron. The patients in each group had a mean age of 73 years and included a slight predominance of women (55.5%). The median prescription duration was twice as long for the anticholinergics compared with mirabegron, 30 vs 60 days.

New-onset dementia, which was identified using a validated administrative data definition, occurred among 3.3% of anticholinergic users during 38,069 patient-years of follow-up and 2.6% of mirabegron users during 17,755 patient-years of follow-up. The new-onset dementia event rate was 41.3/1000 person-years in the anticholinergic group and 34.0/1000 person-years among the mirabegron users.

Dementia risk is similar among anticholinergics

Tolerodine, including both immediate-release and long-acting formulations, was the most commonly used anticholinergic agent (40%) followed by oxybutynin (29%) and solifenacin (26%). In an exploratory analysis, the risk of dementia did not vary between the different anticholinergics.

“Some previous studies suggest that oxybutynin in particular causes cognitive impairment, but we did not find that association,” Welk said.

Additional analyses compared rates of new-onset dementia between anticholinergic and mirabegron users with patients categorized into subgroups according to various demographic and clinical characteristics. The results showed that the risk of dementia development with anticholinergic treatment was highest among men and in patients aged 75 years or younger.

“These findings of significant effect modification are novel and should be investigated further in the OAB population,” Welk said.

NEXT-GEN NEUROSTIMULATOR EARNS FDA APPROVAL

The FDA has approved Axonics Modulation Technologies, Inc’s next-generation rechargeable implantable neurostimulator (INS) for its r-SNM System under a premarket approval (PMA) supplement.

The next-generation INS decreases how frequently patients need to recharge their implanted device to once a month for about 1 hour, Axonics said. This compares with the current recharging interval, which is 1 hour every 2 weeks.

According to the company, this new feature will also give patients the option to customize their charging experience, for example, choosing to charge for only 15 minutes once a week or only 1 hour every 2 months for those patients at lower stimulation intensity levels. In addition, the enhanced INS will experience no battery degradation over the 15-plus-year life of the INS due to the reduced charging burden.

The FDA approved the rechargeable Axonics r-SNM System for the treatment of urinary retention and symptoms of overactive bladder in late 2019. The next-generation Axonics INS is expected to begin shipping to US customers during the third quarter of 2020.

Separately, Axonics has submitted a PMA supplement to the FDA for the purpose of gaining full-body magnetic resonance imaging (MRI) conditional labeling for 3.0T MRI scans. In September 2019, the FDA approved the Axonics r-SNM System with full-body conditional labeling for 1.5T MR scanners. Axonics said it has since performed the required tests to support a PMA supplement for full-body conditional labeling on 3.0T MR scanners for the implantable components of its r-SNM System.
How has FDA’s mesh guidance affected POP treatment?

“Those products off the market. There are issues do well, but it’s more invasive.”

PANKAJ JAIN, MD, MBA

“I don’t do as much vaginally as I used to. For severe prolapse, I do robotic sacrocolpopexies using the mesh that’s still available, and patients do well, but it’s more invasive.”

Pankaj Jain, MD, MBA / Phoenix, Arizona

“I’m fortunate. I trained more recently and do a lot of robotic surgery. From that sense, it hasn’t changed things for me except reinforce my training in a better surgery. I wasn’t doing much transvaginal mesh anyway, because the writing was on the wall. Plus, results weren’t as good. I’m in a big group, and it seems to have affected older surgeons more than me.

It’s a more fellowship-driven field now. Instead of doing certain vaginal surgeries or one specific aspect of the surgery well, now you have to address it in a variety of ways.

From that standpoint, fewer urologists are willing to operate in that space. A number of my older partners trained at Mayo Clinic and used a lot of Xenform. Technically, it’s not “synthetic mesh” but was included in the FDA warning. A lot of my partners have completely stopped doing that surgery. That makes somebody like me busier.

When it initially happened, there were a lot of questions. People wanted things removed that were done 10 years earlier that weren’t hurting them. They wanted the mesh removed because of the warnings. But that’s kind of slacked off. Transvaginal mesh came in kits; doctors trained in weekend courses. Mesh kits weren’t terrible if the patient was chosen correctly and doctors knew what they were doing. But there was a mixture of doctors who didn’t do many procedures and on people who shouldn’t have had that particular surgery. ‘That’s probably where we got ourselves in trouble.’

