OAB/INCONTINENCE
Foray of FPMRS into telemedicine during the coronavirus disease 2019 pandemic

PROSTATE CANCER
Adjuvant RT after prostatectomy does not improve recurrence rate

SEXUAL DYSFUNCTION
Research suggests potential gaps in ED care delivered by nonurologists

BENIGN PROSTATIC HYPERPLASIA
5-year data sustain water vapor thermal therapy benefit in BPH-related LUTS

MALPRACTICE CONSULT
Beware the perils of friendly prescribing

Has a friend, relative, or colleague ever asked you to write a prescription for someone who is not your patient? Refusing such a request can be uncomfortable for the physician being asked, but agreeing to write an informal prescription can lead to dire outcomes for both the prescriber and the patient.

In this month’s Malpractice Consult column, Kenton H. Steele, Esq, outlines the medical-legal risks associated with friendly prescribing, why malpractice lawsuits involving a recipient of an informal prescription can lead to dire outcomes for both the prescriber and the patient.

For the full article, please turn to page 42
THE FIRST AND ONLY FDA-APPROVED TREATMENT FOR LOW-GRADE UPPER TRACT UROTHELIAL CANCER (UTUC) IN ADULT PATIENTS

CHEMOABLATE NOW SPARE THE KIDNEY FOR TOMORROW

JELMYTO® (mitomycin) for pyelocalyceal solution

NCCN RECOMMENDED

National Comprehensive Cancer Network® (NCCN®) recommends mitomycin for pyelocalyceal solution (JELMYTO) as a primary therapy option for certain upper tract tumors

Indications and Usage
JELMYTO® (mitomycin) for pyelocalyceal solution is indicated for the treatment of adult patients with low-grade Upper Tract Urothelial Cancer (LG-UTUC).

Important Safety Information

Contraindications
JELMYTO is contraindicated in patients with perforation of the bladder or upper urinary tract.

Ureteric Obstruction
Ureteric obstruction, including ureteral stenosis and hydronephrosis, occurred in patients receiving JELMYTO. Monitor patients for signs and symptoms of ureteric obstruction, including flank pain, and fever, and for changes in renal function. Patients who experience obstruction may require transient or long-term ureteral stents or alternative procedures. Withhold or permanently discontinue JELMYTO based on the severity of ureteric obstruction.

Bone Marrow Suppression
The use of JELMYTO can result in bone marrow suppression, particularly thrombocytopenia and neutropenia. The following tests should be obtained prior to each treatment: Platelet count, white blood cell count differential and hemoglobin. Withhold JELMYTO for Grade 2 thrombocytopenia or neutropenia. Permanently discontinue for Grade 3 or greater thrombocytopenia or neutropenia.

Embryo-Fetal Toxicity
Based on findings in animals and mechanism of action, JELMYTO can cause fetal harm when administered to pregnant women.

Please see Important Safety Information on the adjacent page for JELMYTO.
IN THE OLYMPUS STUDY,† JELMYTO treatment in patients with low-grade UTUC achieved:

- **58% Complete Response (95% CI: 45, 69)**
- **84% Durability of Response (95% CI: 71, 97)**

of patients treated with JELMYTO achieved a Complete Response (CR)†

N=71

The OLYMPUS Study is ongoing. At the time of data cutoff‡:
- 19 patients remained in CR
- 7 patients had disease recurrence
- 9 patients continued to be followed for 12-month duration of response

- Median duration of response was not reached, with a range of 0-18.8+ months†
- The most common adverse reactions (≥20%) reported were ureteric obstruction, flank pain, urinary tract infection, hematuria, renal dysfunction, fatigue, nausea, abdominal pain, dysuria, and vomiting†

Important Safety Information (cont’d)
a pregnant woman. In animal reproduction studies, administration of mitomycin resulted in teratogenicity. Advise females of reproductive potential to use effective contraception during treatment with JELMYTO and for 6 months following the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with JELMYTO and for 3 months following the last dose.

Common Adverse Reactions
The most common adverse reactions in ≥ 20% of patients treated with JELMYTO were ureteric obstruction, flank pain, urinary tract infection, hematuria, renal dysfunction, fatigue, nausea, abdominal pain, dysuria, and vomiting.

Additional Adverse Reactions Information
Selected clinically relevant adverse reactions in < 10% and ≥ 2% of patients who received JELMYTO include urinary tract inflammation, bladder spasm, urosepsis, hypersensitivity, and instillation site pain.

Use in Specific Populations
Lactation
Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with JELMYTO and for 1 week following the last dose.

Preparation and Administration Information
JELMYTO is for pyelocalyceal use only and not for intravenous use, topical use, or oral administration. JELMYTO must be prepared and administered by a healthcare provider. To ensure proper dosing, it is important to follow the preparation instructions found in the JELMYTO Instructions for Pharmacy and administration instructions found in the JELMYTO Instructions for Administration.

JELMYTO may discolor urine to a violet to blue color following the instillation procedure. Advise patients to avoid contact with urine for at least six hours post-instillation, to void urine sitting on a toilet, and to flush the toilet several times after use.

JELMYTO is a cytotoxic drug. Follow applicable special handling and disposal procedures.

Please see Brief Summary of Prescribing Information for JELMYTO on the following pages.

JELMYTO® (mitomycin) for pyelocalyceal solution

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

Please refer to the JELMYTO Package Insert for Full Prescribing Information, including instructions for preparation and administration.

INDICATIONS AND USAGE

JELMYTO® is indicated for the treatment of adult patients with low-grade Upper Tract Urothelial Cancer (LG-UTUC).

