**Chemothermotherapy shows promise in NMIBC**

**OVERACTIVE BLADDER/INCONTINENCE**
Patient preference survey ranks Botox highest for OAB third-line treatment

**PROSTATE CANCER**
Niraparib shows manageable safety profile in mCRPC with DNA repair gene defects

**KIDNEY CANCER**
Investigators look to neoadjuvant setting to advance RCC paradigm

**SEXUAL DYSFUNCTION**
Newmark provides updates on oral testosterone undecanoate

**BENIGN PROSTATIC HYPERPLASIA**
Update on saw palmetto in lower urinary tract symptoms secondary to BPH
Dear AACU Members:

More than 50 years ago, the AACU became the first national organization solely dedicated to advocacy on behalf of clinical urologists’ interests. At the time, Medicare was a new program and the federal government’s role in healthcare quickly grew by leaps and bounds. Today, the AACU continues to steadfastly advance health policies that protect our patients, practices, and profession through initiatives such as UROPAC, the AACU State Advocacy Network, and our recent partnership with Urology Times.

This strategic alliance gives us the opportunity to share news of our work, and the work of AACU members, on a national stage, including showcasing members in Urology Times publications and on the website at www.urologytimes.com/sap-partner/aacu.

In addition to opportunities to publish, the partnership brings AACU members access to case-based roundtable sessions and discounted educational programs. We are pleased to be able to provide these valuable resources and hope that you and your colleagues find them informative. If you would like additional copies of this publication sent to your office, please email info@aacuweb.org.

We are excited about the partnership and look forward to highlighting AACU and its members through our collaboration with Urology Times.

Best regards,

Damara L. Kaplan, PhD, MD
President
American Association of Clinical Urologists
www.aacuweb.org

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The promise of chemothermotherapy

This issue of Urology Times® includes a number of fascinating Q&A interviews, leading off with our cover interview with Brant A. Inman, MD, MS, FRCSC. He discusses his investigational chemothermotherapy approach for treating non—muscle-invasive bladder cancer. “My hope is that by improving the way we administer these drugs, maybe we can make them work better. Maybe by improving the combinations of drugs, we can make them work better,” Inman says in the interview.

In Coding Q&A, Jonathan Rubenstein, MD, and Mark Painter tackle questions involving whether it is possible to bill N.20.0 and N13.2 on the same Current Procedural Terminology (CPT) line, the use of modifier –S8 with CPT code 51700, and coding for percutaneous pouch lithotomy with lithotripter. In Practice Matters, Robert A. Dowling, MD, provides a list of 6 steps to help practices track ureteral stents. Dowling writes, “Returned ureteral stents are commonly thought of as a patient [adherence] issue, out of the physician’s control, or a malpractice risk for the urologist. Although they can be all of these, I would encourage you to think of the forgotten stent primarily as a patient safety issue—an avoidable bad outcome.” In Money Matters, Jeff Witz, CFP, outlines 8 steps to create your 2022 financial plan.

For this issue’s installment of Speak Out, Karen Nash asked 3 urologists about their thoughts on gender disparities in clinical trials for bladder cancer. “PSA shouldn’t be considered simply a screening test; it’s actually part of the diagnostic work-up. If a patient is 80 years old and has trouble urinating, PSA helps ensure it’s not advanced prostate cancer that I might have missed as a result of not doing PSA testing,” says one urologist.

We close this issue with Malpractice Consult, in which Acacia Brush Perko, Esq., covers a case in which a patient files a lawsuit alleging that an attending physician negligently failed to order a urology consult during a hospital stay. Thanks for reading.

Publisher’s Note
Patients with advanced prostate cancer are at risk for other serious conditions, such as **cardiovascular disease, diabetes, and osteoporosis**—risks that may increase with androgen deprivation therapy.$^{1-5}$


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FDA authorizes trial of novel PSMA-PET imaging diagnostic in prostate cancer

The FDA has authorized the launch of the phase 1/2 COBRA trial exploring the novel prostate-specific membrane antigen (PSMA)-PET imaging agent \( ^{64}\text{Cu-SAR-bisPSMA} \) in patients with biochemical recurrence (BCR) of prostate cancer following definitive therapy.

According to Clarity Pharmaceuticals, the company developing \( ^{64}\text{Cu-SAR-bisPSMA} \), COBRA is a multicenter, open-label, single-arm study with a targeted enrollment of up to 50 patients. The study’s primary end points are the capacity of \( ^{64}\text{Cu-SAR-bisPSMA} \) to detect prostate cancer recurrence, as well as the safety and tolerability of the imaging agent.

Other ongoing trials are also exploring \( ^{64}\text{Cu-SAR-bisPSMA} \). The phase 1 PROPELLER trial (NCT04839367) is examining \( ^{64}\text{Cu-SAR-bisPSMA} \) in patients with treatment-naïve, histologically confirmed prostate cancer who are scheduled for radical prostatectomy. In the phase 1/2a SECURE trial (NCT04868604), \( ^{64}\text{Cu-SAR-bisPSMA} \) is being explored along with the investigational PSMA-targeted therapy \( ^{64}\text{Cu-SAR-bisPSMA} \) in patients with metastatic castration-resistant prostate cancer.

In a news release, Alan Taylor, MD, executive chairman of Clarity Pharmaceuticals, commented, “The preliminary data from our SAR-bisPSMA trials in Australia and the United States look very promising and the high uptake and retention of SAR-bisPSMA shown in preclinical and clinical trials to date may lead to improved detection in patients with prostate cancer, particularly those with low PSA levels. Our team and our collaborators are excited to commence the COBRA trial, generating more data to progress the development of SAR-bisPSMA as we move this product closer to registration in the United States.”

REFERENCE


Phase 3 study launches of UGN-102 in low-grade non–muscle-invasive bladder cancer

The phase 3 ENVISION study has launched an examination of the mitomycin-containing reverse thermal gel UGN-102 as primary chemoablative therapy in patients with low-grade, intermediate-risk non-muscle-invasive bladder cancer (NMIBC).

In the international, single-arm ENVISION trial, enrolled patients will be administered 6 once-weekly intravesical instillations of UGN-102. The enrollment goal is approximately 220 patients, who will be treated across 90 sites. The primary end point is the rate of complete response 3 months after the initial instillation. The key secondary end point will be the durability of these complete responses.

“The start of the ENVISION trial marks the final phase of validating primary chemoablation for the treatment of recurrent intermediate-risk NMIBC,” Sandip Prasad, MD, a urologist at Atlantic Health System, Morristown Medical Center, New Jersey, and lead study investigator for the ENVISION trial, said in a news release. “This study is designed to support the clinical potential of UGN-102 as a new treatment for patients that are underserved by the current standard of care, including those patients at risk for recurrence and those that are unwilling or unable to endure surgery or anesthesia.”

Beyond the ENVISION trial, UGN-102 is also being explored in the ongoing global, randomized, open-label, phase 3 ATLAS trial (NCT04688933), which is comparing UGN-102 with or without TURBT versus TURBT alone in patients with low-grade, intermediate-risk NMIBC.

REFERENCE


FDA grants breakthrough device designation to laser lithotripsy enhancer

The FDA has granted a breakthrough device designation to Applaud Medical for its Acoustic Enhancer technology for use in conjunction with ureteroscopy with laser lithotripsy (URS-LL) for the fragmentation of calcium-based kidney stones.

The Acoustic Enhancer, which is specifically intended for stones that have a diameter of between 6 mm and 20 mm, is a microbubble composed of a gas core with a lipid shell. According to Applaud Medical, acoustic impulses from URS-LL trigger the Acoustic Enhancer to generate additional stone-fragmenting shockwaves when a patient is receiving laser lithotripsy.

Initial efficacy and safety evidence for the Acoustic Enhancer were established in human feasibility trials that included 71 patients. The technology is now being further explored in the phase 3 AEROLITH study (NCT04563039).

The prospective, multicenter, randomized, double-blind AEROLITH trial is recruiting patients aged 18 to 75 years who have up to 3 urinary stones located proximally to the iliac vessels on 1 side. Patients are still eligible if they have bilateral stones, but treatment will only be administered to 1 side. Patients who have a stent in place may still enter the study.

The study is randomizing patients to standard URS-LL with or without Acoustic Enhancer. The primary outcome measured is efficacy, defined as absence of having residual fragments measuring 2 mm or less, and the secondary outcome measure is safety, defined as the total radiant energy used in the treatment. Other key end points include lasering time during treatment, rate of patients receiving further interventional stone treatment, and rates of adverse events.

The study enrollment goal is 196 patients and the study is being conducted at up to 15 clinical sites in the United States. “There is an increasing prevalence of urinary stone disease due to the rising incidence of obesity, diabetes mellitus, hypertension, and dyslipidemia, with obstructions associated with kidney stones at least 6 mm and not more than 20 mm in diameter, putting patients at risk of sepsis, chronic kidney disease, or end-stage renal disease,” Ojas Shah, MD, George F. Cahill Professor of Urology at Columbia University College of Physicians and Surgeons, and director of the Division of Endourology and Stone Disease at Columbia University Medical Center, New York, New York, said in a news release. “Applaud’s Acoustic Enhancer offers a new approach to breaking kidney stones into smaller fragments, potentially reducing the risk of these complications and the development of future obstructions.”

REFERENCES

What will be the next GOAT for bladder cancer?

Regarding the disease state of bladder cancer, we are now fully immersed in the discovery of new therapeutics, particularly as they pertain to immunotherapy. Indeed, these are exciting times for immunotherapy and its use in advanced and metastatic bladder cancer. However, as we look back over the past 50 years, we would be remiss if we didn’t reflect on the historic success of Bacillus Calmette-Guerin (BCG) therapy, the “greatest of all time (GOAT)” when it comes to treatment of high-risk non–muscle invasive bladder cancer. Based on a variety of initial observations and small reports demonstrating the anticancer activity of BCG therapy, Canadian urologist Alvaro Morales, MD, FRCSC, had the foresight to place BCG within the bladder.1 And in 1976, he published the first use of BCG therapy directed at “superficial” bladder cancer.2 Based on these early results in only 7 patients, the National Cancer Institute funded 2 randomized controlled trials to test the effectiveness of the combined BCG regimen in patients with “superficial” bladder cancer, one trial by Southwest Oncology Group (now SWOG) led by Donald Lamm, MD, FACS, and the other at Memorial Sloan Kettering Cancer Center.1,4

Both studies demonstrated that BCG markedly reduced tumor recurrence compared with transurethral surgery alone, confirming Morales’ early observations. Subsequently, many studies have proved the benefit of BCG in eradicating carcinoma in situ (CIS) of the bladder, delaying progression to muscle invasion, and improving the survival of patients with high-risk non–muscle-invasive bladder cancer. It has also proved superior to intravesical chemotherapy.2

In 1990, the FDA approved the use of intravesical BCG. Now, almost 50 years after the first report, BCG therapy remains the gold-standard treatment of high-grade, high-risk noninvasive bladder cancer. The response rates for truly high-risk patients are in the range of 70% to 80%, but for those who recur after receiving BCG, the options are more limited and radical cystectomy becomes a choice for those who are fit and willing. It was in this context that another immune-based therapy, pembrolizumab (Keytruda), was tested and demonstrated benefit in this BCG-unresponsive state. In this setting, approximately 40% of patients may have their CIS eradicated with PD-1 immunotherapy, and in many the response is durable.4

In muscle-invasive bladder cancer, immunotherapy is being trialed as an alternative to chemotherapy in the neoadjuvant space among patients who are ineligible for platinum-based chemotherapy.4 Additionally, we now have FDA-approved adjuvant maintenance therapy following radical cystectomy with nivolumab (Opdivo) among patients with locally advanced pathologic features, regardless of prior neoadjuvant chemotherapy, nodal involvement, or PD-L1 status.7

Finally, among patients with metastatic bladder cancer, immunotherapy’s benefits are now also well established. Findings from several trials have consistently demonstrated that checkpoint inhibitors are active in this disease state, with response rates ranging from 15% to 30% depending on the study and line of treatment.3 Checkpoint inhibitors have also improved survival in the second-line setting, including in patients whose cancer persisted or progressed after prior platinum-based chemotherapy treatment. So the future is bright for immunotherapy in bladder cancer, and we look forward to the next 50 years of discovery and hope for the GOAT’s successors, with cancer eradication and bladder preservation as our primary goals.

REFERENCES

HAVE FEEDBACK?
Send your comments to Cookson, c/o UTeditors@mjlifesciences.com.
INDICATION

NUBEQA® (darolutamide) is an androgen receptor inhibitor indicated for the treatment of patients with non-metastatic castration-resistant prostate cancer.

IMPORTANT SAFETY INFORMATION

Embryo-Fetal Toxicity: Safety and efficacy of NUBEQA have not been established in females. NUBEQA can cause fetal harm and loss of pregnancy. Advise males with female partners of reproductive potential to use effective contraception during treatment with NUBEQA and for 1 week after the last dose.

Adverse Reactions

Serious adverse reactions occurred in 25% of patients receiving NUBEQA and in 20% of patients receiving placebo. Serious adverse reactions in ≥1% of patients who received NUBEQA were urinary retention, pneumonia, and hematuria. Overall, 3.9% of patients receiving NUBEQA and 3.2% of patients receiving placebo died from adverse reactions, which included death (0.4%), cardiac failure (0.3%), cardiac arrest (0.2%), general physical health deterioration (0.2%), and pulmonary embolism (0.2%) for NUBEQA.

Adverse reactions occurring more frequently in the NUBEQA arm (≥2% over placebo) were fatigue (16% vs 11%), pain in extremity (6% vs 3%), and rash (3% vs 1%).

Clinically significant adverse reactions occurring in ≥2% of patients treated with NUBEQA included ischemic heart disease (4.0% vs 3.4% on placebo) and heart failure (2.1% vs 0.9% on placebo).

Drug Interactions

Effect of Other Drugs on NUBEQA - Combined P-gp and strong or moderate CYP3A4 inducers decrease NUBEQA exposure, which may decrease NUBEQA activity. Avoid concomitant use.

Combined P-gp and strong CYP3A4 inhibitors increase NUBEQA exposure, which may increase the risk of NUBEQA adverse reactions. Monitor more frequently and modify NUBEQA dose as needed.
For your patient with non-metastatic castration-resistant prostate cancer (nmCRPC)

HELP HIM LIVE FOR WHAT HE LOVES

PROVIDED THE RELIEF OF AN EXTRA 15 MONTHS WITHOUT PAIN PROGRESSION1,3*
40.3 months vs 25.4 months for ADT alone
Secondary endpoint: HR: 0.65; 95% CI: 0.53-0.79; P<0.0001.

POSTPONED CYTOTOXIC CHEMOTHERAPY—MORE TIME WITHOUT CHEMO1,3
42% risk reduction in time to chemo vs ADT alone
Secondary endpoint: HR: 0.58; 95% CI: 0.44-0.76; P<0.0001. Medians not estimable.

CHOOSE NUBEQA® 1st FOR EXTENDED SURVIVAL.1-3 NUBEQAHCP.COM

Drug Interactions (cont’d)
Effects of NUBEQA on Other Drugs – NUBEQA inhibits breast cancer resistance protein (BCRP) transporter. Concomitant use increases exposure (AUC) and maximal concentration of BCRP substrates, which may increase the risk of BCRP substrate-related toxicities. Avoid concomitant use where possible.
If used together, monitor more frequently for adverse reactions, and consider dose reduction of the BCRP substrate.
NUBEQA inhibits OATP1B1 and OATP1B3 transporters. Concomitant use may increase plasma concentrations of OATP1B1 or OATP1B3 substrates. Monitor more frequently for adverse reactions and consider dose reduction of these substrates.