Sam Kuykendall, MD / Kansas City, Missouri

ADVERTISERS INDEX

Companies featured in this issue

To obtain additional information about products advertised in this issue, use the contact information below. This index is provided as an additional service. The publisher does not assume any liability for errors or omissions.

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COVID-19 continued from page 1

continues to spread across continents, infecting over 3 million people worldwide and causing over 230,000 deaths.1 Many US states have mandated shelter-in-place policies, as outbreaks cluster in multiple regions across the country. Although the mandates vary from state to state, most urology offices have temporarily closed their doors and the rest have limited surgery to only the most urgent cases. This has left numbers of patients seeking assistance, and a backlog of elective procedures.

Additionally, what seems to be lost amid the rationing of services is the mental anguish of patients with cancer diagnoses and other health issues that is amplified by the isolation and loss of social support that may have made things easier to cope with. Patients have been forced to stay home, stuck with any health issues they have, which are deemed not important enough to be dealt with during the lockdown. They are, according to the headline of a recent New York Times article, “The Pandemic’s Hidden Victims: Sick or Dying, but Not From the Virus.”

The first question is, when can we begin to ramp up? This will be determined by a combination of factors including, but not limited to, local, state, and federal guidelines as well as patient confidence. An Ipsos/ABC News poll released April 3 demonstrated wide variability when people were asked when they thought they would resume their normal daily routine. Among those who say their daily routine has changed due to coronavirus, 31% believe a return to normalcy will occur by June 1. One month previously, 44% thought June 1 was the target date.2 This suggests that a slowly rebounding private sector with variable confidence will be a major constraint to reopening medical practices.

Industries and financial institutions have recognized that there will be a gradual rather than a dramatic ramp-up of elective procedures recommencing in the United States. A recent Wells Fargo MedTech forecast stated that recovery of elective procedures will be “U-shaped” (gradual) versus “V-shaped” (quick), that hospitals will prioritize more urgent and life-threatening procedures, such as those for patients with cancer, over elective procedures, and that patients will prefer ambulatory surgery centers or office-based surgery over hospital surgery, due to the perceived risk of contracting COVID-19.3

There will be many hospital obstacles to restarting urologic procedures, including anesthesia (with its attendant precautions and pre-testing for COVID-19), a backlog of cases; the reconfiguration of operating rooms that were modified to become intensive care units; and employee constraints secondary to furloughs and layoffs. Further obstacles include vendor supply chain constraints, regulatory factors, and the potential for an event heretofore ill-prepared for—a second outbreak in the fall.

On top of all these challenges, another one is becoming a major area of concern: the posttraumatic effects of the pandemic on our health care colleagues.

On top of all these challenges, another one is becoming a major area of concern: the posttraumatic effects of the pandemic on our health care colleagues.

The second question is how we will get things moving again. Urologic offices have become very aware of methods designed to safely treat patients while protecting clinical staff. In part, these recommendations have been formulated in partnership with the Centers for Disease Control and Prevention (CDC). Naturally, they are subject to change given the rapidly evolving environment surrounding COVID-19, including diagnostics, screening, and therapeutics, among others.

The following are some recommendations for the screening and treatment of patients with suspected COVID-19 in our practice:

• Follow the CDC’s patient assessment protocol for early disease detection for patients presenting to the practice. Patients should be screened using the Criteria to Guide Evaluation and Laboratory Testing for COVID-19.6

Essential visitors to the facility should also be assessed using these criteria and redirected to remain outside if there are any concerns.

• As part of the return to urologic practice, we expect to continue with telemedicine consulting to some degree. We should anticipate an extension of office hours, weekday and weekend, to ensure a minimum number of patients in the waiting room at any one time. Further, we will require temperature checks and COVID-19 questionnaires for each person to protect both patients and staff.

Current issues and guidelines to consider and keep in mind include the following:

• Most at risk are older patients, those with comorbidities, and younger patients with obesity.

• The virus is highly infectious in close quarters.

• Asymptomatic transmission can occur.

• The virus can remain on surfaces for up to 48 hours.