DOSE AND ADMINISTRATION

Important Administration Instructions

See the instructions for Administration provided separately. JELMYTO is for pyelocalyceal use only. JELMYTO is not for intravenous use, topical use, or oral administration. Advise patients that JELMYTO may discolor urine to a violet to blue color following the instillation procedure. Advise patients to avoid contact with urine for at least six hours post-instillation, to void urine sitting on a toilet, and to flush the toilet several times after use.

Preparation and Handling

See the instructions for Pharmacy for preparation provided separately. JELMYTO is a cytotoxic drug. Follow applicable special handling and disposal procedures. JELMYTO must be instilled as a chilled solution using a Urject12 Lever, a Luer lock syringe, and a ureteral catheter with molded Luer lock connector. Once chilled at 3°C to 5°C (37°F to 41°F), JELMYTO will convert to a viscous liquid for instillation and is stable for up to 1 additional hour. Reconstituted JELMYTO must be instilled within 1 hour after it is converted to a viscous liquid.

CONTRAINDICATIONS

JELMYTO is contraindicated in patients with perforation of the bladder or upper urinary tract.

WARNINGS AND PRECAUTIONS

Ureteric Obstruction

Ureteric obstruction, including ureteral stenosis and hydronephrosis, occurred in patients receiving JELMYTO. In the OLYMPUS study, ureteric obstruction was reported in 58% (n=41) of patients receiving JELMYTO, including 17% (n=12) of patients who experienced Grade 3 obstruction. The median time to first onset was 72 days (range: 15-462). Interventions in the 41 patients experiencing ureteric obstruction included ureteral stent placement (88%), balloon dilatation (32%), and nephroureterectomy (4.9%). In the 36 patients who required ureteral stent placement, the median duration of indwelling stents was 51 days (range: 1-292). Ureteric obstruction did not resolve or resolved with sequelae in 51% (n=21) of these patients. Of the 41 patients who experienced ureteric obstruction, 17% (n=7) experienced Grades 1-2 increase in serum creatinine. In the 42 patients who only received JELMYTO during the treatment phase (no maintenance therapy), ureteric obstruction was reported in 40% (n=17). Monitor patients for signs and symptoms of ureteric obstruction, including flank pain, and fever, and for changes in renal function. Patients who experience obstruction may require transient or long-term ureteral stents or alternative procedures. Withhold or permanently discontinue JELMYTO based on the severity of ureteric obstruction.

Bone Marrow Suppression

The use of JELMYTO can result in bone marrow suppression, particularly thrombocytopenia and neutropenia. In the OLYMPUS study, Grade 3 thrombocytopenia occurred in two patients and Grade 3 neutropenia in one patient. Gross extravasation of JELMYTO via urinary tract perforation or impaired mucosa was not observed in these patients. The following tests should be obtained prior to each treatment: Platelet count, white blood cell count differential and hemoglobin. Withhold JELMYTO for Grade 2 thrombocytopenia or neutropenia. Permanently discontinue for Grade 3 or greater thrombocytopenia or neutropenia.

Embryo-Fetal Toxicity

Based on findings in animals and mechanism of action, JELMYTO can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of mitomycin resulted in teratogenicity. Advise females of reproductive potential to use effective contraception during treatment with JELMYTO and for 6 months following the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with JELMYTO and for 3 months following the last dose.

ADVERSE REACTIONS

Clinical Trials Experience

The safety of JELMYTO was evaluated in OLYMPUS, an open-label, single-arm study in 71 patients with LG-UTUC. For the 71 patients treated with JELMYTO during the treatment period, the median number of instillations was 6 (range: 3-6). Following initial treatment, 29 patients were treated with up to 11 doses of maintenance instillations, with a median of 6 instillations (range: 0-11). Serious adverse reactions occurred in 37% of patients who received JELMYTO. Serious adverse reactions in > 3% of patients included ureteric obstruction (including ureteric stenosis and hydronephrosis), flank pain, and urosepsis. Two deaths occurred due to cerebrovascular accident and failure to thrive. JELMYTO was permanently discontinued due to an adverse reaction in 16 (23%) patients, including 11 patients who discontinued during the treatment phase and 5 who discontinued during the maintenance phase. Adverse reactions resulting in study drug discontinuation of JELMYTO in > 3% of patients who received JELMYTO included ureteric obstruction. Dosage interruptions due to an adverse reaction occurred in 34% of patients who received JELMYTO. Adverse reactions requiring dosage interruption in > 3% of patients who received JELMYTO included renal dysfunction, ureteric obstruction, urinary tract infection, and flank pain. The most common adverse reactions (> 20%) reported were ureteric obstruction, flank pain, urinary tract infection, hematuria, renal dysfunction, fatigue, nausea, abdominal pain, dysuria, and vomiting.

Table 2 summarizes the laboratory abnormalities in OLYMPUS.

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>All Grades</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperkalemia</td>
<td>13</td>
<td>0</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>21</td>
<td>0</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>21</td>
<td>0</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>5</td>
<td>0</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Anosmia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Based on content from JEL-PI-001 Package Insert
Table 1 summarizes the adverse reactions in OLYMPUS.