Metastasis-free survival (MFS) was the primary endpoint, and overall survival (OS) was a key secondary endpoint.1
*Time to pain progression was defined as at least a 2-point worsening from baseline of pain score on BPI-SF (a validated health-related quality-of-life instrument) or initiation of opioids and reported in 28% of all patients on study.

Study design
The efficacy and safety of NUBEQA were assessed in a randomized, double-blind, placebo-controlled phase III study (ARAMIS) in nmCRPC patients on ADT with a PSA doubling time ≤10 months. 1509 patients were randomized 2:1 to 600 mg NUBEQA twice daily (n=955) or placebo (n=554). MFS was defined as time from randomization to time of first evidence of BICR-confirmed distant metastasis or death from any cause ≤33 weeks after the last evaluable scan, whichever occurred first. Treatment continued until radiographic disease progression, as assessed by CT, MRI, 18F bone scan by BICR, unacceptable toxicity, or withdrawal.1,2

Please see the following page for the brief summary of Prescribing Information.

NUBEQA®
(darolutamide) 300 mg tablets

VR=blind independent central review; CT=computed tomography; MRI=magnetic resonance imaging.

P<0.0001. Medians not estimable.
NUBEQA® (darolutamide) tablets, for oral use
Initial U.S. Approval: 2019

BRIEF SUMMARY OF PRESCRIBING INFORMATION
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE
NUBEQA is indicated for the treatment of patients with non-metastatic castration-resistant prostate cancer (mCPRC).

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

ADAMS, a randomized, double-blind, placebo-controlled, multi-center clinical trial, enrolled patients who had non-metastatic: castration-resistant prostate cancer (mCPRC). In this study, patients received either NUBEQA or placebo every 12 hours for 100 mg, a placebo, twice a day.A patients in the ADAMS study received a concurrent (nonrandom) first-line treatment, axiliferin (AXL) or a baseline chemotherapy. The median duration of exposure was 14.8 months (range, 0 to 44.3 months) in patients who received NUBEQA. Overall, adverse reactions occurred in 25% of patients receiving NUBEQA and in 20% of patients receiving placebo. Serious adverse reactions occurred in 1% of patients receiving NUBEQA and 0.2% of patients receiving placebo. Serious adverse reactions included death (0.2%), cardiac failure (0.2%), cardiac arrest (0.2%), and pulmonary edema (0.2%) for NUBEQA. Permanently discontinued due to adverse reactions occurred in 2% of patients receiving NUBEQA or placebo. The most frequent adverse reactions requiring permanent discontinuation in patients who received NUBEQA included cardiac failure (0.1%), death (0.1%), and pulmonary edema (0.1%).

Discharge reactions due to adverse reactions occurred in 4% of patients treated with NUBEQA. The most frequent adverse reactions requiring discharge in patients treated with NUBEQA included cardiac failure (0.7%), hypertension (0.3%), and nausea (0.2%).

Table 1 shows adverse reactions in mCPRC reported to the ADAMS arm with a 2% absolute increase in frequency compared to placebo. Table 2 shows laboratory tests abnormalities related to NUBEQA treatment and reported more frequently in NUBEQA-treated patients compared to placebo-treated patients in the ADAMS study.

Table 1: Adverse Reactions in ADAMS

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>NUBEQA (n=194)</th>
<th>Placebo (n=195)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>16.0</td>
<td>6.6</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>4.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Rash</td>
<td>3.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

1 Includes fatigue and anemia.
2 Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.
3 Additionally, clinically significant adverse reactions occurring in 2% or more of patients treated with NUBEQA included ischemic heart disease (0.6% versus 0.3% in placebo) and heart failure (2.1% versus 0.3% in placebo).

Table 2: Laboratory Test Abnormalities in ADAMS

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>NUBEQA (n=95)</th>
<th>Placebo (n=95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Neutropenia count decreased</td>
<td>20.0</td>
<td>4.0</td>
</tr>
<tr>
<td>ASAT increased</td>
<td>23.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Bilirubin increased</td>
<td>16.0</td>
<td>0.1</td>
</tr>
</tbody>
</table>

*The denominator used to calculate the rate varied based on the number of patients with a baseline value and at least one post-treatment value.

1 Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

7.1 Effect of Other Drugs on NUBEQA

Concomitant use of NUBEQA with a combined 5α-reductase inhibitor and a nonsteroidal anti-inflammatory drug decreases the effectiveness of NUBEQA (see Clinical Pharmacology (12.2)). Concomitant use of NUBEQA with strong CYP3A4 inhibitors decreases the effectiveness of NUBEQA (see Clinical Pharmacology (12.2)).

7.2 Effects of NUBEQA on Other Drugs

Breast Cancer Resistance Protein (BRCAP) and Androgen Receptor Targeting Polyphenols (ARGET) 391 and 123 substitutes
NUBEQA is an inhibitor of BCRP transporters. Concomitant use of NUBEQA increases the AUC and Cmax of BCRP substrates (see Clinical Pharmacology (12.3)), which may increase the risk of BCRP substrate related toxicity. Avoid concomitant use with drugs that are BCRP substrates where possible. If used together, monitor patients more frequently for adverse reactions and consider dose reductions of the BCRP substrate drug.

NUBEQA is an inhibitor of OCT1 (1911 and 1913 transporters). Concomitant use of NUBEQA may increase the plasma concentrations of OCT1 (1911 and 1913 substrates). Monitor patients more frequently for adverse reactions of these drugs and consider dose reduction where patients are taking NUBEQA (see Clinical Pharmacology (12.2)).

References

Review the prescribing information of the ICRP, DATP1911 and DATP1913 substrates when used concomitantly with NUBEQA.

6 USE IN SPECIFIC POPULATIONS
6.1 Pregnancy
Risk Summary
The safety and efficacy of NUBEQA have not been established in females. Based on its mechanism of action, NUBEQA can cause fetal harm and loss of pregnancy (see Clinical Pharmacology (12.1)). Animal embryo-fetal development and reproduction studies were not conducted with darolutamide. There are no human data on the use of NUBEQA in pregnant females.

6.2 Lactation
Risk Summary
The safety and efficacy of NUBEQA have not been established in females. There are no data on the presence of darolutamide or its metabolites in human milk, the effect on the breast-fed child, or the effect on milk production.

6.3 Females and Males of Reproductive Potential

Contraception
Males
Based on the mechanism of action, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 1 week after the last dose of NUBEQA (see Use in Specific Populations (8.3).)

6.4 Pediatric Use

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

6.5 Geriatric Use

The safety and efficacy of NUBEQA in patients 65 years and older and 75 years and older, is not known. No overall differences in safety or efficacy were observed between these patients and younger patients.

6.6 Renal Impairment

Patients with severe renal impairment (eGFR 15-29 mL/min/1.73 m²) who are not receiving hemodialysis have a reduced exposure to NUBEQA and reduction of the dose is recommended (see Dosage and Administration (2.2) and Clinical Pharmacology (12.2)). The dose reduction is needed for patients with mild or moderate renal impairment. The effect of severe hepatic impairment (eGFR ≤ 15 mL/min/1.73 m²) on darolutamide pharmacokinetics is unknown.

6.7 Hepatic Impairment

Patients with moderate hepatic impairment (Child-Pugh Class B) have a higher exposure to NUBEQA and reduction of the dose is recommended (see Dosage and Administration (2.2) and Clinical Pharmacology (12.2)). No dose reduction is needed for patients with mild hepatic impairment. The effect of severe hepatic impairment (Child-Pugh C) on darolutamide pharmacokinetics is unknown.

10 OVERDOSAGE

There is no known specific antidote for darolutamide overdose. The highest dose of NUBEQA clinically studied was 100 mg/day taken daily, equivalent to a total daily dose of 180 mg. Do not limit bleeding times were observed with this dose.

Considering the solubility and bioavailability of darolutamide, an intravenous bolus of a higher than recommended dose of darolutamide is not expected to lead to systemic toxicity in patients with intact hepatic and renal function (see Clinical Pharmacology (12.2)).

In the event of a higher than recommended dose in patients with severe renal impairment or moderate hepatic impairment, if there is suspicion of toxicity, intravenous NUBEQA treatment and undertake general supportive measures until clinical toxicity has been diminished or resolved. If there is no suspicion of toxicity, NUBEQA treatment can be continued with the next dose as scheduled.

13 NONGELINEOUS TOXICITY

13.1 Cardiogenic, Mucolipogenic, Impairment of fertility

Long-term animal studies evaluate the carcinogenic potential of darolutamide have not been conducted.

Darolutamide was teratogenic in an in vitro oocyte maturation assay in human peripheral blood lymphocytes. Darolutamide did not induce mutations in the bacterial reverse mutagenesis Ames assay and was not genotoxic in the in vivo combined bone marrow micronucleus assay and the Comet assays in the live and in suspension of the rat.

Fertility studies in animals have not been conducted with darolutamide. In repeated-dose toxicity studies in main rats (up to 26 weeks) and dogs (up to 39 weeks), tubular dilation of testes, hyalinosis, and atrophy of seminal vesicles, testis, prostate gland and epididymis were observed in dogs at > 100 mg/kg/day (6.8 times the human exposure based on AUC) and > 50 mg/kg/day in dogs (approximately 1 times the human exposure based on AUC).

14 PATIENT COUNSELING INFORMATION

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

Drug and Administration

Inform patients receiving non-radiolabeled blocking hormone (LHRH) analog therapy that they must maintain this treatment during the course of treatment with NUBEQA.

Instruct patients to take their dose of two tablets (tablets daily). Each tablet should be swallowed whole.

Inform patients that if the event of a missed daily dose of NUBEQA, take any missed dose, as soon as they remember prior to the next scheduled dose, and not to take two doses together to make up for a missed dose (see Dosage and Administration (2.7)).

Findings of Fertility

Advise patients that NUBEQA can be harmful to a developing fetus and can cause loss of pregnancy (see Use in Specific Populations (8.1).)

Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 1 week after the last dose of NUBEQA (see Warnings and Precautions (6.1) and Use in Specific Populations (8.3)).

Advise male patients that NUBEQA may impair fertility (see Use in Specific Populations (8.3)).

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Q. Could you explain the rationale for chemothermotherapy versus intravesical chemotherapy alone?

A. I think for many years now, people have recognized that intravesical chemotherapy is not always ideal. [Many patients] have recurrences of bladder cancer or, worse yet, [cancer progression], despite what would appear to be adequate intravesical therapy. The question is: Why is that intravesical chemotherapy not working?

[Many reasons] could potentially exist for this. One would be that the drug is not penetrating adequately into the wall of the bladder. Another might be that the cancer cells in the bladder are resistant to the particular drug being used. Perhaps there are alternative reasons too; it’s possible that the cancer is adapting over time, and a cell that was once sensitive is no longer sensitive. Therefore, there are a variety of potential reasons why we might see intravesical chemotherapy as being less than optimal.

The idea of heat—in combination with intravesical chemotherapy—is to address that problem. Heat makes cancer cells more sensitive to certain types of chemotherapy. For example, if you take a cancer cell at body temperature, which is 37 °C, and you expose it to a [chemotherapy] drug, you will observe a certain drug kill rate. You can take that same cell and expose it to that same chemotherapy drug, but this time at 43 °C, and it turns out that, for many drugs, they work much better. Something about the heating of cancer cells, in many circumstances, will make them more sensitive to certain chemotherapy agents. It’s not all chemotherapies, but a subset of all chemotherapies.

One other thing is that when we warm the bladder by heating its contents, it makes the bladder more permeable to drugs, including chemotherapy drugs, so there’s an improvement in drug delivery.

The last thing we know happens when we heat cancers is that changes occur in the immune response or in the local immune microenvironment surrounding the cancer cell. This also could lead to some changes in how well the treatment works because we may be bringing on a new mechanism.

One thing I also want to just briefly mention is when I’m talking about heating here, I’m talking about heating in what we call the “fever range.” Fever-range hyperthermia is heat somewhere in the 41 °C to 44 °C range, typically 43 °C. Anything above 45 °C, it starts to feel painful because it’s getting pretty hot. When we heat enough to destroy tissues, like if I [were] to toss you in a fire—and we’re talking about temperatures above 60 °C—then we are doing ablative hyperthermia. For bladder cancer, I am not talking about ablation. Rather, [I am] talking about fever-range heating.

Q. What special equipment is needed to do this?

A. You need a bladder heater. There are several alternatives available for this right now, some of which are really expensive and difficult to operate and some of which are simpler.

The first devices...used were extravesical bladder heaters. Imagine a large device that requires a special room to put it in. And you lie on a table, and then balloons of water basically push against your belly. Through these balloons...radiofrequency rays [focus on] the bladder; that radiofrequency radiation causes the bladder to heat up. And you can heat basically any intra-abdominal or pelvic organ in this way. These are big machines and very expensive, costing typically hundreds of thousands of dollars. There are several manufacturers of these kinds of machines out there, and the Pyrexar [Medical] BSD-2000 is one example. The major disadvantage, of course, is the cost. Additionally, you require a medical physicist to run it. It’s just very challenging. We’ve done clinical trials at Duke using this kind of device. It works; it’s just not ideal.
Bladder Cancer

Other devices are simpler. For example, there’s a device called the Synergo, which is an intravesical catheter that has an antenna on its tip that emits radiofrequency. So instead of projecting radiofrequency waves through the body and focusing them on the bladder, this is a catheter that emits radiofrequency waves from within the bladder, and that serves as the heater. The advantage...is that it’s manageable with a special Foley catheter, and there’s no external device. You don’t need a physicist to operate it. The disadvantage is that there can be hot spots because the catheter doesn’t transmit heat uniformly. The device does require fairly constant nursing monitoring, which means that it’s not easy to leave the room and treat the patient. It’s also a fairly expensive device.

The more recent bladder heaters, the ones that we’ve been using at Duke more recently, are intravesical recirculating heaters. These work by having a catheter in the bladder that circulates the fluid within the bladder. That fluid is heated outside the body and then reinfused as a warm fluid. This is, for example, how intravenous [IV] fluid warmers work. If you have an IV fluid, we don’t usually want to pump it into you cold, so the fluid is warmed to body temperature as it’s infusing. The device that we’ve been using is the Combat BRS [combined antineoplastic bladder recirculation system], which is probably the most commonly used kind of recirculating or convective bladder heater. The advantage of these is that they’re much smaller and simpler devices. They’re also substantially cheaper, easier to run, and they don’t require careful monitoring for burns and things like that because the fluid is heated very accurately.

Q. What do the data show in terms of the efficacy of this treatment?
A. Of the clinical trials that are already available, it seems that a couple of patterns have emerged. First, heated chemotherapy seems to be better than room-temperature chemotherapy, at least for mitomycin C. Second is that heated chemotherapy was shown to be similar to BCG in terms of efficacy in one randomized clinical trial. That has not been replicated because the trial is relatively new. But it also brings up the question of...if we combine chemotherapy with heat, can we achieve an efficacy similar to that of BCG?