ACUTE-CARE UROLOGY DURING THE PANDEMIC: LESSONS LEARNED

The worldwide spread of the novel coronavirus SARS-CoV-2 and its constellation of COVID-19 disease manifestations has dramatically disrupted normal life and has altered many aspects of medical practice. Specialty physicians in disease “hot spots,” including many urologists, have nobly performed outside of their normal scopes of practice to support our health systems’ efforts to treat the massive influx of patients with COVID-19.

As urologists at 2 large New York City academic medical centers with associated public city hospitals, Alexander Small, MD, and Rich Matulewicz, MD were responsible for on-call urology coverage during several weeks and stages of the COVID-19 pandemic. Others have described their experiences as off-service frontline physicians and highlighted the changes to outpatient urology care, including the rapid adoption of telemedicine. In a narrative on UrologyTimes.com, Small and Matulewicz share lessons learned during their on-call urology coverage in the midst of the current pandemic in an effort to help others by informing planning.

For this article and others covering the COVID-19 pandemic and its impact on urology, see urology-times.com/coronavirus. Other articles available from this page include the following:

• How relaxing of Medicare rules has affected telemedicine adoption

• State teledicine rules relaxed during crisis

• Pandemic brings new challenges, opportunities—and resilience

• Urology APPs: Making an impact during the COVID-19 pandemic

• What has been the pandemic’s main effect on your practice?

• New York urologist: At the epicenter, optimism reigns

• Leadership tips for your urology unit during the COVID-19 crisis

• ABD makes changes to reduce burden during pandemic

• How “elective” surgery is defined during the crisis.
Symptomatic patients carry the highest viral load for transmission.
Current prophylactic measures that may become permanent include the following:
1. Physical distancing with a recommended perimeter of 6 feet
   To maintain physical distancing within the facility, require patients to sit at least 6 feet or more apart. Patients should be asked to wait in their car if that option is available. Remove magazines. Routinely disinfect the waiting room throughout the day.
2. Use of masks and gloves
   - Follow the CDC's standard precautions and transmission-based precautions, including the use of gloves, gowns, protective eyewear, and NIOSH-certified N95 respirators that have been properly fit tested. This applies to all health care staff interacting with a person under investigation (PUI). If there is a shortage of N95 respirators in the facility, access current CDC respirator recommendations.
3. Frequent disinfection of public and shared spaces and equipment
4. Quarantining of patients who are symptomatic and possibly of those who are asymptomatic carriers
5. Use of COVID-19 screening for active viral infection and for determining immunity
   - Screen may emerge from detection of antigen to assessment of the presence of antibodies
   - Consider the likelihood that presence of antibodies may cause a stop-and-go working situation for health care providers and patients reentering work or office environments
6. Recognizing that health care workers can often be the nidus of transmissions
   - Limit staff exposure to suspected patients, and keep the exam room door closed. Ideally, the designated exam room should be at the back of the office, far away from other staff and patients.
   - Screen health care personnel daily for symptoms, travel, and contacts that may be relevant to COVID-19.
   - Adapting a clinical suspicion of COVID-19 to protect patients and others. The dynamics surrounding the virus will continue to change in the days and weeks ahead. What must not change are physicians’ and care teams’ vigilance and caution. They should be exceptionally proactive in asking the right questions, documenting interactions, rigorously following protocols, and keeping abreast of emerging insights and data on the CDC makes them available.

Opportunities lie ahead
Our biggest challenge is to ensure everyone’s safety. Until we have reliable point-of-care antibody testing, we will need to proceed slowly. In the interim, there has been a tremendous explosion in telemedicine that has accelerated the virtual interaction between health care providers and patients. Among the available options are Epic’s MyChart video visits (which has had bandwidth and sign-on issues), Zoom’s waiting rooms, virtual physical therapy.
- Other modalities such as Uberdoc provide a more seamless method for connecting patients to physicians with a more efficient initial reimbursement. Remote diagnostics will also become a great source of information and revenue. For example, Stream Dx allows the remote evaluation of urinary flow rates. Other companies are working on the remote measurement of post-void residual urine volumes.
- Using smartphones to measure heart rate, EKG rhythms, serum oxygen saturation, and serum glucose is already underway, with applications to test other blood parameters on the horizon. This will eventually result in decreased physical office visits as well as emergency department consultations.