Table 1: Adverse Reactions (≥ 10% All Grades) in Patients Who Received JELMYTO in OLYMPUS

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>JELMYTO* (n=71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
</tr>
<tr>
<td>Ureteric Obstructiona</td>
<td>58 (17)</td>
</tr>
<tr>
<td>Ureteric stenosis</td>
<td>44 (8)</td>
</tr>
<tr>
<td>Hydronephrosis</td>
<td>18 (6)</td>
</tr>
<tr>
<td>Pelvi-ureteric obstruction</td>
<td>6 (1.4%)</td>
</tr>
<tr>
<td>Urinary tract obstruction</td>
<td>6 (1.4%)</td>
</tr>
<tr>
<td>Ureteric obstruction</td>
<td>2.8 (1.4%)</td>
</tr>
<tr>
<td>Obstructive uropathy</td>
<td>14 (0)</td>
</tr>
<tr>
<td>Flank painb</td>
<td>39 (2.8%)</td>
</tr>
<tr>
<td>Urinary tract infectionc</td>
<td>34 (4.2%)</td>
</tr>
<tr>
<td>Hematuria*</td>
<td>32 (2.8%)</td>
</tr>
<tr>
<td>Renal dysfunctionc</td>
<td>25 (2.8%)</td>
</tr>
<tr>
<td>Dysuria</td>
<td>21 (0)</td>
</tr>
<tr>
<td>Pollakiuria</td>
<td>13 (0)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>24 (1.4%)</td>
</tr>
<tr>
<td>Abdominal painf</td>
<td>23 (1.4%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>20 (4.2%)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
</tr>
<tr>
<td>Fatiguef</td>
<td>24 (1.4%)</td>
</tr>
<tr>
<td>Chills</td>
<td>11 (0)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>11 (0)</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>13 (0)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>13 (0)</td>
</tr>
</tbody>
</table>

*Graded per National Cancer Institute Common Terminology Criteria for Adverse Events. Version 5.0 (NCICTCAE v5).

Table 2 summarizes the laboratory abnormalities in OLYMPUS.

Table 2: Select Laboratory Abnormalities (≥ 10%) Worsening from Baseline in Patients Who Received JELMYTO in OLYMPUS

<table>
<thead>
<tr>
<th>Laboratory Abnormality*</th>
<th>JELMYTO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>37 (0)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>21 (2.9)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>21 (2.8)</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
</tr>
<tr>
<td>Estimated Glomerular Filtration Rate</td>
<td>37 (10)</td>
</tr>
<tr>
<td>Creatinine Increased</td>
<td>32 (0)</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>30 (2.8)</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>17 (0)</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>16 (16)</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>13 (1.4)</td>
</tr>
</tbody>
</table>

*Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary - Based on findings in animals and mechanism of action, JELMYTO can cause fetal harm when administered to a pregnant woman. There are no available data on JELMYTO use in pregnant women to inform the drug-associated risk. In animal reproduction studies, administration of mitomycin resulted in teratogenicity. Advise pregnant women of the potential risk to a fetus.

Lactation

Risk Summary - There are no data on the presence of mitomycin in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with JELMYTO and for 1 week following the last dose.

Females and Males of Reproductive Potential

Pregnancy Testing - Verify pregnancy status in females of reproductive potential prior to initiating JELMYTO.

Geriatric Use

Of the total number of patients in the OLYMPUS trial, 75% (53 patients) were 65 years of age and over and 37% (26 patients) were 75 year of age and over. Clinical studies of JELMYTO did not include sufficient numbers of younger patients less than 65 years old to determine whether they respond differently from older patients.

Renal Impairment

No data are available in patients with severe renal impairment. Avoid use of JELMYTO in patients with a Glomerular Filtration Rate of < 30 mL/min.

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Princeton, NJ 08540
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Based on content from JEL-PI-001 Package Insert

SELECTED CLINICALLY RELEVANT ADVERSE REACTIONS:

Selected clinically relevant adverse reactions in < 10% and ≥ 2% of patients who received JELMYTO in OLYMPUS include urinary tract inflammation, bladder spasm, urosepsis, hypersensitivity, and instillation site pain.
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Efforts to mitigate the BCG shortage continues

MIKE HENNESSY SR
Mike Hennessy Sr is chairman and founder of Urology Times® parent company, MJH Life Sciences™

A n inescapable, continuing consequence of the coronavirus disease 2019 pandemic is worry over the current situation placing unmet needs on products and services, such as ventilators and intensive care unit beds. This month’s cover feature concerns a different shortage, that of the non–muscle invasive bladder cancer treatment BCG. Urology Times® Editorial Consultant J. Brantley Thrasher, MD, interrogates Seth P. Lerner, MD, regarding the origins of the shortage, what is being done to increase supply, and what other options exist for clinicians unable to obtain the treatment for their patients. Although Merck’s announcement regarding the forthcoming BCG manufacturing facility in the US is certainly welcome news, the fact that the facility’s construction will take approximately 5 to 6 years means that other trials and management strategies are still necessary.

A report on the use of telemedicine for following patients undergoing midurethral sling placement postoperative visits is the subject of this month’s From the Board editorial, written by Urology Times® Editorial Council member Priya Padmanabhan, MD. “With the foray into telemedicine during the COVID-19 pandemic, we have witnessed rapid growth in our knowledge and patient accessibility. It is clear that virtual visits are a viable option, well liked by patients and physicians alike,” Padmanabhan writes.

We also report on a recent study evaluating the use of tele-cystoscopy for patients undergoing bladder cancer surveillance. Other bladder cancer topics covered include a small study examining dual immune checkpoint blockade with the PD-1 inhibitor tislelizumab and the PD-L1 inhibitor BGB-A333 for urothelial carcinoma, as well as a report on comprehensive genomic profiling in patients with upper tract and bladder urothelial carcinoma.

For this issue’s Journal Article of the Month column, Badar M. Mian, MD, examines a recent meta-analysis of 3 randomized controlled trials that evaluated evantuated and early salvage radiation therapy in men with postprostatectomy high-risk and locally advanced prostate cancer.

Also in prostate cancer, Associate Editorial Director Jason J. Broderick reports on the Centers for Disease Control and Prevention’s recent analysis indicating a rise in the incidence of metastatic prostate cancer in the United States. We also cover recent research regarding high-intensity focused ultrasound, rucaparib (Rubraca), darolutamib (Nubeqa), the use of prostate magnetic resonance imaging for active surveillance, and more.