Right now, BCG is the best agent for high-risk non–muscle-invasive bladder cancer, but it has suffered from a number of problems, including a lack of availability. Lately, [worldwide drug shortages] make BCG treatment very, very challenging for many physicians and patients. Even if heated intravesical chemotherapy is a treatment that is no better than BCG, it may be a reasonable alternative to BCG because it’s more available and manufacturing is more reliable than BCG.

Q. How well tolerated is chemothermotherapy? What adverse events have you seen?
A. The [adverse] effect profile appears very similar to other intravesical therapies. The main things are urgency and frequency of urination, irritation in the bladder during treatment, and urinary tract infections [that are] probably associated with the catheterization more than the device itself. Those are the main things, so it seems to be very well tolerated.

One thing we did notice at Duke when we were using higher-dose intravesical chemotherapy, in particular higher-dose mitomycin in combination with heating, is an increased incidence of drug-sensitivity reactions. The patients seemed to have a higher rate than we would usually observe of allergy-type reactions to mitomycin, including skin rashes and such. Others have not confirmed this yet because we’re the only group that has used higher mitomycin C doses. I’m not sure if that’s unique to our center or not.

Q. My understanding is that you’ve been able to make this available to select patients in the US through a special arrangement. Could you discuss this and also what you’ve personally experienced and learned in using this therapy so far?
A. Because of the worldwide drug shortage in BCG, we were looking for options at Duke to treat patients with high-risk non–muscle-invasive bladder cancer or patients in whom BCG has previously failed and [patients] we couldn’t give BCG because it just wasn’t available. Our options were to use standard intravesical chemotherapy, which historically has not done that well, or to remove someone’s bladder surgically. Many patients are not ready to go to that step, so we were looking for an alternative.

Given initial promising results in Europe, I applied to the FDA for a humanitarian-use exemption to utilize the Combat BRS bladder heater that is available in Europe but not in the United States to administer chemotherapy agents. They approved me to use this device with mitomycin C. We treated a number of patients with the Combat BRS device and mitomycin C at higher doses. We found it to be pretty efficacious, and we recently published our data on this. That study is not really a clinical trial, per se; it’s a humanitarian exemption protocol that allows us to use it during the worldwide drug shortage. So it’s a way of, we hope, improving the efficacy of existing agents when the standard of care is not available.

Q. Do you see this coming to North America anytime soon?
A. The answer to that will depend on the results of several clinical trials that have been completed and are currently going to be reported in the next year or two. For the FDA to approve this device and make it available, there has to be evidence that it has benefit. [A] number of clinical trials that have been done or that are currently enrolling in Europe and elsewhere...are going to answer that question. I suspect that if the data look favorable on these clinical trials, a package will be presented to the FDA to seek device approval for the United States.

Q. Do you have any final thoughts on this technology and how it could contribute to the bladder cancer armamentarium?
A. That’s a good question. I personally am not married to any particular technology. I’m not sure whether heat alone or other new technologies are ultimately going to be the standard of care or not. But I do think that we need to improve on what we have right now. [For] patients in whom BCG doesn’t work, we’re using chemotherapy drugs, typically as monotherapies and more recently as combinations. My hope is that by improving the way we administer these drugs, maybe we can make them work better. Maybe by improving the combinations of drugs, we can make them work better.

It’s my hope that eventually we’ll find a cocktail that beats BCG, stops these tumors from coming back, [and] stops these tumors from getting worse so that patients with non–muscle-invasive bladder cancer aren’t faced with the need to make a decision to have their bladder removed or not.

Special thanks to Urology Times® Co–Editor-in-Chief Michael S. Cookson, MD, MMHC, for his assistance with this article.
Findings from a recent study showed that gender disparities exist in clinical trials used to guide National Comprehensive Cancer Network (NCCN) recommendations for urothelial carcinoma (UC). This study was presented at the Society of Women in Urology 11th Annual Clinical Mentoring Conference.1

Although women make up 30.5% of patients with UC in an administrative database, findings showed that only 20% of patients in NCCN-cited systemic therapy trials were women. “We have to be more mindful and thoughtful about the fact that certain populations are underrepresented in clinical trials, and that’s likely due to a number of factors,” coauthor Padraic O’Malley, MD, MSc, FRCS, a clinical assistant professor in the Department of Urology at the University of Florida College of Medicine in Gainesville, said in an interview with Urology Times®.

To compare the gender ratio in UC clinical trials vs the general US population of UC patients, investigators analyzed version 1 of the 2021 NCCN guidelines for UC and gathered data from the National Cancer Database (NCDB) program. Comparisons of gender proportions between the 2 data sets were made using chi-square tests. Univariable and multivariable analysis was also conducted to determine predictors of systemic therapy.

A total of 58,031 patients with a diagnosis of stage II to IV UC and treated with systemic therapy between 1998 and 2018 were identified from the NCDB, and 31 trials (10,158 patients) cited by the NCCN guidelines were reviewed. Of the UC clinical trials, 7 (22.6%) were US trials, 8 (25.8%) were non-US trials, and 16 (51.6%) were US and non-US trials. Eighteen percent (115/650) of patients in the US trials were women, 21% (544/2630) in the non-US trials were women, and 20% (1361/6878) in the US and non-US trials were women ($P=.2168$).

The main finding of this study was that significant gender disparities existed among the trials referenced by the NCCN guideline and that these disparities were based on trial randomization, phase, inclusion of upper tract disease, and type of systemic therapy (chemotherapy vs immunotherapy).

For instance, more advanced trials enrolled a lower percentage of women, which O’Malley referred to as a more “nuanced” finding. Twenty-seven percent (85 of 317) of patients in phase 1 trials were women compared with 20% (1141 of 5819) in phase 3 trials. In addition, women were significantly less likely to receive systemic therapy (odds ratio, 0.93; 95% CI, 0.89-0.96; $P<.001$) in the NCDB population.

REFERENCE
Patient preference survey ranks Botox highest for OAB third-line treatment

Just 13% of patients said they would prefer sacral neuromodulation

A team of investigators analyzed factors that influence patients when choosing third-line treatments for overactive bladder (OAB) to better understand patient needs, barriers to third-line therapy, and what influences patient satisfaction in that setting. Findings from the study were presented at the Society of Women in Urology 11th Annual Clinical Mentoring Conference.

“Patients are [often] overwhelmed by these choices...and don’t really understand the risks and benefits when they’re first told about them,” study coauthor Anjali Kapur, MD, a urology resident at Stony Brook Medicine in New York, said in an interview. “So our goal was to educate these patients thoroughly on the risks and benefits of each of these therapies and try to understand what guides their choice of third-line therapy based on their lifestyle and what suits them.”

The prospective cohort in this study comprised 85 patients who were eligible for third-line OAB therapies. Patients who were younger than 18 years, did not speak English, or had a developmental disability were excluded from participating.

A 6-minute educational video was created by investigators to inform participants on all 3 third-line therapies currently offered to patients with OAB in the real world: intradetrusor onabotulinumtoxinA (Botox), percutaneous tibial nerve stimulation (PTNS), and sacral neuromodulation (SNS).

After viewing the video, participants were asked to fill out a survey and rank their preferences for third-line therapies on a scale of 1 to 3. The participants also chose specific features of each therapy that they found the most and least appealing.

Results showed that 38% (32 of 85) of patients preferred onabotulinumtoxinA, 37% (31 of 85) preferred PTNS, and 13% (11 of 85) preferred SNS; 13% (11 of 85) did not prefer any of the options (Figure).

“I was actually a little surprised that only 13% of patients stated they didn’t find any of these procedures appealing,” said coauthor Jason Kim, MD, a clinical assistant professor of urology at Stony Brook Medicine. “We know there’s a significant proportion of the population that is undertreated, and given the fact that...many patients don’t go on to third-line therapy, I would have expected...more patient dissatisfaction with the 3 treatment choices.”

Furthermore, findings suggested significant associations between onabotulinumtoxinA and age and PTNS and age. More patients who were 65 years and older chose onabotulinumtoxinA as their No. 1 therapy ($P=.003$), and more patients aged 18 to 64 years preferred PTNS as their No. 1 therapy ($P=.044$). Education level and income did not play a significant role in preference.

Data also revealed that the most attractive feature of onabotulinumtoxinA was its lasting effect (48%) and that its least attractive feature was the potential for catheterization due to urinary retention (52%). The most attractive features of PTNS were that it does not require surgery (35%) and that no significant complications have been reported (36%); its least attractive feature was the need for frequent office visits (59%). The most and least attractive features for SNS were the potential long-term relief without frequent office visits (54%) and the need for an implanted device (29%).

Kapur highlighted the value of this study’s results for counseling future patients. “The study shows that we really do need to try to anticipate what the needs are of our patients and [determine] what those barriers may be to the patients actually going through with the therapy and then being satisfied,” she said.

Kim added, “I think there’s a disconnect between the patients saying they’re interested in these therapies and the patients that actually go on to [receive] them, and I’d like to study where the disconnect comes from.”

REFERENCE
Redefining the landscape of prostate cancer diagnosis, evaluation and clinical management

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Q. Please give an overview of the development of the midurethral sling for the treatment of SUI.

A. The first slings were reported probably in the early 20th century. Initially physicians used fascia from the patient's own body, but that required a bit of a surgery—a dissection taking a nice piece of fascia out and putting it under the bladder neck and proximal urethra. To avoid the morbidity of fascial harvest, many people tried different synthetic materials. There were often a lot of problems; they didn't integrate in the tissues that well, and not all of them worked that well.

In the mid-1980s to early 1990s, 2 professors in Scandinavia—Dr Ulmsten and Dr Petros—came up with a different theory of how stress incontinence in women developed and a slightly different way of using slings to treat them. The big innovation was they moved the sling from the bladder neck area to the mid- to distal urethra. They tried a lot of different materials, and they finally found that a woven polypropylene mesh that had large pores actually worked quite well and was well integrated into the body.

Essentially, after trial and error with animals and eventually humans, they came up with what became known as the midurethral sling. The first one was called a TVT—a transvaginal tape. The idea was that this would be a procedure that could be done with minimal anesthesia—just some sedation and local. It was introduced in the mid-1990s.

Q. What makes the midurethral sling an innovation in the treatment of SUI?

A. ‘[T]he fact that you no longer have to do a big dissection to harvest the patient’s own tissue. People generally use some sort of fascia from the patient, and they would take it either from the leg, from the fascia lata, or they would make a prepubic or suprapubic incision to harvest a nice piece of fascia from the lower abdominal wall. [Although] that works very well and we still do that, it does increase, to some degree, the patient morbidity. There are physicians who aren’t as comfortable doing that, and there are some patients who don’t want to have a big surgery. Clearly, that surgery cannot be done under sedation in most cases.’
So introducing something...with a prefashioned sling, [something] we’re able to utilize with the patient in an ideal situation just under some deep sedation and local, really opened up the ability for many more women to be treated and allowed many more physicians to be trained and to utilize this technology.

Now, it is a little bit of a double-edged sword because there has been controversy in the past decade over the use of mesh. Much of the controversy applied more to large prolapse meshes, but there clearly were some concerns with the midurethral sling. There have been lawsuits. Some of this was based around how some people who started doing this had not been adequately trained. It was almost too easy to do, so they would do it; but I would suggest that there are nuances that really allow one who’s well trained to do a much better job.

As with anything, there are potential complications. [Some studies have looked] at potential complications between midurethral slings and fascial slings, and in the big picture, they’re very similar. There may be different types of complications, but the overall rates are similar. Again, as with anything, if you do enough of these, there can be some major complications. But I will say that the FDA reviewed the data and essentially came out years ago and were fine with them.

I will also say that most of the organizations that are involved in this area, from the American Urological Association to the American College of Obstetricians and Gynecologists, Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction (SUFU), American Urogynecologic Society (AUGS), and a lot of other organizations, have joined in on a position paper that goes over a lot of the details of the midurethral sling and supports it.

The most recent iteration of this was just published about 2 months ago. It was primarily sponsored by SUFU and by AUGS. It’s available online on a lot of different websites, and it was supported by many of these other organizations too. There are also different versions.

There is a version that is almost a physician statement that goes over what everyone thinks about this midurethral sling, and [there are] also FAQs for physicians as well as FAQs for patients. I keep them printed out and give these FAQs to my patients because they really go over everything: What is it made of? How is it done? What are the outcomes? What are the potential risks? What are the facts about lawsuits?...So it’s a very helpful item.

Q. How has the midurethral sling improved the treatment of SUI?

A. [Two] common treatments...were typically used prior to the midurethral sling. One was a retropubic bladder neck suspension, or otherwise called a Burch suspension, which entails going into the abdomen. It used to be an open abdominal procedure, so it had a lot more morbidity. Now a lot of people might do it laparoscopically or robotically. It’s a good operation for appropriate patients. The other operation was the autologous fascial sling, which again, is a good operation for many patients. But all of these are more invasive. Introducing something that...I would call, “less invasive [and] more reproducible” really opened treatment to many more patients.

Now again, as we touched upon, there has been some concern with mesh, and [some practitioners have] gone back to using [Burch suspension] or fascial slings for more of their patients. We still do use those procedures in select patients or perhaps for a patient who had a prior midurethral sling and had a complication or something of that nature.

But I think in the big picture, by introducing something that was much more step by step—you do A, you do B, you do C—made it much more straightforward and opened it up to many more patients to be successfully treated. As I mentioned, in certain respects, that’s a double-edged sword because it may have opened it up to some surgeons who may not have been ideal for doing this procedure. But overall, it’s been a very positive thing, and it’s really opened the door to [treat] many more patients.

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**FDA approves eCoin tibial neurostimulator for overactive bladder**

By Jason M. Broderick

The FDA has approved the eCoin leadless tibial neurostimulator for the treatment of urinary urge incontinence.1

The approval was based on results from a pivotal, open-label, single-arm trial that were previously published in the *Journal of Urology*.2 The eCoin device met the primary end point of the study by achieving at least a 50% improvement in urgency urinary incontinence in 68% of patients after 48 weeks of treatment.

"Under 5% of [overactive bladder] patients select burdensome third-line interventions due to invasiveness or potential side effects of available therapies and limitations in access, resulting in a staggering unmet clinical need. The effortlessness provided by the automatic nature of eCoin neuro modulation therapy will potentially better treat the vast population—often desperate for relief—who are not well managed by the current options available to them," Rebecca McCrery, MD, an investigator in the eCoin pivotal trial and urologist at Nebraska Medicine, said in a news release.

The eCoin device is a tibial neurostimulator that is the shape and size of a nickel. It is implanted in the lower leg under local anesthesia in an office or outpatient procedure by a urologist or urogynecologist. The procedure takes about 20 minutes.

**REFERENCES**

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Niraparib shows manageable safety profile in metastatic CRPC

Objective response was reached by 34.2% of patients with a BRCA mutation

JASON M. BRODERICK
Associate Editorial Director, Urology Times®

The PARP inhibitor niraparib (Zejula) demonstrated promising clinical activity in patients with metastatic castration-resistant prostate cancer (mCRPC) and DNA repair gene defects (DRDs), such as BRCA1/2 mutations, according to findings from the phase 2 GALAHAD trial (NCT02854436) published in the Lancet Oncology.1

At a median follow-up of 10 months, an objective response was reached by 34.2% of patients with a BRCA mutation and measurable disease. The median duration of response was 5.55 months.