Finally, this pandemic will create a new paradigm of how we provide and are compensated for the delivery of more efficient health care. Resource utilization and cost-effective care will become more valuable, and those who operate more efficiently will be better placed than those who simply do more, in terms of quality versus quantity-based reimbursement.

Another potential positive outcome could be how we will do business, a rethinking of revenue: for example, expense models that seem antiquated and deleterious compared with a more thoughtful group approach.
Four lessons urology practices can learn from the COVID-19 pandemic

Replacing office visits with virtual visits may become the new normal

I n a previous column, “Disaster preparation: Make sure your practice is ready” (December 2018, P. 37), I wrote: “Natural disasters serve as a reminder that most urology practices are small businesses and should have a basic plan in place for dealing with events that cause the temporary or permanent closure of the office. Your plan should address the needs of patients, staff, providers, and the business. Benjamin Franklin said, ‘By failing to prepare, you are preparing to fail.’ While the chances are small you will face a natural disaster, preparation is your best defense.”

Of course, I had no idea that 1 year later we would face a global pandemic that, as I write this article, has disproportionately affected the United States and has claimed some 25,000 US lives as of mid-April. No medical practice could have anticipated the scale of this disruption, and it is likely that many small businesses will not survive. It is widely believed an economic recession awaits those businesses that do survive the next few months.

In this article, I will offer a possible vision of what urology practice could look like in the near and intermediate future, and why. I will also share several lessons for urology practices that have come out of the present situation.

The urology office of the future may be primarily designed, built, and operated for the procedural aspects of care, resembling an ambulatory surgery center more than a traditional office.

Cancelation, postponement of elective procedures
In early March 2020, the US Centers for Disease Control and Prevention, many specialty societies, and many state governors called for canceling or postponing elective procedures, surgeries, and nonurgent outpatient visits. The initial rationale for these recommendations was to preserve valuable resources, but as the coronavirus disease 2019 (COVID-19) spread through communities, the broader concern focused on not exposing people to each other and “flattening the curve” of patients requiring those precious resources.

Niche urology practices that have focused primarily or entirely on elective care (vasectomy, erectile dysfunction, uncomplicated benign prostatic hyperplasia) will be significantly impacted. Other practices that have not pursued an intentional strategy may have never understood until recently exactly how much of their practice involved elective, nonurgent care.

While the definition of elective is obvious in some cases, there has been considerable debate as to what other procedures or visits can be postponed without jeopardizing the health of the patient. Prostatectomy for intermediate-risk prostate cancer? A routine visit for active surveillance? A visit for a patient on intermittent androgen deprivation therapy?

We don’t know the answers to these questions because, generally, these types of procedures are scheduled according to personal habits or loose guidelines, not a firm knowledge of the impact of delay. The first major lesson of this crisis is that practices will develop a clearer understanding of what proportion of their business depends on truly elective, semi-urgent, and truly urgent presenting problems, and thus how vulnerable they are to a persistent economic recession. That understanding may guide a strategy for diversification of the business.

Similarly, urology practices tend to think of their business as divided into new patients and established patients. Mature practices may be full of established patients who come in for their “annual visit”; at the other end of the spectrum is the young practice where almost every patient is “new.”

In general, new patients have problems requiring diagnostic evaluation and treatment—bigger sources of revenue for a practice than well-established patients. Some practices are intentional in creating and maintaining a balance of new versus established patients, discharging enough patients in a clinically appropriate way to make room for new patients. The second major lesson of this crisis is that a practice full of annual established patient visits is vulnerable to disruption and that the true value of a practice is to the patient with new and/or acute problems that can only be addressed by a urologist. This understanding may inform a review of your own control over the practice and whether there is an opportunity to restrict the balance of patients.

Urologists may also categorize their skills, and thus their practice, as cognitive and procedural; indeed, this mix of medicine and surgery is often what attracts physicians to the specialty. It is a diversification that may also serve to temper the
PANDEMIC LESSONS
continued from page 40

disruption of the current crisis.