In sexual dysfunction, this issue includes articles about potential gaps in erectile dysfunction care delivered by nonurologists, as well as the use of cologenastrin chloride (Stixal) in patients with acute-phase Peyronie disease. In benign prostatic hyperplasia, we report on a recent study of Rezum water vapor thermal therapy, and in stone disease, look for an article about ureteral stent-stacking software.

Moving on to our Business section, Jonathan Rubenstein, MD, and Mark Painter address coding and reimbursement questions, including a query regarding the forthcoming changes to evaluation and management (E/M) coding in 2021. The E/M changes are also the subject of this month’s Speak Out, in which Karen Nash asked 3 urologists about their readiness for these changes.

Continuing with the theme of looking to next year, for this issue’s Money Matters column, Jeff Witz, CFP, breaks down key personal finance tasks to complete before the end of 2020. For this issue, we are also very pleased to welcome contributor Kenton H. Steele, Esq, who joins Acacia Brush Perko, Esq, as a Malpractice Consultant. Steele’s first installment is an excellent overview on the issue of “friendly prescribing.” Stay safe, and thanks for reading.

REFERENCE
Onvansertib shows promise in abiraterone-resistant mCRPC

Adding the oral PLK1 inhibitor onvansertib to abiraterone acetate (Zytiga) and prednisone showed promising clinical activity in patients with metastatic castration-resistant prostate cancer (mCRPC) with initial resistance to abiraterone, according to phase 2 findings shared during the 2020 Prostate Cancer Foundation Scientific Retreat.1,2

Initial study results for 26 evaluable patients showed that 8 (31%) reached the primary study end point of disease control (90% prostate-specific antigen progression) following 12 weeks of treatment. After the same length of treatment, another 14 patients (54%) achieved stable disease (SD), with 8 of these patients having SD for at least 7 months.

REFERENCES

FDA grants nivolumab/cabozantinib combo priority review in RCC

The FDA has granted a priority review designation to supplemental applications for the combination regimen of nivolumab (Opdivo) plus cabozantinib (Cabometyx) as a treatment for patients with advanced renal cell carcinoma (RCC).3

The applications for the regimen—which comprise a supplemental biologics license application for the PD-1 inhibitor nivolumab and a supplemental new drug application for the multitkine inhibitor cabozantinib—are based on findings from the phase 3 CheckMate 9ER trial (NCT03141177). Study results showed that the combination reduced the risk of disease progression or death by 50% compared with sunitinib, and review of nivolumab/cabozantinib showed promising clinical activity in patients with abiraterone-resistant metastatic urothelial cancer previously treated with a PD-1 or PD-L1 inhibitor. Patients were then stratified by prior chemotherapy: cohort 1 included patients previously treated with platinum-based chemotherapy and cohort 2 included patients without prior platinum-based chemotherapy who were also ineligible for cisplatin.

REFERENCE

Treatment starts in pivotal study of novel device for women with OAB

The first US patient has been implanted in the OASIS trial of the Renova iStim tibial neurostimulation system for the treatment of women with overactive bladder (OAB), according to BlueWind Medical, the developer of the device.4

The multicenter, open-label, prospective, international trial of disitamab vedotin in this setting. Paper presented at: 2019 American Society of Clinical Oncology Annual Meeting showed that the ADC achieved a confirmed objective response rate of 51.2%, with confirmed responses reported in 22 of 43 patients. The best overall response was a partial response in 26 patients. An additional 13 patients reached stable disease for a disease control rate of 90.7%.5

REFERENCES

Disitamab vedotin gets FDA breakthrough therapy designation

The FDA has granted disitamab vedotin (RC48) a breakthrough therapy designation for the treatment of patients with HER2-positive locally advanced or metastatic urothelial carcinoma following treatment with platinum-based chemotherapy, according to RemeGen, the company developing the antibody-drug conjugate (ADC).6

The designation will expedite the development and review of disitamab vedotin in this setting. Phase 2 data presented at the 2019 American Society of Clinical Oncology Annual Meeting showed that the ADC achieved a confirmed objective response rate of 51.2%, with confirmed responses reported in 22 of 44 patients. The best overall response was a partial response in 26 patients. An additional 13 patients reached stable disease for a disease control rate of 90.7%.5

REFERENCES

Treatment begins in study of rechargeable SNM device for OAB

The first patient has been implanted with the InterStim Micro neuromodulation system in patients with overactive bladder.7

The study is examining the rechargeable sacral neuromodulation (SNS) system in patients with overactive bladder. The study is examining the InterStim Micro in patients across all 4 symptoms for which the SNS device is indicated: urinary urge incontinence, urinary frequency, nonobstructive urinary retention, and fecal incontinence. Patient follow-up will go on for 2 years, with key study end points being patient-reported outcomes, disease-specific quality-of-life questionnaires, and symptom diaries.

REFERENCE

Enfortumab vedotin impresses in post-immunotherapy bladder cancer

The antibody-drug conjugate (ADC) enfortumab vedotin–ejfv (Padcev) induced a response in over half of patients with advanced urothelial cancer who previously received a PD-1/PD-L1 inhibitor but were ineligible for cisplatin, according to findings from the pivotal phase 2 EV-201 trial.1

In the cohort of patients—who had also not had prior platinum-based chemotherapy—enfortumab vedotin achieved an objective response rate of 52% per the review of an independent panel. All patients in the single-arm, international EV-201 trial (NCT03219333) had locally advanced or metastatic urothelial cancer previously treated with a PD-1 or PD-L1 inhibitor. Patients were then stratified by prior chemotherapy: cohort 1 included patients previously treated with platinum-based chemotherapy and cohort 2 included patients without prior platinum-based chemotherapy who were also ineligible for cisplatin.