“Niraparib is tolerable and shows antitumor activity in heavily pretreated patients with metastatic castration-resistant prostate cancer and DRDs, particularly in those with BRCA alterations,” wrote the study authors, led by Matthew R. Smith, MD, PhD, director of the Genitourinary Oncology Program at Massachusetts General Hospital Cancer Center and an associate professor of medicine at Harvard Medical School, Boston, Massachusetts.

In the multicenter, open-label, single-arm GALAHAD trial, investigators evaluated the efficacy and safety of niraparib in the treatment of adult patients with mCRPC and DRDs who had received treatment with next-generation androgen receptor (AR)—targeting therapies and docetaxel.

To be eligible for enrollment, patients with mCRPC had to be biomarker positive for DRD and have progressed on at least 1 AR-targeted therapy and at least 1 taxane-based chemotherapy. No prior PARP inhibition or platinum-based chemotherapy was permitted, and patients could not have had a prior diagnosis of myelodysplastic syndromes or acute myeloid leukemia.

Niraparib was administered at 300 mg once daily until end of treatment, and patients were followed up every 3 months until therapy was complete. The primary end point was objective response rate (ORR) of soft tissue (visceral or nodal disease), as defined by RECIST version 1.1 criteria, with no evidence of bone progression according to Prostate Cancer Working Group 3 criteria in those with biallelic BRCA mutations.

Overall, 289 patients enrolled in the trial between September 28, 2016, and June 26, 2020. Of these patients, 63% (n = 182) had been treated with at least 3 systemic therapies for prostate cancer. The final efficacy analysis included 77% (n = 223) of the enrollment population. Of this group, 142 patients had BRCA1 or BRCA2 mutations and 81 patients did not have BRCA mutations but did harbor 1 of the following non-BRCA DRD alterations: ATM, BRIPI, CHEK2, FANCA, HDAC2, and PALB2. Further, among the 142 patients with BRCA mutations, 76 had measurable disease. In the non-BRCA group, 47 of 81 patients had measurable disease.

Twenty-six (34.2%) of the 76 patients with a BRCA mutation and measurable disease had an objective response. There were 2 complete responses and 24 partial responses. Eight (31%) of the 26 responders remained in response at the time of data cutoff.

Among the 47 patients without BRCA mutations, the ORR was 10.6% (n = 5), and all responses were partial responses.

All 289 patients were included in the safety analysis population. Treatment-emergent adverse events (TEAEs) across all grades that occurred most frequently were nausea (58%), anemia (54%), and vomiting (38%). The most common grade 3 or higher TEAEs were anemia (33%), thrombocytopenia (16%), and neutropenia (10%). Two deaths caused by adverse events (urosepsis and sepsis) were potentially related to niraparib treatment.

Based on earlier findings from the GALAHAD study, the FDA previously granted niraparib a breakthrough therapy designation for the treatment of patients with BRCA1/2-mutant mCRPC who had previously received taxane-based chemotherapy and an AR inhibitor.

In the concluding remarks of their manuscript, the authors wrote, “These results suggest that niraparib has promising clinical activity with a manageable safety profile when administered as a monotherapy for treatment-refractory metastatic castration-resistant prostate cancer with BRCA alterations or select non-BRCA alterations. Such findings underscore the need for and importance of molecular testing to inform management, along with continued research to establish treatment paradigms with appropriately targeted therapies for patients with prostate cancer.

“Efforts to investigate and better understand predictive markers and signatures of both response and resistance to treatment with PARP inhibitors such as niraparib are needed to guide therapy selection and optimize treatment outcomes,” they added.

REFERENCE

Klein discusses how IsoPSA works for prostate cancer risk assessment

In this video, Eric A. Klein, MD, provides an overview of the IsoPSA test and how it works.
Genetic testing is lagging in prostate cancer

Less than 20% of patients reported undergoing testing

JASON M. BRODERICK
Associate Editorial Director, Urology Times®

A n international survey showed alarmingly low rates of genetic testing in patients with metastatic castration-resistant prostate cancer (mCRPC), according to results published in the journal Future Oncology.1

The investigators specifically assessed rates of testing for homologous recombination repair mutations (HRRm). The findings showed that despite approximately 75% of surveyed clinicians having access to genetic/genomic testing, only 18.1% of patients with mCRPC received HRRm testing.

“Overall testing rates were low, with physicians mostly testing patients they considered higher risk. Increased awareness and education are needed to encourage broader testing, to understand familial risk, and to identify patients with worse outcomes or those eligible for life-prolonging treatments,” wrote the authors, led by Andrea Leith of Adelphi Real World. Genomic testing in mCRPC has become critical with the emergence of PARP inhibitors such as olaparib (Lynparza) and rucaparib (Rubraca) for the treatment of patients with HRRm-associated mCRPC.

The study involved a real-world, point-in-time survey of oncologists, urologists, specialist surgeons, and their patients in the United States, Europe (EU5), and Japan. The surveys were completed between January 2020 and August 2020. Overall, 391 physicians completed surveys with questions about their genomic testing access/practice for patients with mCRPC. The investigators also collected 1913 patient forms.

Of the 391 physicians, 73.7% (n=288) reported that they had access to genetic/genomic testing; however, only 347 (18.1%) of the 1913 patients reported that they received HRRm testing.

The rates of HRRm testing were highest in the United States and Germany at 38% and 34%, respectively. The rates were much lower in the EU5, United Kingdom, and Japan at 16%, 6%, and 3%, respectively.

For all countries surveyed except Japan, BRCA1 (≥82% of patients) and BRCA2 (≥79%) were the most frequently tested genes. In Japan, the most commonly tested gene was ATM.

Across all patients, the HRRm positivity rate was 34%, which according to the investigators indicated that, “physicians were mostly testing mCRPC patients whom they considered higher risk, despite guideline recommendations for genetic testing for HRRm in all patients with metastatic prostate cancer.”

Across all regions, the most-cited challenge for conducting genetic testing was cost, noted by 167 (42.7%) of the 391 physician respondents. Another common barrier reported across all countries was “limited physician awareness of genomic/genetic testing for prostate cancer.” This was particularly an issue in Japan (42.2%) and the United Kingdom (40.5%). Specifically for US physician respondents, the most common barriers to testing reported were cost (50%), not reimbursed (26%), sending out for tests (25%), inadequate sample available (25%), and patient refusal (25%).

“Although advances in this area are still relatively recent and developing (especially in terms of approved treatment options and implementation of guideline recommendations for treatment and genetic/genomic testing), it is important to raise awareness of and access to HRRm testing for patients with mCRPC,” the authors wrote in their conclusion. “It is also important to consider potential challenges, including practical considerations for integrating genetic/genomic testing into clinical practice, and to explore solutions for overcoming those potential barriers.”

REFERENCE

UrologyTimes.com
Rate of prostate cancer is nearly 2 times higher in African American men

Persistent residual metastatic burden for African American men was observed

Results also showed that African American men were 29% more likely to receive a diagnosis of prostate cancer using a diagnostic prostate biopsy than White men (HR, 1.29; 95% CI, 1.27-1.31; P < .001). African American men who received treatment for prostate cancer experienced a lower risk of metastasis (HR, 0.89; 95% CI, 0.83-0.95; P < .001), whereas African American men classified as “other” race who received treatment were more likely to develop metastasis (adjusted HR, 1.29; 95% CI, 1.17-1.42; P < .001).

Furthermore, a persistent residual metastatic burden for African American men was observed across all National Comprehensive Cancer Network risk groups. In the low-risk group, 4 African American men experienced this burden per 100,000 vs 2 White men; in the intermediate-risk group, 13 vs 6, respectively; and in the high-risk cohort, 19 vs 9.

To the authors’ knowledge, this was the largest study to investigate racial and ethnic disparities across the range of prostate cancer statuses in an equal-access VA setting.

“There is a lot of work still to be done,” Yamoah concluded. “But [these] data [give] us the information we need to develop strategies to combat prostate cancer disparities here in the US and globally.”

REFERENCES
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Researchers hoping to improve outcomes in patients with locally advanced renal cell carcinoma (RCC) are increasingly focusing on the adjuvant and neoadjuvant settings.

For example, adjuvant pembrolizumab (Keytruda) was recently approved for the treatment of patients with RCC at intermediate or high risk of recurrence following nephrectomy, and further research is looking to bring this approach to therapy—not just with immunotherapy but also with targeted therapy—into practice ahead of nephrectomy to further prevent the risk of recurrence.

One such trial is the global phase 3 PROSPER RCC study (NCT03055013) examining neoadjuvant and adjuvant nivolumab (Opdivo) in patients with high-risk RCC scheduled for radical or partial nephrectomy. Naomi B. Haas, MD, is the medical oncology study monitor for the trial.

In an interview during the 2021 International Kidney Cancer Symposium, Haas, the director of the Prostate and Kidney Cancer Program and professor of medicine at the Hospital of the University of Pennsylvania in Philadelphia, discussed the potential of the neoadjuvant approach in treating patients with RCC as well as ongoing research in this setting.

**Q. Can you discuss the success of the neoadjuvant targeted/immunotherapy strategy in the treatment of patients with RCC?**

**A.** A number of VEGF TKI [tyrosine kinase inhibitor] approaches have been taken in the neoadjuvant setting. The general approach has been, given that cabozantinib [Cabometyx] is one of the VEGF TKIs, that it is thought to be one of the most active in RCC.

One of the challenges with VEGFR TKIs, in general in the neoadjuvant setting, has been that they interfere with wound healing to some extent. Cabozantinib has a half-life of about 5 days, so the timing of it has to be such that it can be administered, and then I allow enough time to stop [treatment so that] the patient can safely proceed with surgery but also not be off the drug so much that a rebound effect [occurs]. And I think we’ve seen with other trials that that is indeed possible.

The neoadjuvant approach has been an important approach for the immune checkpoint inhibitors. People [previously] have made comments without any data, only based on personal experience [about the efficacy of immune checkpoint inhibitors]. Several years ago, somebody stood up at a meeting and made the comment that there might be more scarring seen with immune checkpoint inhibitor therapy before surgery and that makes surgery difficult. [A couple of neoadjuvant phase 2 trials have shown] that it is a safe approach and [that] it hasn’t made surgery impossible in these patients because immune checkpoint inhibitor therapy doesn’t interfere with wound healing. And I think the concerns about things like pneumonitis and intubating a patient have not borne out—that increasingly people are feeling a little bit better about offering that as a neoadjuvant approach.

**Q. What are the key challenges with designing neoadjuvant trials in this disease?**

**A.** One of them is good coordination between the urology and the medical oncology teams. Usually the urologist is the first person to see the patients, so urologists have to be aware of neoadjuvant approaches and have to be willing to have that conversation with patients ahead of time to alert them to clinical trials. It’s not the standard of care right now to offer neoadjuvant [treatment] for RCC, but certainly, there’s a lot of surgical experience in urothelial malignancies and also in other disease sites, such as colorectal cancer and breast cancer, where it is common. One of the impediments is the urologist bringing it up to the patients.

The second is being able to coordinate care because generally these drugs are administered by a medical oncologist. So [it is the] speed in getting patients [to treatment that is key] and having a multidisciplinary approach. The other [challenge] is making a trial simple enough for the medical oncologist, the urologist, and the patient to all feel that it’s easily accomplished and easy to enroll.

**Q.** What are your expectations for neoadjuvant trial design going forward?

**A.** I think it’s not going to go away. I think that neoadjuvant therapy trials can also help to understand the biology of the tumors and who is benefiting and who isn’t benefiting from these approaches by doing some of the valuable correlative and molecular work that is needed. I think that one of the other take-home messages is that there’s still a relative lack of consensus, so we do need to wait for some of the bigger trials.

For example, the PROSPER trial is trying to address both the feasibility, the safety, and also the signal that is achieved by offering neoadjuvant therapy to patients. I think one of the other [important] messages is that we need to figure out how to address these kinds of trials so they’re available to everybody and not just at tertiary cancer centers.

**REFERENCE**

Newmark provides updates on oral testosterone undecanoate

Jatenzo is the first FDA-approved oral softgel formulation of testosterone undecanoate (TU) used to treat patients with a deficiency or absence of endogenous testosterone. In a recent study presented at the 2021 Sexual Medicine Society of North America Fall Scientific Meeting, Jay Newmark, MD, MBA, and coauthors reported promising findings on the first experiences of patients using Jatenzo in the real world. Newmark is the chief medical officer at Clarus Therapeutics in Northbrook, Illinois.

Q. Please discuss the background for this study.
A. Jatenzo is the first oral testosterone replacement therapy that’s been approved by the FDA in over 40 years. The previous product, methyltestosterone, was known to cause hepatotoxicity, and therefore is almost never used today. Jatenzo is formulated as a self-emulsifying drug delivery system and avoids the first pass effect through the liver. Owing to its unique mechanism of absorption, Jatenzo does not cause hepatotoxicity. Jatenzo comes in 3 softgel strengths and 5 dose options. We wondered, given the wide eugonadal range, which is generally accepted to be between 300 ng/dL and 1000 ng/dL, is dose titration necessary, or would a single-dose strength suffice? Our objectives were to assess the ability of any given dose of Jatenzo without dose adjustment to restore testosterone to the eugonadal range at steady state, then compare that with the real-world dose titration experience of patients treated with Jatenzo. We accomplished this by performing pharmacokinetic [PK] simulations using a robust population PK model developed for testosterone in 474 hypogonadal men who were treated with oral TU in prior PK studies. Testosterone levels were simulated following oral twice-daily dosing at a steady state with no dose adjustments. For each dose strength, we calculated the average concentration over a 24-hour period and the percent of subjects within the eugonadal range. We compared this [with] prescription data to evaluate the frequency of real-world dose titration.

Q. What were some of the notable findings of this study? Were any of them surprising to you or your coauthors?
A. We were surprised to see that [most of the] subjects in these simulations had testosterone levels within the eugonadal range for all 3 dose strengths. These range from almost 61% for the 237-mg twice daily dose up to 74% for the 396-mg twice daily dose, and these findings were consistent with some of our results in earlier phase 3 studies. In addition, mean testosterone levels increased by dose from 398 ng/dL for the 237-mg twice-daily dose up to 728 ng/dL for the 396-mg twice-daily dose. When comparing this [with] prescription data, we found almost 40% of patients had changed their dose within the first 6 months.

“We were surprised to see that [most of the] subjects in these simulations had testosterone levels within the eugonadal range for all 3 dose strengths.”

JAY NEWMARK, MD, MBA

Q. How does this research build on previous studies of oral TU?
A. In phase 3 studies, we found that over 87% of men were able to titrate their dose to the eugonadal range. This study expands on this by looking at dosing without titration and finds that [most] men on any of 3 dose strengths were able to normalize testosterone levels without the need for titration.

Q. What is the take-home message for the practicing urologist?
A. The treatment of male hypogonadism involves both normalizing testosterone levels [and] improving hypogonadal symptoms. Since any dose strength can normalize testosterone levels in most patients, having an option to titrate dose is likely necessary to optimize patient symptoms.

REFERENCE
Comparing PSMA and PET/CT imaging modalities

The past several years have seen myriad advances in prostate cancer imaging modalities. Steven Finkelstein, MD, and Louis J. Mazzarelli, MD, recently discussed a published head-to-head comparison of 2 prostate cancer imaging techniques in a UroView™ presentation. The manuscript by Birgit Pernthaler, MD, and colleagues, compared ¹⁸F-fluciclovine (Axumin) and ⁶⁸Ga-PSMA-11 (Gallium Ga 68 PSMA-11) in PET/CT imaging from a sample of 58 patients with recurrent prostate cancer.¹

“A local recurrence can occur at the site of the primary tumor in the prostate. However, the accurate detection of prostate cancer remains a challenge. Classically, we haven’t had the best imaging available.”