The Centers for Medicare & Medicaid Services has issued several waivers and other flexibilities to address the public health emergency. Notable among these changes are those that expand access to telehealth for patients and their providers. Many commercial payers have followed suit, though each with slightly different rules for conducting and billing for the visit. This represents a lifeline for the cognitive side of the urology practice. Many new and established patient visits can now be conducted with the patient and the physician remote from each other using interactive audiovisual technology, in many cases for the same reimbursement as if patient and provider were face to face.

Adoption of this interim solution has been rapid, even as the bugs are still being worked out. The third major lesson of this crisis is that many patients and their problems can be adequately assessed and treated without the need to physically touch the patient. This disruptive innovation is likely to forever change the urology practice, if the flexibilities and reimbursement rules become permanent. The urology office of the future may be primarily designed, built, and operated for the procedural aspects of care, resembling an ambulatory surgery center more than a traditional office. The term “office visit” may be replaced by “telehome visit” as patients come to expect this new normal.

Transitioning staff to “remote” status

Finally, the national efforts to address the public health emergency have resulted in a surge of “remote” workers in the patient care field. It is now apparent that schedulers, call center employees, billing personnel, administrative staff, and even providers do not necessarily need to be in the office in order to do their jobs in a urology practice. The fourth major lesson of this crisis is that there are opportunities for efficiency and cost savings by transitioning employees to part- or full-time remote offices. The urology office of the future may have less square footage devoted to “the back office.”

Bottom line: One of the tools to deal with uncertainty is to see the possibilities. When the acute public health emergency is over and the future is more certain than it is today, the possibilities include having a practice that does not rely as heavily on elective visits and procedures, cultivates patients that truly need the skills of a urologist, thins out the unnecessary annual visits, and embraces virtual visits using modern technology.
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CPT 51798 will not be paid if performed in place of service 21, 23.

Q: I need some guidance on billing for the bladder scan procedure (51798). As it is a technical-only code, can this be billed in place of service (POS) 21 when a patient is inpatient or in ED POS 23 when performed outside of a uroflow procedure? Also, can it be billed in POS 22 as part of the uroflow procedure with 51741 and 51784? Typically, I have billed this with POS 11, but I need some guidance on whether it is billable to ED, inpatient, or outpatient hospital.

A: First, you are correct that current procedural terminology (CPT) code 51798, measurement of postvoid residual (PVR), is a technical-only code and therefore has no work value. Unfortunately, if you look into Medicare’s resource-based relative value scale (RBRVS), the actual value assigned to the Nonfacility Practice Expense Value is NA (not applicable), meaning the code will not be paid if performed in a place of service 21 or 23. The service is considered paid for in the facility payment provided to your hospital.

As for the second part of your question about POS 22 (on-campus outpatient hospital), this is also a facility place of service and therefore the 51798 will not be paid. As you indicated, it is appropriate to report 51741 and 51784 for any place of service listed above (21, 22, or 23), with modifier -26. You will be paid the facility rate for the services. Typically, the facility rate does not change the work Relative Value Units associated with the procedure, but often pays slightly less due to a lower practice expense value.

Remember, using data in each case to appropriate use of the data based on the code and value.

Q: Are you familiar with a hospital facility billing for postvoid residual (PVR) scanning when done by a nurse in the patient’s room?

A: As noted in our answer to the previous question, the facility payment for either the inpatient or outpatient hospital setting includes payment for the PVR. As this is a packaged service, the hospital would not bill separately for the PVR regardless of who provided the service.

Typically, the facility rate does not change the work Relative Value Units associated with the procedure, but often pays slightly less due to a lower practice expense value.

Q: Our payers are denying payment on all our claims when we bill 99213-25 and 51798. What modifier should we add to the 51798?

A: For Medicare, using current procedural terminology (CPT) code 51798 with an outpatient evaluation and management (E/M) code should not require a modifier on either code. However, we have seen some denials from Medicare without the use of modifiers, for various reasons. Most of those reasons involve a request for medical records. These requests are a nuisance but can easily be overturned. We have seen other denials that do not include a request for medical records but instead indicate that the service is bundled with or included in payment for the other service. For Medicare, we typically resubmit above 99213-25 and 51798.