REFERENCE

Enfortumab vedotin shows promise in chemo-naive mCRPC

The antibody-drug conjugate (ADC) enfortumab vedotin–ejfv (Padcev) induced a response in over half of patients with advanced urothelial cancer who previously received a PD-1/PD-L1 inhibitor but were ineligible for cisplatin, according to findings from the randomized phase 3 CheckMate 9ER trial. Ann Oncol. 2020;31(4). Abstract 696O


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UroPipeline / UPDATES ON DRUGS, DEVICES, AND TESTS BY JASON M. BRODERICK

Urology Times / NOVEMBER 2020
Foray of FPMRS into telemedicine during the coronavirus disease 2019 pandemic

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The coronavirus disease 2019 (COVID-19) pandemic has triggered a rapid rise in the use of telemedicine across all specialties, including female pelvic medicine and reconstructive surgery (FPMRS). In an attempt to flatten the curve of transmission, we have made radical changes in the way we provide quality, comprehensive care for our patients.

Telemedicine has classically been useful for providing behavioral therapy, conservative and pharmacological treatment. In these cases, treatment is based on symptom improvement and not physical exam. FPMRS encompasses a spectrum of conditions with varied treatments. An initial challenge exists in identifying the appropriate patients for postoperative telemedicine visits. The nature of the condition, the follow-up questions, and the necessary tests dictate the need for an office-based postoperative visit.

The effectiveness of virtual postoperative tension-free vaginal tape visits was first highlighted by Jefferis et al. Recently, in an international, prospective, multi-institutional, randomized control trial, the use of telemedicine in the early postoperative follow-up period after midurethral sling was presented at the 2020 American Urological Association Virtual Experience. A total of 237 patients were randomized 1:1 to telemedicine or office-based 3-week follow-up. Seventy percent of patients were equally “very satisfied” with their surgical outcomes. Predictors of satisfaction included non-Caucasian ethnicity and no college-level education. Sixteen (13.2%) patients requested crossover to office-based visits. Age greater than 65 years was the only predictor of this crossover. The telemedicine group was the most adherent to 3- to 5-month office-based follow-up.

Patients undergoing midurethral sling placement are ideal for postoperative virtual visits. Clinicians may assess success in most cases with subjective questions and quality-of-life questionnaire and, again through appropriate questions, easily identify irregularities. Complications such as an obstructing sling or mesh erosion create symptoms that a patient will easily notice. In such cases, clinicians may ask the patient to come in for a physical exam and testing.

The use of early virtual follow-up provides a balance of patient satisfaction, clinical utilization, and resource conservation. Reimbursement is based on a 90-day global period post sling. With equal satisfaction of both types of visits, a 3- to 5-month office-based visit is beneficial to the patient and clinic. Prior to COVID-19, only 15% of providers reported using telehealth regularly. This was related to obvious barriers that are rapidly being overcome, including lack of training, gaps in technology access and familiarity, apprehension around adoption of the new platform, and reimbursement.

With the foray into telemedicine during the COVID-19 pandemic, we have witnessed rapid growth in our knowledge and patient accessibility. It is clear that virtual visits are a viable option, well liked by patients and physicians alike. Both virtual and office platforms may provide excellent care without compromising quality. The changes in reimbursements are promising. Time will tell how FPMRS further utilizes telemedicine.

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Telemedicine is viable option for most early midurethral sling post-op visits

Patients in telemedicine group more likely to adhere to follow-up visits

Lisette Hilton
Urology Times® Correspondent

Telemedicine visits in the early postoperative period after midurethral sling placement are a safe and feasible communication option compared with traditional in-person visits. Outcomes for patients using telemedicine were equal, and patients were as satisfied as those who had office-based postoperative visits, according to an international, prospective, multi-institutional, randomized, controlled trial.

The investigators, who presented their results at the 2020 American Urological Association Virtual Experience, randomized a total of 237 patients with a midurethral sling 1:1 to 3-week postoperative telemedicine (by phone) or office-based follow-up visits. They found no differences between the groups for hospital admissions, emergency department visits, and unplanned office visits or calls. Furthermore, about 70% of patients in both groups were very satisfied with their surgical outcomes. Predictors of satisfaction were non-Caucasian ethnicity and no college education.

“Sixteen patients (13.2%) using telemedicine follow-up requested crossover to an office follow-up. Most of those patients were older than 65 years. Also, patients in the telemedicine group were more likely than those in the office group to adhere to their 3- to 5-month follow-up visits.”

The take-home message for practicing urologists is that not all patients need an office visit for their 3-week follow-up after routine sling or other surgeries, according to study author Samir Derisavifard, MD, who was a urology fellow at Cleveland Clinic in Ohio when he conducted the study and now practices at the USMD Health System in Arlington, Texas.

“A question of resources”

“Only patients who are having complaints or are feeling unwell should come in,” Derisavifard said. Otherwise, a simple phone call from the physician is just as safe and effective for the 3-week postoperative visit.

“It’s a question of resources,” Derisavifard noted.

Urologists should look carefully at how they use resources in today’s practice for several reasons, according to Derisavifard. Coronavirus disease 2019 exposure is 1 such reason to consider telephone or virtual visits, as is the fact that with reimbursement in a 90-day global period, offices are not reimbursed specifically for the visit.

“The data show the office-based visit is not a benefit to the patient and not a benefit to the clinic, so with a phone call, we’re making all the parties happier and running things more efficiently. I think efficiency and quality are the key factors here,” Derisavifard added.