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“Some common sites of recurrence after a total radical prostatectomy include the vesicourethral anastomosis, the urinary bladder neck, and the rectovesical space,” said Finkelstein, a radiation oncologist with Florida Cancer Affiliates in Panama City, part of The US Oncology Network. “A local recurrence can occur at the site of the primary tumor in the prostate. However, the accurate detection of prostate cancer remains a challenge. Classically, we haven’t had the best imaging available.”

“Conventional imaging had many limitations with respect to the ability to identify recurrent prostate [transit-amplifying] cells,” said Mazzarelli, a diagnostic radiologist at Lawrence + Memorial Hospital in New London, Connecticut, part of the Yale Health Network. “CT scans, Mazzarelli continued, were not previously useful for imaging the prostate and surrounding areas. “Not uncommonly, over the last 15 years that I’ve been practicing, before the advent of incredibly exciting molecular imaging techniques, we were asked to identify prostate recurrence in patients with low or even high PSA [levels], and we weren’t able to do that with conventional imaging,” Mazzarelli said. “We weren’t able to see the anatomy locally.”

Newer methods, such as the advent of the 2 radiotracers, represented a huge change, Mazzarelli explained. “Of course, ¹⁸F-fluciclovine was the first, and now ⁶⁸Ga-PSMA-11 is available,” he said. “It’s an exciting time.”

Mazzarelli and Finkelstein focused their conversation on findings from the study by Pernthaler et al, which indicated that ¹⁸F-fluciclovine detected prostate cancer recurrence at a rate of 79.3% vs ⁶⁸Ga-PSMA-11 at 82.8% (P = .64).

“In terms of the physiology, ⁶⁸Ga-PSMA-11 and Axumin are different in the sense that ⁶⁸Ga-PSMA-11 has a PSMA-directed targeting membrane whereas Axumin is an amino acid–based compound,” said Mazzarelli. “Therefore, the physiology in the body will be different. When we look at ¹⁸F-fluciclovine, we look at background uptake in muscle and bone and much less genitourinary or urinary excretion. When we look at PSMA, we look at an agent that has more urinary excretion but is more sensitive with respect to uptake within bone and soft tissues.”

“A key takeaway from the paper, Finkelstein said, was “the advantage of ¹⁸F-fluciclovine in detecting curable, localized metastases, and bone metastases at lower rates than ⁶⁸Ga-PSMA-11. However, Pernthaler and colleagues wrote that these differences were not statistically significant (Table).³

A key takeaway from the paper, Finkelstein said, was “the advantage of ¹⁸F-fluciclovine in detecting curable, localized metastases, and bone metastases at lower rates than ⁶⁸Ga-PSMA-11. However, Pernthaler and colleagues wrote that these differences were not statistically significant (Table).³

RADIOTRACER PERFORMANCE

All 58 patients in the study had undergone either surgery or radiation therapy, and their median age was 70.1 years (range, 53-85). Patients had mean PSA levels of 14.9 ng/mL (range, 0.2-230.4) at the time of their scans and 16.6 ng/mL (range, 2.4-79.2) at the time they received their diagnosis.

The most common tumor stages were T3/T4 (57%), followed by T1/T2 (29%) and not determined (14%). Most patients had no nodal involvement (57%), 21% had undetermined nodal involvement, 19% had nodal status N1, and 3% had Nx nodal status. Approximately one-third (34%) had no metastases and 52% had undetermined metastases.

Although the 2 methods detected recurrence at similar rates overall, ¹⁸F-fluciclovine detected local recurrence in 37.9% of the overall sample of patients compared with 27.6% with ⁶⁸Ga-PSMA-11.

On the other hand, ¹⁸F-fluciclovine detected local pelvic lymph node recurrence, extrapelvic lymph node metastases, and bone metastases at lower rates than ⁶⁸Ga-PSMA-11. However, Pernthaler and colleagues wrote that these differences were not statistically significant (Table).³
disease in close anatomic relation to the urinary bladder, whereas 68Ga-PSMA-11 fails because of accumulation of activity in the urinary bladder. However, 18F-fluciclovine is almost equivalent to 68Ga-PSMA-11 in detecting distant sites of prostate cancer,” he noted. “For most situations outside the urinary bladder area, 68Ga-PSMA-11 was superior.”

Mazzarelli commented that some nuance was necessary to interpret the results.

“That needs to be considered when we think about these radiotracers, because one radiotracer, we believe, outperforms the other when it comes to outside the [prostate] bed,” Mazzarelli explained. Specifically, future studies should focus on perfecting a technique for using both agents, he suggested.

“How would we optimize 68Ga-PSMA-11 or 18F-fluciclovine PSMA to perform better locally?” Mazzarelli continued. “One thing you do is acquire images—as some institutions have, like my own—beginning with the thighs going toward the vertex. You decrease the amount of radioactive tracer within the bladder. From a PSMA perspective, you have the patient void when they come to the imaging facility and right before getting onto the scanner.”

**IMPLICATIONS FOR THE FUTURE**

Both experts agreed that the paper carried implications for advancing the understanding of heterogeneity within the larger context of prostate cancer.

“We’re heading toward a theragnostic world where we’ll be able to use small molecule targets to identify small volume of disease by a PSMA study because most agents being developed are PSMA based,” said Mazzarelli. “How does that affect a patient who has a 18F-fluciclovine study that is positive for lesions that the PSMA study doesn’t pick up? I believe these patients have some degree of heterozygosity. How that is impactful for the patient is another question.”

Finkelstein added that the findings showed promise in developing tailored treatments for patients based on the individual characteristics of their recurrence.

“We’re heading toward a theragnostic world where we’ll be able to use small molecule targets to identify small volume of disease by a PSMA study because most agents being developed are PSMA based.”

**LOUIS J. MAZZARELLI, MD**

**“We’re heading toward a theragnostic world where we’ll be able to use small molecule targets to identify small volume of disease by a PSMA study because most agents being developed are PSMA based.”**

“Being a radiation oncologist, the theragnostic [implications] are exciting to me,” Finkelstein said.

“We’re able to take images to see exactly where there’s evidence of cancer recurrence and provide the right personalized therapy to target those sites of disease using radiation modalities,” he added.

Finkelstein also noted that the increasing usage of piflufolast F 18 (18F-DCFPyL; Pylarify) for PET imaging following its FDA approval in 2021 is bound to shed new light on imaging for prostate cancer recurrence.2

“A limitation previously had been where you could get gallium scans,” Finkelstein said.

REFERENCES


Update on saw palmetto in lower urinary symptoms secondary to BPH

Benign prostatic hyperplasia (BPH) is a very common condition for which many types of treatments exist, ranging from medications to minimally invasive surgical techniques. But despite a recent surge in the number of available treatments for this condition, a need exists for therapies that are “based on herbal medicine or alternative treatments,” according to Bilal Chughtai, MD, who spoke about this topic during a recent UroView™ program. Chughtai is an associate professor of urology at Weill Cornell Medicine and an associate attending urologist at NewYork-Presbyterian Hospital in New York, New York.

“When it comes to supplements, I can tell you from personal experience that patients are always very interested,” he said. “They inquire whether there are things that can help modulate or reduce the burden of...disease or reduce progression. Are there things that they can do with their diet to improve their condition as well? There's definitely a clear need for alternative therapies when it comes to BPH.”

The current market for alternative and complementary medicine for BPH is quite large. Chughtai said an Amazon search will return approximately 30,000 products, ranging from Serenoa repens, also known as saw palmetto, to pygeum to stinging nettle. Saw palmetto, he noted, is one of the best-studied supplements for prostate health.

“Ultimately, saw palmetto has a very compelling mechanism of action in a couple of different ways,” he said. “The first is that it can help modulate the androgen receptor signaling, helping to reduce the conversion of testosterone to dihydrotestosterone, which is a much more potent form of testosterone.

“The second mechanism...is that it may help with the inflammatory signal pathway. As we know, as prostates enlarge, there's definitely an inflammatory component to it. This inflammatory component can come from a multitude of reasons, whether it's subclinical infections, natural parts of aging, or the fact that you have this imbalance of apoptosis and proliferation. This leads to free radicals that can attract different lymphocytes. When you have these lymphocytes present, this may lead to more inflammation. Saw palmetto may actually help with reducing this inflammatory pathway as well.”

**EXTRACTION METHODS**

Saw palmetto can be extracted multiple ways, according to Chughtai. One such method is through the use of hexane; Permixon is a hexane-derived saw palmetto compound.

“Unfortunately, hexane has been linked, especially in high doses, with a possible carcinogenic effect,” Chughtai said. “Therefore, hexane-derived saw palmetto is not really available in the United States, although the amount of hexane in any of these supplements is minuscule.”

Another method is supercritical carbon dioxide extraction, or an ethanol extraction. “With each extraction method, you get a different fatty acid signature,” Chughtai explained. “Ultimately, when you look at the ethanol derived or the hexane derived, you can have the appropriate fatty acid signature that can end up leading to a more active compound for the saw palmetto.”

Chughtai pointed out that saw palmetto supplements are not regulated in the US market, so it can be very difficult to ascertain the variables from a given bottle, such as how the saw palmetto was extracted, how ripe the berries were, and whether batch-to-batch variation is present. The US Pharmacopeia (USP) is an independent, not-for-profit company that seeks to “help standardize and enrich the supplement market,” Chughtai said.

“This is done by standardizing labeling [and] what's in the bottle and [by] ensuring that the compound you have is what it is and there are no harmful additives or other components,” Chughtai said. Currently, the only USP-verified saw palmetto product is sold under the brand name Flomentum.

Like USP, the European Pharmacopoeia works to ensure patients receive standardized compounds. In Europe, Chughtai said, it’s common to use saw palmetto compounds in patients with lower urinary tract symptoms (LUTS) secondary to BPH. In the US, however, the American Urological Association (AUA) does not recommend the use of supplements for LUTS secondary to BPH.

“[The AUA] stance is that it’s a relatively unregulated market,” Chughtai said. “If you look at the studies that have been done with most of the supplements, there isn’t a clear-cut standardization. The data have been mixed at best, especially when you look at trials such as CAMUS [NCT00603304] or STEP.”

“We should be able to guide our patients, to some degree, on what supplements have the most promising data or have the highest chance of working. At the same time, we must ensure that we’re following the standard of care for our patients and providing high-quality care for them.”

BILAL CHUGHTAI, MD

With many of the studies of saw palmetto, Chughtai explained, there wasn’t a complete standardization of the compound being used. Another factor with these studies was “the absence of clear-cut entry criteria and exactly how patients fell off,” Chughtai said. “Ultimately, when you take a very heterogeneous group, a lot of times you lose signals, making it hard to determine exactly how this compound would be helpful. When it comes to the clinical trial data as a whole, unfortunately, the data have been mixed.”

In the case of *S repens*, Chughtai noted that the data are promising for the compound’s ability to help with LUTS secondary to BPH; some
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of the data are even comparable with those of medications such as α-blockers and 5α-reductase inhibitors. Two European studies both reported on the efficacy of S. repens for improving LUTS secondary to BPH,1,2 and a recent 3-part global review of the English and non-English-language literature showed that “[lipidosterolic extract of S. repens] efficacy is the predominant finding in clinical trials.”3-5

S. repens has no contraindications for its use, although Chughtai urged caution when using the treatment “to ensure that patients are screened and fall under the correct category.” He explained that patients should have mild symptoms, an International Prostate Symptom Score of 8 to 13, a maximal flow rate of approximately 15, and “a not very high” postvoid residual volume.

HIGH SAFETY PROFILE
Regarding safety, Chughtai said that S. repens has a “very high safety profile,” with the most common adverse event being gastrointestinal upset (likely occurring in approximately 1% of patients).

“Ultimately, when it comes to a compound that’s able to preserve sexual function, minimize changes for the patient, but improve lower urinary tract symptoms, Permixon has shown exquisite safety,” Chughtai said.

When it comes to discussing supplements with patients, Chughtai said that although the conversation is “very complex,” it can give providers a valuable opportunity to build a strong relationship. He highlighted the importance of suggesting high-quality supplements that have been independently evaluated by the USP.

“When it comes to supplements, as physicians, it’s important for us to have some understanding of them,” he said. “We should be able to guide our patients, to some degree, on what supplements have the most promising data or have the highest chance of working. At the same time, we must ensure that we’re following the standard of care for our patients and providing high-quality care for them.”

REFERENCES

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Novel immunotherapy agents emerge in the treatment of bladder cancer

Urology Times® Viewpoints program brings together expert panels for in-depth discussions on key clinical topics. In this discussion, 5 clinicians discuss the emergence of novel immunotherapy agents for treatment of bladder cancer, including increased administration in community urology practices, and recommendations for sequencing newer therapies into treatment algorithms. What follows is an edited excerpt of that panel discussion. The panelists included moderator Leonard G. Gomella, MD; Sam S. Chang, MD, MBA; Karim Chamie, MD, MSHS; Matthew Galsky, MD; and Petros Grivas, MD, PhD.

GOMELLA: We're going to talk about non–muscle-invasive bladder cancer first, and I'd like to ask Dr Chamie to comment a little bit about the factors that you consider, particularly with the patient with high-risk non–muscle-invasive bladder cancer. What are the factors that you look at when you're considering how you're going to be treating this patient?

CHAMIE: Patients with high-risk non–muscle-invasive bladder cancer have high-grade T1 or CIS [carcinoma in situ] or have had multiple recurrences of high-grade disease. The things that I account for as far as offering treatment options would be tumor grade, BCG responsiveness, time to recurrences from BCG, and multifocality—sometimes you can pick up variant histology. Those are all factors that play a role.

As far as subsequent treatment options, it’s based on those factors. So if a patient has high-grade T1 or a multifocal CIS, those are the patients that I'm going to give BCG for 3 years based on the SWOG [Southwest Oncology Group] protocol of induction and maintenance. Those are the patients that I'm going to try to prioritize as far as trying to get them a full dose of BCG if possible. If patients may not have access to full-dose BCG, we try to get them onto a clinical trial that does.

For instance, there is the N-803 study [NCT04340596], where patients are offered full-dose BCG for BCG-naive patients, either BCG plus N-803 or BCG alone. There's the CheckMate 7G8 study [NCT04149747] of nivolumab [Opdivo] plus BCG vs BCG alone. There's the KEYNOTE-676 study [NCT03711032] of pembrolizumab (Keytruda) plus BCG vs BCG alone. There are multiple studies, including Pfizer's anti–PD-1 plus their IDL [intermediate density lipoprotein] inhibitor. There are a number of other drugs that are actually being rolled out in this disease space. This is a wonderful opportunity for patients to get a full dose of BCG if they're interested in getting into cutting-edge clinical trials.