Private payers are a different story. We have seen a requirement from many payers for reporting modifier -25 with the E/M code, as you indicate above. When claims are coded as you have noted, the denial may require a bit more investigation. Again, look for a denial that includes a medical record request. If records have been requested, you may have been flagged as an over user of CPT code 51798 and you will be required to submit records frequently to prove that 51798 is medically appropriate for that patient on that date of service.

If the denial indicates the service is bundled or included, we encourage you to check the payer’s website for payment policies and procedures. The payer may have announced that the PVR is no longer payable separately when performed on the same date as an E/M service; in this case you will need to contact the payer for a carve-out or a rule change.

If there is no clear indication that the payer has specifically bundled the service, we have reported the E/M visit with modifier -25 and then reported the PVR with modifier -59 to bypass the black box computer edit. You will need records to support the medical necessity and performance of the service if records are requested. We recommend that you check with your payer prior to using modifier -59 in this regard, as this is not a typical use of the modifier.

Of course, there is always the straight line appeal each time the service is denied. But if you appeal and win you may be required to continue to appeal each time for payment. Now you are in a game of attrition. You will need to wear the payer down by refusing to give up. Good luck.
CARES Act: Here’s what physicians should know

Bill provides coverage of nonreimbursable expenses attributed to COVID-19

Q: The CARES Act has many features designed to provide relief during the coronavirus disease 2019 (COVID-19) pandemic. What are the most important features I should know?

A: On March 27, President Donald J. Trump signed into law the Coronavirus Aid, Relief, and Economic Security (CARES) Act in an effort to support US businesses and families. The bill was extensive and wide reaching.

The following details are the most important for individuals to know:

• Payments of $1200 (single/head of household) and $2400 (joint filers) will be sent to taxpayers within certain income limits. An additional $500 payment is available for each qualifying child. These payments will be determined based on your most recently filed tax return or Social Security benefit statement, if no return was filed. The amount of the payment is reduced by 5% of the amount by which income exceeds $75,000 (single), $112,500 (head of household), or $150,000 (joint filers).

• Required minimum distribution (RMD) rules are waived for 2020 distributions from IRAs, including inherited IRAs, and 2019 distributions taken in 2020, which had a required beginning date of April 1, 2020. RMDs are also waived for 2020 distributions from certain defined contribution plans including 401(k), 403(b), 457(b), and IRA-based plans.

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Financial TIPS

Under the Coronavirus Aid, Relief, and Economic Security Act:

• Small businesses, including medical practices, with no more than 500 employees are eligible to apply for the Small Business Administration (SBA) Payroll Protection Program. This allows a small business to apply to an SBA-approved lender for a loan of up to 250% of its average monthly payroll costs to cover 8 weeks of payroll, as well as help with other expenses like rent, mortgage payments, and utilities. The maximum loan amount is $10 million. Sole proprietors, independent contractors, and other self-employed individuals are eligible. A loan can be forgiven based on the business maintaining employee and salary levels. For any portion of the loan that is not forgiven, the terms include a maximum duration of 10 years and a maximum interest rate of 4%.

• Employers and self-employed individuals may defer payment of the employer share of applicable Social Security taxes beginning on the date of enactment through the remainder of 2020. The deferred amount may be paid over 2 years, half in 2021 and half in 2022. These taxes are being deferred, not forgiven, so businesses should be mindful about planning to pay these tax liabilities when they are eventually due.

• $100 billion has been made available through the Public Health and Social Service Emergency Fund to provide immediate financial relief by covering nonreimbursable expenses attributable to COVID-19. Health care entities, including physician practices, that provide health care, diagnoses, or testing are eligible. Nonreimbursable expenses attributable to COVID-19 qualify for funding. Examples include increased staffing or training, personal protective equipment, and lost revenue.

• Physicians who provide volunteer medical services during the public health emergency related to COVID-19 have liability protections. These new protections are in addition to those provided by the Volunteer Protection Act of 1997.
In the age of physician burnout, is it time for a “quadruple aim”?