Patients with a sling are ideal for telemedicine, according to senior author Howard B. Goldman, MD, professor and vice chairman of the Glickman Urological and Kidney Institute at Cleveland Clinic.

“We are treating a subjective issue, stress incontinence,” Goldman said. “The patient can easily tell us whether that problem has gone away. The complications that could arise are generally things that patients would notice subjectively. If the sling ended up too tight, they might have trouble urinating. If we ask the right questions, patients can tell us whether that is occurring.”

Another potential complication is exposure of some of the sling in the vagina, which would be an issue if the patient were sexually active and if they or their partner had discomfort in that exposed area.

“If they tell us that they had sex and there were no problems and their partner had no issues, that is all we need to know,” Goldman said.

“Frankly, if the patient is dry, voiding well, having no pain, and sexually active with no issues, there is really nothing we are going to find on physical exam that we would do anything about,” he added.

Goldman said he uses telemedicine regularly in other areas of urology practice, for patients with an overactive bladder, for example. Telemedicine is ideal for symptom-based conditions, for which an exam is not that important, he said.

“However, for something like pelvic organ prolapse, the patient can tell you they feel a vaginal bulge. But you really need an exam to see what it is and decide on appropriate treatment,” he said.

However, barriers exist in implementing telemedicine. Finding the right platform for a seamless experience remains an issue. And patients might take telemedicine visits less seriously, potentially wasting a clinician’s time. Derisavifard said he has had calls with patients while they are cooking or driving.

“Clearly, we are all still understanding the best way to incorporate telemedicine into our practices. Ideally it is most successful when the nature of the visit does not require an examination and the technology and etiquette on both ends of the encounter allow for a professional and productive conversation. Here we are showing that it is possible and should be seriously considered as a viable option moving forward without compromising the quality of care we provide,” Derisavifard concluded.

REFERENCE


“If the patient is dry, voiding well, having no pain, and sexually active with no issues, there is really nothing we are going to find on physical exam that we would do anything about.”

HOWARD B. GOLDMAN, MD
Study findings show viability of telemedicine approach to cystoscopy

Cheryl Guttman Krader, BSPharm
Urology Times® Contributing Editor

Tele-cystoscopy has the potential to expand the availability of cystoscopy for bladder cancer surveillance to patients living in underserved areas, according to findings from a pilot study published in the *Journal of Urology*.1

Tele-cystoscopy represents a collaborative approach to providing necessary surveillance for patients with urothelial bladder cancer in the face of urologist workforce shortages while also addressing liability and quality issues faced by urologists. It involves cystoscopy performed by an advanced practice provider (APP) with real-time monitoring and interpretation by a remote urologist.

Researchers from the University of Virginia and Cleveland Clinic conducted the pilot study to evaluate the clarity of the transmitted videos, APP proficiency, and diagnostic capability of the tele-cystoscopy. Analyses were based on cystoscopies performed in 6 patients seen at 3 telemedicine centers. Each patient underwent both tele-cystoscopy performed by a trained APP guided by a remote urologist and traditional cystoscopy done by an onsite urologist.

The onsite tele-cystoscopy video, transmitted video from the tele-cystoscopy procedure, and onsite video from the traditional cystoscopy were reviewed by 11 board-certified urologists who were blinded to the cystoscopy operator and location. According to their reviews, tele-cystoscopy provided reasonable image quality and excellent thoroughness of examination (92% for observes all regions, identifies ureteral orifices, and retroflexion).

Tele-cystoscopy was also found equivalent to traditional cystoscopy with respect to identification of abnormalities and action decisions. Neither the provider performing the cystoscopy nor the location of the procedure had a significant effect on ability to make a diagnosis using the video or the decision for action.

Safety was good. No patients developed a urinary tract infection nor any other complications. In addition, patient satisfaction with the experience was high.

Patients were eligible for enrollment in the pilot study if they had a history of microscopic hematuria, gross hematuria, urothelial cancer, or refractory lower urinary tract symptoms. Five of the 6 patients included in the analysis were undergoing surveillance for urothelial cancer. The urologists who reviewed the captured videos included 7 academic physicians and 4 who were in community practice.

Overall, 36 video recordings were captured, each urologist reviewed between 3 and 6 videos, and each video was evaluated twice by each reviewer.

Video clarity was assessed based on image resolution and speed of transmission and was found to be poorer for the transmitted video compared with the onsite video from traditional cystoscopy. The difference was attributed to video transmission rather than operator performance.

Practitioner proficiency ratings judged visualization of bladder abnormalities, recognition of abnormalities, rating of overall technique, and postulation regarding whether the operator was a physician or APP. Thoroughness of examination and identification of an abnormality were found to be similar for the procedures done by APPs and urologists. Overall technique score was higher for the urologists but the difference compared with the APPs was not statistically significant.

Diagnostic capability was assessed based on whether the cystoscopy thoroughly examined all major bladder landmarks, if a diagnosis could be made based on the video, and what action the reviewer would recommend taking after the examination. Comparison of reviewers’ action decisions showed high diagnostic agreement.

Of note, when the University of Virginia investigators were developing their tele-cystoscopy program, they first optimized the technical infrastructure needed so that the real-time video images would have sufficient clarity for remote interpretation. In addition, they created a cystoscopy training program for APPs that included a competency scoring system.2

REFERENCE

Dual immunotherapy regimen shows early promise in urothelial carcinoma

Immune checkpoint blockade with PD-1 and PD-L1 inhibitors induced overall response rate of 42%

Jessica Hergert
Assistant Web Editor, OncologyLive®

Dual immune checkpoint blockade with the PD-1 inhibitor tislelizumab and the PD-L1 inhibitor BGB-A333 induced an overall response rate (ORR) of 42% in a small study of patients with urothelial carcinoma.3

The findings showed that among 12 patients receiving the immunotherapy combination, there were 3 complete responses (CRs), and 2 partial responses (PRs). Another 4 patients achieved stable disease, with 2 patients having progressive disease, and 1 patient not being evaluable. The median duration of response was 9.1 months. The ORR hit 67% (2 CRs; 2 PRs) among the subgroup of patients with PD-L1–high tumors. Among those with PD-L1–low tumors, the ORR was 17%.