As far as BCG-unresponsive disease, there are a number of clinical trials in this disease space. Most have tried and failed. Pembrolizumab gained FDA approval based on the KEYNOTE-057 [NCT02629961] study, in which we found 41% of the patients had a complete response at 3 months. And if you follow these patients at a year, half of those with a complete response maintain that complete response. We find that if they go 6 to 9 months without a recurrence, they tend to remain disease free. We found that two studies published in Lancet Oncology a couple of years ago. Bristol Myers [Squibb] is also looking at the CheckMate 9UT study [NCT03519256] in this disease space. Urologists are probably going to end up offering patients with BCG-unresponsive bladder cancers one of these drugs if patients are unwilling or unfit to undergo a radical cystectomy or are unwilling to undergo radiation therapy.

GOMELLA: Dr Grivas, could you talk about nonmetastatic muscle-invasive bladder cancer?

GRIVAS: Thank you. I can tell you that at the University of Washington, Seattle Cancer Care Alliance we have a multidisciplinary bladder cancer clinic, which is a time-efficient wonderful ‘one-stop-shop’ for patients. We have attendings and trainees from urologic oncology, medical oncology, radiation oncology, radiologist, pathologist, ostomy nursing, advanced practice providers, research and clinic coordinators. We see each patient in a very comprehensive way. We evaluate films/scans and pathology slides. We look at all those aspects of care, considering performance status, organ function and medical comorbidities. I can tell you that this is a really comprehensive evaluation resulting in a very concrete treatment plan for the patient in a very efficient manner. Most patients with muscle invasive bladder cancer end up having radical cystectomy with pelvic lymph node dissection, preceded by cisplatin-based chemotherapy in fit patients, that has level 1 evidence. We try to implement that level 1 evidence using cisplatin-based neoadjuvant chemotherapy in fit patients. In our experience 10% to 20% of select patients may end up going for bladder preservation based on clinical criteria that we use.

We definitely incorporate the guidelines, such as NCCN [National Comprehensive Cancer Network], ASCO [American Society of Clinical Oncology], AUA [American Urological Association], in our decision-making process and we individualize treatment based on several patient- and cancer-related characteristics. For example, for bladder preservation, we take into account the size and location of the tumor, as well as the number of tumors. Is it in the trigone area blocking the ureter causing hydrourephrosis; is there diffuse carcinoma in situ or extensive variant histology? Also, we look at the bladder function and capacity, and the symptomatology from the bladder, as well as prior therapies—all those factors come into play in this multidisciplinary decision-making process.

The other consideration is the ongoing clinical trials. That’s what we consider both in the neoadjuvant/adjuvant/metastatic setting and also in the setting of bladder preservation. SWOG 1806...
[NCT03775265] is a good example that many of us are participating in. This trial is supported from the NCI National Clinical Trials Network (NCTN) is evaluating concurrent chemoradiation plus/minus atezolizumab [Tecentriq], an immune checkpoint inhibitor, after maximal resection of the bladder tumor (via TURBT). This clinic represents a great opportunity to improve upon our clinical trial offerings to patients and incorporate clinical trials as options along with the standard of care discussions. In that context, we’ll discuss neoadjuvant therapies, adjuvant therapies; even if someone gets therapy off trial, we discuss that in great detail. We may also discuss about adjuvant clinical trials and nivolumab [Opdivo], which is now an FDA-approved option in the adjuvant setting based on the Checkmate 274 phase III trial. Thus, all these various treatment discussions and considerations take place in the context of our multidisciplinary clinic.

**GOMELLA:** Dr Chang, what is the urologist’s view on immuno-oncology agents in bladder management?

**CHANG:** As with almost every disease process that we treat—prostate cancer, renal carcinoma, bladder cancer—we need to go beyond just resection and removal. It took us a long time to get on the bladder cancer neoadjuvant chemotherapy train, and we’ve improved with that. But with trials that have shown a benefit to adjuvant therapy, such as nivolumab following cystectomy in patients with or without chemotherapy beforehand, clearly, we need to involve our oncology colleagues in not only a neoadjuvant but also an adjuvant setting. Importantly, there are trials that are open looking at immuno-oncology therapies either by themselves or in combination with chemotherapy that perhaps would give us benefit in the perioperative setting.

There are also combinations of such things as enfortumab [vedotin-ejv (Padcev)] and pembrolizumab that are being looked at neoadjuvantly, followed by cystectomy and then additional therapy afterward. Unquestionably, radical cystectomy as the single modality can be curative for certain patients—that’s still a truth—but the majority of patients will benefit from some form of combined therapy and may ultimately not require cystectomy.

**GOMELLA:** Dr Chang, what’s your perspective on the advances in treatment of all sorts of urothelial carcinomas over the last a couple of years from the urology standpoint? What do you think the real major advances have been?

**CHANG:** It’s been mind-blowing. We rarely didn’t have early guidelines when establishing the treatment protocols with BCG. And now in terms of options, the treatments, innovations, and interventions for all advanced cancers have exploded. [It started] with prostate cancer and kidney cancer, now with bladder cancer in terms of combinations of therapies, timings of therapies. It can be confusing, I think, for a urologist in terms of the amount, complexity, and sometimes conflicting data.

For me, the biggest breakthroughs are: [No. 1]: We have options for cisplatin-ineligible patients, which we’ve never had before. Being able to offer something that may actually show benefit is significantly a huge improvement. Two, the adjuvant interventions like avelumab [Bavencio] after chemotherapy and nivolumab following cystectomy are a huge advantage and change in paradigm in terms of alternatives for patients with more advanced disease.

I think now the next big wave will be what’s going to be the best neoadjuvant treatments prior to cystectomy, and importantly, concurrent therapy and bladder-sparing modalities.

**GOMELLA:** Dr Galsky, what are your thoughts on these advances in recent years?

**GALSKY:** I would agree with all those comments. I would add the ability to achieve durable responses, albeit in a subset of patients with metastatic disease, that can last years. Seeing that many patients who often have limited [adverse] effects from treatment has been a huge advance. The development of the first small molecule directed against a recurrent mutation in patients with metastatic bladder cancer is another advance. A precision treatment directed against an activating mutation, a receptor tyrosine kinase, FGFR3 alterations—that’s a major advance and a proof of concept in this disease. ctDNA [circulating tumor DNA] is going to be paradigm shifting in terms of how we incorporate multimodality treatment across various disease settings.

**GOMELLA:** So you’ve all alluded to what Dr Galsky touched upon as we move into second-line therapies for the mutational and biomarker profiles in bladder cancer. Dr. Galsky, can you comment a little bit more about that—how these analyses might be guiding you in the future, particularly the second-line therapy?

**GALSKY:** There are a lot of recurrent genomic alterations in urothelial cancers, and some of the pathogenic consequences of these alterations we understand much better than others. And unfortunately, to date, only one is really treatment informing, [and] that is alterations in FGFR3, which can be associated with sensitivity to an orally bioavailable small molecule inhibitor of this activated receptor tyrosine kinase. We are doing genomic testing on all patients with metastatic disease because now we do have a molecular alteration that is “actionable,” that informs how we treat patients. The concept will be valuable in the future when we uncover additional alterations linked to specific treatment responses.

**ABOUT THE PANELISTS**

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**UrologyTimes.com**

(MARCH 2022 | 35)
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Contraindications
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For this month’s Diversity in Urology column, Urology Times spoke with gender-affirming surgeon Geolani Dy, MD, about her experience pursuing health care for a marginalized population of patients. She discusses why urologists should consider the issues that transgender and gender-diverse people face outside the clinic when providing care, and how they can build a more inclusive practice for these patients. Dy is an assistant professor of urology and plastic and reconstructive surgery at Oregon Health & Science University in Portland, Oregon. She has also led the creation of the Transgender and Non-Binary Allied Research Collective (TRANS-ARC) and coleads Urologists for Equity.

Q. What does diversity, equity, and inclusion mean to you?
A. Principles of diversity, equity and inclusion can be applied to any setting. To share some commonly accepted definitions, diversity is the range of human differences, including what we can see on the outside and what is not visible to others, including gender identity, sexual orientation, socioeconomic status, things that really influence our identities and experiences but aren’t immediately visible. Equity is fairness and impartiality, considering the barriers that may disproportionately disadvantage certain groups over others, and being able to address those. Finally, inclusion is creating inclusive environments and spaces so that the people who enter those spaces feel welcome, valued, and heard.

And so, DEI in health care can be applied everywhere, from the clinical setting, how we treat patients, to creation of our workforce, training a new generation of urologists and other health care providers to embody those principles as well.

Q. What motivated you to go into the field of gender-affirming care?
A. I had always wanted to be a surgeon. My dad was a plastic surgeon and since [the age of] 3 I said that I wanted to be a surgeon too. I felt a strong calling as I moved through my education to serve marginalized communities. I had been introduced to trans health and gender-affirming surgery in bits and pieces throughout med school and residency, and after digging into the needs of the trans and gender diverse community outside of structured learning opportunities, I realized that this was a community I really wanted to learn about and serve as a surgeon. I grew up in the Bay Area in California and through family friends [I] saw trans people in my life earlier on. I think that some of the earliest informal exposure to queer communities may have helped set the stage.

Q. Can you describe the scope of issues surrounding transgender health care today?
A. We are at a crossroads as far as trans health goes in the United States….There seems to be broadening social acceptance overall and more clinicians who are stepping up to provide gender-affirming therapies, yet at the same time [there are] threats of legislation that would restrict access to care and too few providers to meet demand for gender-affirming care.

We need to keep in mind that overall, trans communities are still significantly marginalized. There’s stigma and discrimination…in general society but also in health care settings, which really influences people’s mental health and general well-being. So thinking beyond access to gender-affirming care, which we’ve seen is associated with improvements in quality of life and mental health, we do need to think about those other aspects, [such as] physical safety, shelter, [and] job security. There are so many broader issues that affect the trans community outside of what may come up in clinical interactions.

Q. How can urologists and other health care professionals promote the voices of transgender patients inside and outside the clinic?
A. I think it is important to be aware that for every patient that you see in clinic who identifies as trans, there are many more who aren’t able to access this care or [who] face even more significant barriers to getting to the doctor’s office. [Also, it is important] to provide an affirming environment, regardless of whether a patient is coming to you for voiding dysfunction, kidney stones, evaluation of hematuria, or orchiectomy, which might be the first step in their surgical journey.

There are many ways to provide an affirming environment in urologic care. What we are working toward is having more trans representation within health care teams—trans urologists, APPs [advanced practice providers], nurses, medical assistants, and schedulers. There are other immediate actions you can take to educate your staff in trans health—basics [such as] Who are trans and gender-diverse people? What do these terms mean? What are pronouns? Having staff wear those on their badges or…pins [and] creating clinic signage and literature that represents a variety of genders outside the binary, if possible, can create a more inclusive space. Having gender-neutral bathrooms, asking someone what their pronouns are and utilizing their chosen name and pronouns throughout visits and documentation, providing a variety of gender identity markers on clinical intake forms, and utilizing questionnaires that are appropriate for someone’s gender identity—all of these are important. In the urology setting, a lot of times we’ll have patient questionnaires that are very gendered; however, realizing that some women who seek your care may have prostates too, and being able to address that appropriately in clinic, is important to creating an affirming space. And then, I think, the key is using trauma-informed principles in all clinical interactions. That means [recognizing] that living in this society as a trans person will have associated traumas, especially in health care settings. Being aware of that, working to create a space of physical and emotional safety, offering choice and empowerment in clinical interactions, and then focusing on strength and resilience are some trauma-informed care principles that you can apply.
What is the role of prostate-specific antigen screening in your practice?

I like to get a baseline PSA [prostate-specific antigen] [level] for patients in their 40s, particularly if they’re seeing me for a prostate issue. As patients get into their 70s, I start the conversation about stopping PSA testing because it loses value.

If a PSA level goes up and, as importantly, if there’s a change in PSA velocity, we may do a course of antibiotics, then recheck the PSA. It may come down because inflammation was involved. If it doesn’t, the patient has time to adjust to the idea of a biopsy.

We don’t want to go back to the days before PSA testing because then we clearly saw much more advanced disease with much less we could do about it. The PSA has been valuable, but as with any other tool it may be overused at times or misunderstood.

The PSA screenings we used to do in September—big events getting men who wouldn’t come in otherwise—have fallen by the wayside, reasonably so, because in the last years of those screenings, many men already had had [their PSAs checked] and were just coming for a second one.

There’s been a shift in the individuals getting treated for prostate cancer. They’re living a better quality of life, provided we catch them early enough.”

Sherman M. Hawkins, MD
Goldsboro, North Carolina

I use PSA testing to make sure patients with high-risk prostate cancer, specifically, and advanced prostate cancer, or even metastatic prostate cancer, don’t go undiagnosed. Prostate cancer remains the No. 2 or No. 3 cancer killer of males in America. So PSA is an important adjunct to DRE [digital rectal exam] in efforts to give those patients a diagnosis earlier. We don’t get as clear a benefit with intermediate- and low-risk prostate cancer.

Every patient with urinary issues should have a physical exam, including a DRE. The PSA should be considered at age 40, even in the absence of risk factors, and absolutely at 40 with risk factors—positive family history, African American individuals, genetic predisposition. Then we can talk about monitoring frequency.

I follow the guidelines. Being mindful, a really healthy 70-year-old man may live to age 95. Anybody in practice 25 years knows our patient demographic has changed. Patients used to be in their 60s. Now they’re routinely in their 70s and 80s, if not 90s. I would like consensus among urologists that high-risk prostate cancer in otherwise healthy males should be treated.

Do I do PSAs on patients older than 70? Yes. Annually? As a rule, no.

PSA shouldn’t be considered simply a screening test; it’s actually part of the diagnostic work-up. If a patient is 80 years old and has trouble urinating, PSA helps ensure it’s not advanced prostate cancer that I might have missed as a result of not doing PSA testing.

I’m using PSA as I always have. I followed patients with lower-risk cancer before it was recommended. Simple math showed that most of our patients weren’t dying of prostate cancer.”

Mark K. Plante, MD
Burlington, Vermont

Most men are being referred to me because their PSA levels started increasing. Anyone with prostatic symptoms, voiding symptoms, etc., warrants a PSA check. If the PSA [level] falls within range for the age group, I may recheck it right away or in 3 months to determine the trajectory of the PSA levels and whether there’s a need for further investigation.

Nowadays, if some of our primary care doctors see an elevated PSA [level] or abnormal DRE [result], they’ll order an MRI. It’s not common among primary care doctors, but ours do it because they know the MRI is being utilized more in prostate cancer screening. Often patients come to me, as a robotic surgery specialist, already prescreened with a PSA level and/or an MRI.

MRIs help catch intermediate- to high-risk prostate cancers more likely to benefit from treatment vs lower-risk [cancers] you should probably just watch with active surveillance.

We still follow patients with a negative MRI or biopsy, just not as closely, to make sure their PSA isn’t increasing at an alarming rate. I’ll probably do a PSA test every 6 months for a couple years, then push it out further if the PSA level stabilizes.

Typically, if someone comes in with an elevated PSA, I recheck to make sure it’s a true value, then get PSA levels every 3 months to determine data points to check the trajectory of the PSA’s velocity, whether it’s increasing at an alarming rate or it’s steady and their PSA is always high.

Coupled with their physical examination, family history, race, those are all factors included in determining how to manage people.”

Layron Long, MD
Corvallis, Oregon

Exercise confers benefits for prostate cancer-specific anxiety

In this interview, Kerry S. Courneya, PhD, discusses the background and notable findings of the recent Journal of Urology study, “A Randomized Trial of the Effects of Exercise on Anxiety, Fear of Cancer Progression and Quality of Life in Prostate Cancer Patients on Active Surveillance.” Courneya is a professor and Canada Research Chair in physical activity and cancer and director of the Behavioral Medicine Laboratory and Fitness Center at the University of Alberta in Edmonton.