In 2008, investigators at the Institute for Healthcare Improvement (IHI) described the Triple Aim as simultaneously “improving the individual experience of care; improving the health of populations; and reducing the per capita costs of care for populations.” IHI and its close colleagues had determined that both individual and societal changes were needed. Since 2008, there has been an emphasis on achieving the Triple Aim, which centers on improving the health and well-being of the American population while reducing the cost of care. This requires a broad collaboration that extends far beyond the bricks and mortar of doctors’ offices and hospitals. But unless we focus on physician satisfaction, the Triple Aim cannot be achieved.

Perhaps the Holy Grail is a quadruple aim, which would divert some attention to physicians and their staff. Taking into consideration this fourth goal could help mitigate the burnout crisis impacting so many urologists today.

We are confronted with declining reimbursements, rising overhead costs, and having to see more patients in the same amount of time. Patients want readily available access to urologic care, emails and phone calls returned in a timely fashion, and more time with their doctor. This is a high bar for the contemporary urologist to meet and one that results in a high incidence of burnout.

Professional burnout is characterized by loss of enthusiasm for work, cynicism, and a low sense of personal accomplishment. It is associated with early retirement, alcohol use, and suicidal ideation. More physicians are experiencing dissatisfaction with their practice, which is an early warning sign of burnout. The concept of burnout is also relevant for urologists in training; according to a 2019 Urology article, 40% of American residents experience burnout.

The wide gap between patients’ expectations and the reality of the medical practice results in a high rate of physician burnout. Surgeons’ lounges and physician dining rooms abound with doctors stating they would not become doctors if they had it to do again and would not recommend a health care profession to their children. A common complaint is that physicians are required to spend an inordinate amount of time on computers and less time on patient care. Notably, patients also complain that physicians focus more on the computer and entering data than on them.

Urologists say that the electronic medical record makes physicians behave like administrative assistants and prevents them from functioning as physicians caring for patients. A 2013 survey of 30 physician practices found that electronic health record (EHR) technology has worsened professional satisfaction through time-consuming data entry and interference with patient care. In a 2011 survey, more than three-fourths of physicians reported that the EHR increases the time it takes to plan, review, order, and document care.

The Triple Aim, which has lofty goals of improving outcomes, reducing costs, and patient satisfaction, cannot be achieved unless we add the fourth goal of physician satisfaction. We call upon our leadership and the American Urological Association (AUA) to help us reach this fourth aim.

Some suggestions for moving us toward a quadruple aim include the following:

- Reduce the time the urologist spends on the computer entering patient data. Make more use of nurses, medical assistants, or other staff who can enter some or all documentation into the EHR, assisting with order entry, prescription writing, and charge capture.
- Use previsit planning and pre-appointment laboratory testing to reduce time wasted on the review and follow-up of laboratory results. For example, if a man comes for his annual exam, request prostate-specific antigen testing before the visit with the urologist and have the test results available prior to the office visit. This improves the efficiency of the office and enhances patient satisfaction.
- Develop AUA guidelines to legally expand roles allowing nurses, nurse practitioners, physician assistants, and medical assistants to assume responsibility for urologic care under supervision.
- Provide AUA guidelines on the use of new technology such as telemedicine. Using telemedicine will certainly increase practice efficiency and productivity. Legal caveats must be made clear on a state by state basis so that urologists can safely and securely use telemedicine without worrying about running afoul of the law.

Address the chasm between society’s expectations and the shrinking capacity of urologists, especially in rural areas. More financial and personnel resources should be dedicated to improving physician satisfaction.

It has been said that a successful marriage requires a happy spouse, because “If mama ain’t happy, ain’t nobody happy.” The same might be said for physician satisfaction: If the urologist isn’t happy, then no one, neither patients nor staff, is going to be happy. Let’s turn our attention to making the urologist happy.

REFERENCES
The UroLift System procedure is FDA-cleared for the treatment of symptoms due to urinary outflow obstruction secondary to BPH, including lateral and median lobe hyperplasia, in men 45 years of age or older. Results and patient experience may vary. Most common adverse events reported include hematuria, dysuria, micturition urgency, pelvic pain, and urge incontinence. Most symptoms were mild to moderate in severity and resolved within 2 to 4 weeks after the procedure. Consult the Instructions for Use (IFU) for more information.

1. Roehrborn, Can J Urol 2015
3. AUA BPH Guidelines 2003, 2010, 2018

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