“Simultaneous PD-L1 and PD-1 blockade has been hypothesized to provide synergistic antitumor effects, as inhibitors may have distinct mechanisms of action,” lead study author Juan Martin-Liberal, MD, PhD, a consultant medical oncologist in the Melanoma, Sarcoma, and Genitourinary Tumors Unit at the Institut Català d’Oncologia Hospitalat, in Barcelona, Spain, said when presenting the data during the 2020 European Society for Medical Oncology Virtual Congress. “[Although] these differences should be taken cautiously given the sample size, these data have provided insights into combining tislelizumab, a clinical stage anti–PD-1 antibody, with anti–PD-L1 antibodies.”

Martin-Liberal shared data from the phase 2B portion of the phase 1/2 BGB-900-101 study. Patients had locally advanced or metastatic urothelial carcinoma that had progressed after at least 1 platinum-containing regimen. Patients had a median age of 69.3 years, and 92% of patients were male. Ten patients had received 1 prior line of systemic therapy. PD-L1–high status was defined

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Genomic profiling of urothelial cancers finds many with actionable alterations

Wayne Kuznar
Urology Times® Correspondent

Comprehensive genomic profiling shows that more than one-third of patients with upper tract and bladder urothelial cancer have tier 1-2 genomic alterations, defined as those that potentially can benefit from approved or investigational targeted therapies.

Using a modified European Society for Medical Oncology Scale for Clinical Actionability of molecular Targets, of 2463 patients with urothelial cancer who underwent comprehensive genomic profiling, 39% harbored 1 or more tier 1-2 genomic alterations, and 29% had a tier 3 genomic alteration “that provides a strong rationale for clinical trial consideration,” according to researchers led by Andrea Necchi, from Fondazione IRCCS-Istituto Nazionale dei Tumori, Milan, Italy.

For their study, which appears in *Urology* Europe, tumor tissue samples for comprehensive genomic profiling were obtained from 479 patients with upper tract urothelial cancer and 1984 with bladder urothelial cancer. The distribution of genomic alterations was as follows:

- **The most frequently altered genes in both groups were** TERT (promoter region), TP53, and CDKN2A.
- **TERT** (68% vs 47%; *P* < .001) and **TP53** (58% vs 49%; *P* = .04) alterations were significantly more common in bladder cancer, while **CDKN2A** (35% vs 40%; *P* = .4) was more common in upper tract urothelial cancer.
- **RBI** alterations were more significantly frequent in bladder cancer versus upper tract (21% vs 8%; *P* < .001).
- **FGFR3** (26% vs 19%; *P* = .02) and **HRAS** (6.9% vs 2.8%; *P* = .006) alterations were more common in upper tract urothelial cancer versus bladder cancer. **FGFR3** mutations were more common in upper tract urothelial cancer (21% vs 14%; *P* = .002) while **FGFR3** amplifications (0.4% vs 0.5%), rearrangements (3.3% vs 3.9%), and cases with multiple **FGFR3** alterations (1.3% vs 1.0%), occurred at similar rates between patients with upper tract urothelial and bladder cancer.
- **The enrichment of HRAS** alterations in upper tract urothelial cancer arose from a greater frequency of alteration in renal pelvis tumors versus urothelial tumors (9.5% vs 1.8%; *P* = .002).
- **Non-FGFR3** kinase fusions were observed in only 1% of patients, including **BRAF/RAF1** fusions in 0.5%.
- **BRAF** mutations and/or fusions were found in 2% of cases and were mutually exclusive with **FGFR3** alterations (*P* = .002).
- **No significant differences in genomic alterations were observed between samples from the primary tumor and metastatic sites, except for the enrichment in primary site tumors of **RBI** in bladder urothelial cancer.**

There were no differences in tumor mutation burden—high (≥20 mut/Mb) or microsatellite-instability–high (MSI-H) status between primary tumor and metastatic sites, but upper tract urothelial cancer was enriched for MSI-H relative to bladder urothelial cancer (3.4% vs 0.8%; *P* = .001).

Genomic profiling of cell-free circulating tumor (ct)DNA was performed for 126 patients. Overall, there was a 69% positive percent agreement between ctDNA and tumor tissue, and 71% of cases shared at least 1 mutation. This concordance decreased with greater time lapse between acquisition of the 2 specimens.

According to the authors, “This study provides an additional rationale for the routine incorporation of ctDNA assays in clinical trials and possibly in clinical practice, especially when a recently obtained tumor tissue sample is not available and/or to complement tumor tissue analysis.”

They continued, “Outside of clinical trials, our study findings have potential implications for the selection of erdafitinib [Balversa], a pan-FGFR inhibitor, which currently has accelerated approval by the US Food and Drug Administration for the treatment of platinum-treated advanced urothelial carcinoma. The potential roles of ctDNA as a putative prognostic biomarker and its ability to detect actionable genomic alterations in patients with and without available tumor tissue are experiencing growing interest among investigators.”

**REFERENCE**

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**IMMUNOTHERAPY**

Continued from page 11

as PD-L1 staining on 25% or more of tumor or immune cells with the VENTANA SP263 assay. Patients received 1350 mg of intravenous (IV) BGB-A333 and 200 mg of IV tislelizumab every 3 weeks. The median treatment duration was 6.2 months and the median follow-up was 10 months.