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The urologist in the world of precision medicine

Over the past few years, and particularly the past 12 months, we have witnessed the inclusion in the common parlance of prostate cancer the term precision medicine in the management of advanced disease. What exactly is precision medicine? When we launched LUGPA approximately 15 years ago, we struggled with defining the inherent advantages of defining what a large, vertically integrated, single-specialty group brought to health care and our patients. One of the original board members put it very simply: cheaper, faster, and better.

Often, we use the terms personalized medicine and precision medicine interchangeably. I believe all medicine is personalized. We make a diagnosis, consider pertinent details of the individual’s medical history that will influence our decision-making, and prescribe the appropriate therapy accordingly. It is not a one-size-fits-all approach. The National Cancer Institute formally defines precision medicine as “a form of medicine that uses information about a person’s own genes or proteins to prevent, diagnose, or treat disease.”

To break it down more simply: the correct therapy for the correct patient.

In general, we have managed all our genitourinary malignancies based on histopathologic criteria. Urothelial vs squamous vs adenocarcinoma of the bladder. Seminoma vs non-seminomatous germ cell of the testes. Obviously, for prostate cancer, it has been based on the redefined Gleason Score and Grade Group. For decades, we have recognized the hormonal influence and its effect on prostate cancer growth and progression. The past decade has led to a better understanding of the role of the androgen receptor (AR) and its mutagenicity to maintain function in advanced disease with subsequent development of newer, more novel molecules directed at the AR axis. However, all patients with progressive disease are started on baseline androgen deprivation therapy. We do not routinely measure for expression or activity. It is the foundation and fundamental to the management of disease that has been in practice for decades.

Contrast to our colleagues who manage breast cancer (another endocrine-driven cancer akin to prostate) where the histology is clearly important, but molecular expression of multiple receptor types will determine therapy. It is the standard of care before initiating treatment and how family members should be potentially screened and evaluated for risk. In fact, the presence of certain germline mutations (ie, BRCA1) may predict the risk of the molecular pattern (triple-negative receptor status). Over the past 8 years, we have tried to bridge this deficit and gain a better understanding of molecular drivers, especially as more agents are being used earlier in the disease spectrum and downstream mutations are the result. We must better educate ourselves on what they are, what insight can be gained, the timing of when to incorporate, and perhaps most importantly, what the limitations are.

Over the past few years, the menu has expanded and added more into our lexicon for prostate cancer: AR splice variants, proprietary somatic gene signatures, circulating tumor cells, cell-free DNA, DNA damage repair genes (encompassing both mismatch repair and homologous recombination), tumor mutation burden, prostate-specific membrane antigen, and beyond. For the most part, they all have value, and the question is how to best incorporate them into our practice to best manage our patients, whether it be newly diagnosed or those with progressive disease? To do so, we must take the time to understand how they all differ and what is actionable to prescribe appropriate next line of therapy—the correct therapy for the correct patient.

In conclusion, the urologist in the world of precision medicine must take the time to understand how different modalities differ and what is actionable to prescribe appropriate next line of therapy—the correct therapy for the correct patient.
Moving transperineal prostate biopsy into the clinic

Learning curve for technique is short, but capital expenditures are required

ASHLEY E. ROSS, MD, PHD; AND EDWARD M. SCHAEFFER, MD, PHD

Ross is an associate professor of urology at the Northwestern University Feinberg School of Medicine in Chicago, Illinois. Schaeffer is a professor of urology at the Northwestern University Feinberg School of Medicine in Chicago, Illinois.

The diagnosis and management of prostate cancer remains a large part of virtually all urology practices. Prostate-specific antigen screening dramatically increased the number of men presenting with suspicion for prostate cancer, and transrectal ultrasound (TRUS)-guided prostate biopsy became routinely performed in our clinics.1,2 Over the past decade, it became clear that the diagnosis of clinically significant prostate cancer should be prioritized, as well as the development and implementation of fluid-based biomarkers, and prostate imaging with MRI currently allows for a reduction in unnecessary prostate biopsies (those diagnosing stage I prostate cancer or not identifying disease).3,4 Moreover, biopsies informed by MRI can increase the detection of clinically significant disease and reduce the need for repeat procedures.6

Currently, most TRUS-guided prostate biopsies performed in the United States sample the prostate using a transrectal approach. The procedure is relatively well tolerated, aided by use of locoregional anesthesia applied to sensory branches of the pelvic plexus and by performing biopsies primarily above the dentate line. A significant limitation to this approach is the need to penetrate the rectal wall. Doing so results in an increased risk of postbiopsy infection and, most worrisomely, sepsis, which requires hospitalization and can cause significant morbidity. Indeed, risks of infection after transrectal prostate sampling during biopsy have been increasing, driven primarily by an increased in fluoroquinolone-resistant enteroccocus in the population.7

Infection following transrectal approaches to prostate biopsy are estimated to occur in approximately 5% to 7% of cases and those requiring hospitalization in about 1% to 3% of cases.8 In a large study of men undergoing prostate biopsy within a single-payer system in Canada, hospitalization rates following biopsy was 2%, with 70% of these being infectious related.9 Infection rate increased more than 4-fold over the 10-year study period. This coincides with a doubling in the rate of fluoroquinolone-resistant Escherichia coli (FQRE) found in the rectal flora of men over the past decade. Currently, the rates of FQRE are between 10% and 20%, and men harboring these bacteria in their lower gastrointestinal tract have a 4-fold increased risk of postbiopsy infection.7

Despite a lower risk of infectious complications, transperineal prostate biopsies have only recently seen increased routine use in diagnostic biopsy. One reason for a delay in implementation may have been the cumbersomeness and patient discomfort associated with traditional grid stepper approaches for perineal-based sampling.

TECHNIQUES TO MITIGATE INFECTION RISK

Several techniques have been described to limit infection following transrectal prostate biopsy, including povidone-iodine rectal preparation, the use of targeted prophylaxis based on rectal swabs, and augmented prophylaxis with multiple antibiotics. Infection rates remain higher with transrectal techniques despite these approaches, and use of antibiotics, particularly fluoroquinolones, is generally problematic. In Europe, fluoroquinolone use has been restricted since 2019, and in 2016, the FDA recommended limiting use of fluoroquinolones because of their “disabling and potentially serious adverse effects.”

Transperineal prostate biopsy under TRUS guidance moves the procedure to a clean rather than contaminated method for sampling prostate tissue, and thus can dramatically limit infection. In meta-analyses comparing transperineal with transrectal approaches, the rates of infection with transperineal approaches were reduced by approximately 2-fold, and rates of sepsis were reduced by approximately 9-fold.8,10 Guideline bodies advising interventional radiologists suggest antibiotics be omitted entirely for percutaneous procedures primarily because of the low risk of infection with such procedures and to enforce optimal antibiotic stewardship and reduce antibiotic resistance on a population level. Although most urologists continue to utilize antibiotics with transperineal approaches to prostate biopsy, recent evidence establishes the safety of omitting antibiotics entirely and should discourage their use. For instance, Sieta et al recently published a multi-institutional series of 450 consecutive patients undergoing transperineal biopsy without antibiotic prophylaxis and reported an infection rate of 0.44% (both urinary tract infections), with no patients requiring hospitalization.11 This rate mirrors smaller studies demonstrating no sepsis or infections requiring intravenous antibiotics following transperineal biopsies in smaller series.

Despite a lower risk of infectious complications, transperineal prostate biopsies have only recently seen increased routine use in diagnostic biopsy. One reason for a delay in implementation may have been the cumbersomeness and patient discomfort associated with traditional grid stepper approaches for perineal-based sampling.
manipulate the transrectal ultrasound probe. As the stepper stabilizers decreases degrees of freedom for each biopsy, multiple needle punctures across the perineum are required, which translates into a large area of skin requiring anesthesia. Subsequently, these biopsies have been performed in the operating room under general anesthesia with operative times that approach 1 hour in length. The need for anesthesia increases both risk and cost to the patient. Furthermore, transperineal saturation biopsy, although the gold standard for biopsy detection of prostate cancer, is also associated with increased rates of urinary retention (potentially because of the use of general anesthesia and/or the use of extensive sampling).

**SEVERAL ACCESS SYSTEMS ARE AVAILABLE**

Presently, freehand tethered transperineal access systems have been described and have become clinically available. These devices link a biopsy sheath to the biplanar ultrasound and allow for the flexibility of freehand biopsies while aligning the needle with the piezo electrodes in the sagittal plane. When compared with grid stepper systems, time of procedure is reduced by over 50%. These freehand systems, such as PrecisionPoint, are additionally compatible with multiple MR/US fusion platforms (eg, UroNav, bkFusion, Koeldis Trinity). Importantly, as an access sheath with 1 entry point on either side of the patient’s perineum is used, freehand tethered systems allow for limited local and regional analgesia, and thus can be routinely performed in the clinical setting. In this regard, multiple techniques for anesthetizing the pain afferents to the prostate have been described. Many approaches recognize that afferents to the prostate and deep structures of the perineum from the pudendal nerve, perineal nerve, and pelvic plexus all run through the periaipical triangle (bounded by the medial edge of the levator ani, the apical prostate, and urethral sphincter and external anal sphincter). Infiltration of lidocaine in this area can provide an extremely effective block, and buffering of lidocaine with sodium bicarbonate increases its potency by moving lidocaine molecules into their active noncationic form while decreasing the burning sensation experienced by many patients.

Beyond providing a lower rate of serious infectious complications, transperineal prostate biopsies may provide improved diagnosis of clinically significant prostate cancer. In relatively small series, transperineal biopsy approaches have demonstrated increased detection rates when compared with transrectal techniques. Much of this may be secondary to an increased ability to sample the anterior and apical prostate, an area that may be more difficult to assay in transrectal approaches. Furthermore, in contemporary series comparing freehand tethered perineal biopsy approaches to grid stepper perineal biopsy approaches, diagnostic rates of clinically significant prostate cancer were not compromised. Of additional note, use of a freehand rather than grid-based technique resulted in a 10-fold lower rate of urinary retention (1% vs 10%) and greatly reduces procedural time.

Stepwise innovations have thus allowed for transperineal TRUS-MR fusion-guided prostate biopsies to be performed routinely in our clinical practices. Currently, our practice is to perform these procedures routinely in the clinic without antibiotics, with local/regional buffered lidocaine as the only analgesic, and with short procedural times. Although evidence and personal experience suggests this approach is well tolerated with lower complications and high diagnostic yield, formal study of transperineal vs transrectal MRI-targeted biopsies is ongoing in a multi-institutional randomized trial (NCT04815876). Even if transperineal biopsy is favored in this study, there will be barriers to implementation. Thankfully, the learning curve for performing transperineal biopsies is short. However, adoption of the technique in our clinics requires capital expenditures for biplanar ultrasound probes and compatible machines, as well as an increased per-case cost for disposables, such as the probe tether and access sheath. Urologists are currently absorbing these additional costs, as no unique Current Procedural Terminology code for transperineal biopsies performed in the office exists.

**REFERENCES**

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Can N20.0 and N13.2 be billed on the same CPT line?

Payer edits referencing ICD-10-CM guidelines such as “Excludes 1” are on the rise

Q. When billing for an evaluation/management (E/M) visit, a patient has a left nonobstructed kidney stone (N20.0) and a right hydronephrosis ureteral stone (N13.2). In International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) under N20, it shows EXCLUDED 1: that with hydronephrosis (N13.2). Can I bill N20.0 and N13.2 on the same Current Procedural Terminology (CPT) line (E/M line)? I have run into denied claims in the past, and I am not sure whether I should bill only 1 ICD-10-CM or 2.

A. We are seeing an increase in payer edits that are referencing ICD-10-CM guidelines such as “Excludes 1” notes. As you mentioned, code N20 includes the note:

“Excludes 1:
• nephrocalcinosis (E83.5)
• that with hydronephrosis (N13.2)”

The note applies to all N20 codes, including N20.0, N20.1, and N20.2. The ICD-10-CM guidelines state that if code(s) notes include an Excludes 1 list, the ICD-10-CM codes listed under the note should not be reported in conjunction with the codes for which the note is listed. Interestingly, if you look under code N13.2, you will not see a reciprocal reference. In short, it is not correct coding to list code N20.0 and N13.2 for the same patient encounter.

It is correct coding to list a single diagnosis if the code accurately describes the patient’s condition. Therefore, you should not receive a denial if only 1 ICD-10-CM code is listed for the claim. If the patient has other conditions that are not listed in the notes as “Excludes 1” or “Includes codes,” it is appropriate to list more than 1 ICD-10-CM code, with few exceptions.

Q. A patient presented for a voiding trial to the office a week after a laparoscopic radical prostatectomy (CPT code 55866), which is a 90-day global procedure. The advanced practice provider instilled 200 mL of saline and removed the catheter. This was planned to be done prospectively and documented by the surgeon at the time of the procedure. I was instructed, therefore, that CPT code 51700 with modifier –58 should be billed. Is this correct? I read National Correct Coding Initiative (NCCI) Policy Manual for Medicare Services chapter 7 (11), and it sounds like it should not be billed. But I am not sure.

A. Modifier –58 is defined as a staged or related procedure performed during the postoperative period of the first procedure by the same physician. Appropriate use of this modifier on a procedure performed within the global of another procedure is when a procedure or service during the postoperative period was either (a) planned or anticipated (staged); (b) more extensive than the original procedure; or (c) for therapy following a surgical procedure. Inappropriate use of this modifier is for reporting the treatment of a complication from original surgery that requires a return to operating room (use modifier –78) or service not separately payable that does not require a return to the operating room for these complications (do not charge).

So the question raised was whether filling the urinary catheter within the global period is billable, even when planned. We agree with your concern and agree that this is not a billable situation. You mention NCCI Policy Manual chapter 7, which is one of the reasons this cannot be billed. And there are other reasons.

First, CPT code 51700 describes “bladder irrigation, simple, lavage and/or instillation.” The description of work includes placing a urinary catheter, draining the bladder, and irrigating or instilling a medication into the bladder. As we are aware, the overarching criteria to bill any procedure is medical necessity. It would have been just as easy to have the patient clamp the catheter for several hours before removal of the catheter; there is no medical necessity to instill or lavage this catheter.

Second, any procedure with a 90-day global (considered a major procedure by Medicare) is subject to the Global period definition. For major and minor surgical procedures, postoperative E/M services related to recovery from the surgical procedure during the postoperative period are included in the global surgical package, as are E/M services related to complications of the surgery. Diagnostic procedures to ensure the success of the procedure are included. If this was deemed necessary due to the concern about a complication, all procedures for complications handled outside a dedicated procedure room are included in the global period.

The Global Surgery Booklet from Medicare Learning Network specifically states that Medicare includes “miscellaneous services, such as dressing changes, local incision care, removal of operative pack, removal of cutaneous sutures and staples, lines, wires, tubes, drains, casts, and splints; insertion, irrigation, and removal of urinary catheters, routine
peripheral intravenous lines, nasogastric and rectal tubes; and changes and removal of tracheostomy tubes” in the global surgery payment when provided in addition to the surgery. This information is also repeated in paragraph 40.1.A of chapter 12 in the Medicare Claims Processing manual in the definition of a global period.7

Finally, as you mention, NCCI Policy Manual chapter 7 (11) states that “CPT code 51700 (bladder irrigation, simple, lavage and/or instillation) is used to report irrigation with therapeutic agents or as an independent therapeutic procedure. It is not separately reportable if bladder irrigation is part of a more comprehensive service, such as to gain access to or visualize the urinary system. Irrigation of a urinary catheter is included in the global surgical package. CPT code 51700 shall not be misused to report irrigation of a urinary catheter.”

Q. How do I code for percutaneous pouch lithotomy (stone in Indiana pouch) with lithotripter?
A. The answer is determined by the surgical approach. Is the endoscope placed into the skin opening of the Indiana pouch using the current opening, or is a new percutaneous tract created directly into the pouch itself to perform the procedure?

If the “natural” new opening is used, the most accurate code to use is CPT code 52317 (litholapaxy: crushing or fragmentation of calculus by any means in bladder and removal of fragments; simple or small [less than 2.5 cm]) or CPT code 52318 (litholapaxy: crushing or fragmentation of calculus by any means in bladder and removal of fragments complicated or large [over 2.5 cm]) based on the stone burden and based on whether this was felt to be a complicated procedure even if the stones were less than 2.5 cm. (Please describe in the operative note.) CPT confirmed this in the 2016 editorial revision to guidelines under the endoscopy, cystoscopy, ureteroscopy, cystoureteroscopy subsection for these procedures. Because cutaneous urinary diversions utilizing ileum or colon serve as functional replacements of a native bladder, endoscopy of such bowel segments, as well as performance of secondary procedures, can be captured by using the cystoureteroscopy codes. For example, endoscopy of an ileal loop with removal of ureteral calculus would be coded as cystoureteroscopy (including ureteral catheterization); with removal of ureteral calculus (52320).

The options for coding if a new percutaneous tract was created directly into the Indiana pouch should not include: CPT codes 30080 (percutaneous nephrostolithotomy or pyelolithotomy, with or without dilation, endoscopy, lithotripsy, stenting, or basket extraction; up to 2 cm), CPT code 30081 (percutaneous nephrostolithotomy or pyelolithotomy, with or without dilation, endoscopy, lithotripsy, stenting, or basket extraction; over 2 cm), or CPT code 50561 (renal endoscopy through established nephrostomy or pyelostomy, with or without irrigation, instillation, or ureteropyelography, exclusive of radiologic service; with removal of foreign body or calculus). The important part of the descriptions of these 3 procedures is not the word percutaneous but rather the words nephrostolithotomy or pyelolithotomy and renal endoscopy, meaning these codes describe percutaneous procedures specifically into the kidney itself, not a bladder or conduit.

If access to the Indiana pouch requires incision, code 51050 (cystolithotomy, cystotomy with removal of calculus, without vesical neck resection) or 51065 (cystotomy, with calculus basket extraction and/or ultrasonic or electrohydraulic fragmentation of ureteral calculus) would be more appropriate for removal of a stone from the Indiana pouch. ●

REFERENCES
Six steps to help you track ureteral stents

Think of the forgotten stent primarily as a patient safety issue

Hippocrates wrote, “The physician must be able to tell the antecedents, know the present, and foretell the future—must mediate these things and have 2 special objects in view with regard to disease: namely, to do good or to do no harm.” He wrote these words in the fifth century BC, and the modern interpretation of the phrase—“First, do no harm”—is that physicians should recommend tests or treatments for which the potential benefits outweigh the risks of harm. Creating a culture of patient safety takes this concept further: Physicians arguably should recognize serious safety risks—even if they are uncommon—and stringently practice the behaviors that prevent harm to patients. For example, a surgical time-out prevents wrong-site surgery, 2 patient identifiers on a specimen label prevent most labeling errors, and high-level disinfection or sterilization of instruments prevents patient-to-patient transmission of bacteria, fungi, and viruses.

To prevent these harms, these behaviors must become ingrained, habitual, part of our culture, and practiced 100% of the time. In a urology practice, harms may occur because the simple behaviors known to reduce or prevent some harms are not practiced each and every time. The culture of safety is still evolving, and events may seem so rare that it feels like “overkill” to expend energy on prevention.

In this article, I will examine prevention strategies for one of those harms that should resonate with most urologists—the forgotten ureteral stent.

It is indisputable that a retained ureteral stent can and does cause harm. That harm can result from encrustation, infection, obstruction, or complications from the treatment of these preventable problems. That harm can include loss of a kidney or death.1 How often does this harm occur? Estimates show that 1.5% to 12.5% of stenting procedures result in a forgotten stent in the modern era.2

Urologists perform stent insertions hundreds of times in their careers, so even if the incidence is “only” 1%, every urologist has patients at serious risk for this preventable harm. Most urologists have seen patients with retained stents, even if they did not perform the original surgery. This is not a rare event, it can be life threatening, and it is largely preventable.

Many patients with a forgotten ureteral stent are labeled nonadherent; this label implies they knew they had a stent, fully understood the consequences of not having it removed, and chose to harm themselves.

What are the actual factors that lead to a retained stent and its complications? Lack of insurance or access to care is a common reason but not the only reason cited by patients with forgotten stents.1 Other patients report forgetting about the stent or never knowing they had a stent or needed follow-up. Patients at higher risk of a forgotten stent include those who are male sex, ethnic minorities, unemployed, and non–English speaking.3

There are also physician and practice risk factors. Many patients at risk for retained stents are seen emergently outside the office and undergo unscheduled surgery. These patients may escape preoperative registration with the practice and some of the safeguards that come with office policies. The only opportunity to confirm contact information and arrange follow-up might depend upon the physician.

Poor communication, delayed charge posting, incomplete record keeping, and inconsistent patient engagement are potential risk factors in the treating physician or practice. Some patients with chronic ureteral stents undergo periodic stent exchanges—this is a risk factor, as is the common practice of relying on the patient to initiate contact in a few months for their exchange.

Although some of these factors cannot be controlled, recognizing them is an important part of a strategy to prevent harm from the forgotten stent.

What behaviors can prevent a retained stent and its attendant harms? What follows are my 6 suggestions for behaviors to practice each time, every time a stent is inserted:

1. Affix a hospital-style wristband (available from your facility or on Amazon for less than 15 cents apiece) with the date of anticipated stent removal to the patient’s wrist; the band is not to be removed until the stent is removed. If the patient speaks a limited English, inform and apply the wristband in their preferred language. Patients with chronic stent exchanges may use a medical alert silicone version of the wristband.

2. Verify the telephone number of the patient or their emergency contact by calling the number from the facility phone before the patient is discharged.

3. For patients with a tether who are instructed in self-removal, give the patient a return form stating, “I removed
Omicron-related expenses hit hospitals hard in January

TODD SHRYOCK

Shryock is a managing editor for Medical Economics®.

Hospitals and health systems were hit hard in January as the Omicron variant surged. COVID-19 cases and hospitalizations peaked at record levels in January because of the rapid spread of the highly contagious variant. The 7-day moving average of new COVID-19 cases jumped 93% within a 2-week period, from 417,524 on January 1, to an all-time high of 807,115 on January 15. This drove a corresponding increase in COVID-19-related hospitalizations, with the 7-day moving average of new daily admissions climbing 54% over the same period, from 14,017 on January 1 to a peak of 21,622 on January 15.

As a result, hospitals suffered financially, according to the Kaufman Hall Hospital Flash Report for February.1 Hospital margins were negative for the first time in 11 months. The median Kaufman Hall Operating Margin Index was –3.68% without CARES and 3.3% with CARES support.

Outpatient volumes and revenue dropped abruptly as providers delayed nonurgent, outpatient care to mitigate Omicron’s spread and ease demands on hospitals that saw a stark increase in sicker patients requiring longer hospital stays. Meanwhile, hospital expenses continued to climb, spurred by widespread labor shortages and global supply chain challenges. From December to January:

• The median change in operating margin (without CARES) dropped 71.3%.
• Operating room minutes declined 15.7%.
• Average length of stay was up 8.6%.
• Labor expense per adjusted discharge jumped 14.6%.
• Total expense per adjusted discharge rose 11.6%.

Consistent with past surges, hospital performance likely will stabilize somewhat in coming months as a result, but January’s losses could have repercussions throughout 2022. Nationwide labor shortages continue to drive up labor expenses while supply chain challenges are contributing to inflation of non-labor costs, exacerbating hospital operating pressures amid unstable pandemic volumes and revenue.

REFERENCE


5 Track every stent insertion and removal. This can be a manual process (ie, a registry), a software-assisted reminder or patient engagement tool,2 or a data-driven analysis. The process should include the stent insertion date, the documented stent removal date, and a method for contacting patients with removals that are overdue or not recorded. If your process occurs outside the medical record, be sure to document removal in the record. Think of this like a sponge count—the case isn’t complete until you have verified there isn’t a foreign body left in the patient. You don’t do a sponge count in 98% of open or vaginal cases; you do it in all cases to prevent the rare complication (gossypiboma) from a retained foreign body.

6 Make reasonable efforts to contact those patients who have stent removal that is undocumented or overdue. This includes phone calls, portal messages, emergency contacts, and certified letters. When it comes to a stent, no news is never good news. The bottom line and why it matters: Retained ureteral stents are commonly thought of as a patient adherence issue, out of the physician’s control, or a malpractice risk for the urologist. Although they can be all of these, I would encourage you to think of the forgotten stent primarily as a patient safety issue—an avoidable bad outcome.

Become a safety enthusiast. Using a safety paradigm may help you reduce or even eliminate this problem in your practice. As Benjamin Franklin once said, “An ounce of prevention is worth a pound of cure.”

REFERENCES


UrologyTimes.com
Eight steps to create your 2022 financial plan

Having a year-to-year strategy helps you achieve short- and long-term goals

Creating a financial plan allows you to set goals and keep track of financial benchmarks throughout the year. Creating a year-to-year plan can ensure you are staying on track to accomplish your short-term and long-term goals. Each year, I provide a checklist to get you started on creating a plan. There will certainly be other things you want to address; however, getting these 8 financial priorities in place is a good start.

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

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

Emergency funds. These can be a financial lifesaver! A sudden job loss, major surprise expense, or unexpected health issue can change your financial picture quickly. The general rule of thumb is to maintain an emergency fund equal to 3 times your monthly living expenses if you are a dual-income household and 6 months of monthly living expenses if you are a single-income household or if one person's income is relied upon to provide for the family's standard of living. During the COVID-19 pandemic, it is a good idea to bolster these funds with an extra month or two of savings.

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

Retirement plan contributions. If you already contribute to an employer plan such as a 401(k) or 403(b), keep it going. The Internal Revenue Service increased the maximum contribution amount to $20,500 per year ($27,000 per year for individuals older than 50 years). You should max out 401(k)s and 403(b)s before utilizing other tax-advantaged retirement accounts because they are protected by federal law if you are ever sued and have a judgment against you. If you own your practice, determine whether you are utilizing the best type of retirement plan for your specific situation.

Traditional and Roth individual retirement accounts (IRAs). If you are already maxing out employer-provided retirement accounts and wish to save additional amounts toward retirement, consider contributing to a traditional or Roth IRA. These accounts also offer excellent tax-advantaged growth and are protected in most states from lawsuits. The contribution limit remains unchanged at $6000 per year for 2022 ($7000 for individuals older than 50 years). Please note: Deductibility and the ability to contribute are determined by your income, so it is important to be aware of the limitations.

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

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

Having these 8 important components well in hand will give you a good foundation to start moving toward a financially secure future. We recommend speaking with your financial advisor about other areas of your financial plan that could use improvement.
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Lawsuit alleges urethral injury following ED visit

Plaintiff claims defendant negligently failed to order urology consult

On February 26, a 56-year-old man presented to the emergency department (ED) with a chief complaint of fever, chills, and body aches for 2 days. His medical history was positive for a urethral stricture, for which he began receiving treatment when he was age 24 years. Prior to this ED visit, the patient underwent several procedures to dilate his urethra and had been seen in the ED on numerous occasions for urinary tract infections. Several attempts were made in the ED by the nursing staff to catheterize the patient, without success. The patient was given intravenous fluid and voided; however, he began to demonstrate tachycardia and hypotension.

The patient was admitted to the hospital due to a suspected urinary tract infection. Urine and blood cultures were ordered, and the patient was started on ceftriaxone (Rocephin) for possible sepsis. His admitting diagnoses included dehydration, urinary tract infection, hypotension, and rule-out sepsis.

The patient was seen by the attending physician. After testing and 5 days of hospitalization, the patient was discharged from the hospital by the attending and given instructions to continue antibiotics and follow-up with his primary care physician.

Five days later, the patient was seen by a urologist, with complaints of hematuria and difficulty voiding. He reported a recent injury to his urethra from the ED visit on February 26. The urologist attempted to perform a cystoscopy in hopes of examining and dilating the urethra. However, he was unable to successfully pass the scope beyond the stricture due to the presence of multiple false passages. The urologist opted to take the patient to the operating room and insert a suprapubic catheter to allow inflammation around the stricture to resolve.

The patient sued the ED physician, the attending physician, and the hospital, claiming malpractice and urethral injury. The ED physician and hospital were dismissed under confidential terms prior to trial. The case proceeded to trial against the attending physician only.

According to the patient, the attending physician negligently failed to request a consult with a urologist during his hospital stay and failed to refer him for an emergent urology consult on discharge. Had he done so, the patient claimed he would not have needed the suprapubic catheter that stayed in place for 7 months.

The attending physician negligently failed to perform a genitourinary examination of the patient at any time during his stay, negligently failed to request a consult with a urologist while the patient was at the hospital, and did not refer the patient to a urologist at discharge. The patient’s expert testified that had a urologist been consulted, additional attempts at placing a Foley catheter using a guide wire would have been made in effort to relieve urinary retention and avoid the need for the suprapubic catheter.

Defense counsel for the attending physician argued that his client met the standard of care and that nothing he did or failed to do caused the patient’s injury. The defense expert testified that prior to the patient’s discharge, the attending physician ordered a renal ultrasound and another set of blood and urine cultures. The renal ultrasound revealed a distended bladder with an irregular posterior bladder wall. In addition to the orders for laboratory studies, the attending physician adjusted antibiotic therapy. During the next 3 days, the patient responded well to the antibiotic therapy, and his white blood cell count gradually returned to normal. The defense expert further testified that the attending physician complied with the standard of care. He testified that the primary reason for hospital admission was a life-threatening urinary tract infection that was adequately treated and that the standard of care did not require a urology consult under the circumstances because any further attempts at catheterization would have been contraindicated due to the patient’s serious infection.

The defense’s urologist opined that the patient had a chronic problem with a urethral stricture and noted that the natural history of chronic strictures involves recurrent procedures designed to dilate the stricture and, at times, require placement of a suprapubic catheter to allow inflammation around the stricture to resolve.

After a 7-day trial and jury deliberations of nearly 2 days, the jury returned a verdict 10-2 for the plaintiff on negligence and 12-0 for the defense on causation.

LEGAL PERSPECTIVE

In a malpractice case, a plaintiff must prove both negligence and causation. Here, the jury found the plaintiff proved his negligence case but failed to prove that the negligence caused the plaintiff’s injury. Ultimately, this case resulted in a win for the defense.
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