The disease control rate (DCR) varied based on 1-2 genomic alterations, defined as those that potentially can benefit from approved or investigational targeted therapies.

In PD-L1–high patients, the DCR was 75%. In PD-L1–low patients, the disease control rate was 50% compared with 50% in PD-L1–low patients.

In the overall population, the median progression-free survival (PFS) was 6.1 months. In the PD-L1–high subgroup, the median PFS was 10 months compared with 4.1 months in the PD-L1–low subgroup.

Safety was evaluated in 39 patients, which included patients from phase 1 of the trial. Treatment-related adverse events (TRAEs) across all grades occurred in 20 patients, with the most common being fatigue (n = 4), maculopapular rash (n = 4), myalgia (n = 4), nausea (n = 4), pruritus (n = 1), asthenia (n = 2), back pain (n = 2), and diarrhea (n = 2). A total of 7 patients experienced a grade 3 or higher TRAE, including 1 report of fatigue and 1 report of maculopapular rash.

Two patients in the phase 2B portion of the study experienced immune-related AE s, which consisted of grade 3 endocrine disorders, grade 3 hypophysitis, grade 2 musculoskeletal and connective tissue disorder, and grade 2 myositis. There were no patient deaths related to study treatment.

**REFERENCE**
BCG SHORTAGE continued from page 1

Association of Clinical Urologists, the Urology Care Foundation, LUGPA, and the Bladder Cancer Advocacy Network (BCAN) met with representatives from Merck at the GU Cancers Symposium. We crafted a joint statement to try to help urologists manage patients during this shortage. We provided some guidelines to prioritize BCG for the patients who most needed it, such as patients with high-risk, high-grade non–muscle-invasive disease at their first diagnosis. Getting those patients through the induction and the first 3 months of maintenance treatments is critical. For patients who have already had a year or 2 of maintenance, we recommend curtailing that treatment.

With the statement, we were also trying to help urologists look for alternatives to BCG; namely intravesical chemotherapy for patients with intermediate-risk disease, where there's less of a distinction about the superiority of BCG over chemotherapy. We're trying to help urologists understand the AUA guidelines and where we think BCG can be most effective. But despite all of these efforts, the shortage persists, so we have to look for other strategies to help solve the problem.

Q: What are the recommendations for urologists currently?  
A: In high-risk patients for whom clinicians do not have access to BCG, we recommend a combination of chemotherapy drugs that can be delivered intravesically. We're currently using gemcitabine and docetaxel. This combination was originated by Michael O'Donnell, [MD] at the University of Iowa, and a number of centers are using it quite successfully for patients for whom we don't have BCG, or for patients who recur, after induction and 1 round of maintenance where they don't necessarily need to go on to a cystectomy.

Another strategy is to extend the use of a vial of BCG by dividing it into 2 or even 3 doses. There's actually a J code for that, but unfortunately, the payors haven't given us a way to charge for that appropriately. This remains a challenge for many practices, and efforts are needed to resolve this with CMS and other payors. Another strategy is proper use of perioperative single-dose chemotherapy for low- and intermediate-risk patients to try to reduce the risk of recurrence and the subsequent need for BCG. A recent Southwest Oncology Group (SWOG) trial showed that a single dose of perioperative intravesical gemcitabine, reduced the risk of recurrence by almost 50% at 4 years in patients with low-grade disease. 2 In patients with intermediate-risk disease—patients with multifocal or recurrent Ta low-grade cancer—an optimized regimen of mitomycin C first described in 2001 is easy to use and improves the efficacy of mitomycin. 3

What are the recommendations for urologists currently who do not have access to BCG?  
J. BRANTLEY THRASHER, MD

In high-risk patients for whom clinicians do not have access to BCG, we recommend a combination of chemotherapy drugs that can be delivered intravesically.

Q: What is the FDA doing to help address the shortage?  
A: The FDA is being very proactive. They fully recognize and appreciate the importance of solving this problem. The group of stakeholders that met at the 2019 ASCO Genitourinary Cancers Symposium convened again at the 2020 symposium. There were 2 representatives from the FDA at that meeting, and they expressed a very strong interest in working with us and anyone else in the community to try to solve this shortage.

The reality of it is that we need to get new strains of BCG into the US market. They have to go through the standard FDA approval process. In SWOG, we're currently conducting a trial led by Robert Svatek, [MD] (NCT03091660). This is a 3-arm, 969-patient trial for patients who have high-risk, high-grade disease and are BCG naïve. In the control arm, patients receive induction and maintenance TICE BCG, which is the current standard of care. We have a contract with Merck to guarantee the supply of TICE BCG for this trial. Patients in the other 2 arms receive the Tokyo-172 strain that was developed in Japan and has been around for decades. There are data suggesting that it is equivalent in efficacy to the Connaught strain and we will compare the efficacy of the Tokyo strain to TICE. We are also evaluating intradermal vaccination to prime the immune system prior to starting BCG treatment in order to improve the response rate. Failure-free survival at 1 year is the primary outcome measure. Two thirds of patients receive intravesical Tokyo-172, and half of those patients get vaccinated with Tokyo-172 BCG.

We've had multiple conversations with the FDA regarding the trial. They are very interested in looking at the patients with carcinoma in situ, who make up about one third of the patients in this trial. If the data support the efficacy of the Tokyo-172 strain for these patients, it's a potential pathway for regulatory approval for this BCG strain.

Companies are looking at bringing other strains into the US market. One company is looking at the Russian strain, which is used mostly in Europe and other parts of the world. They will also have to go through a very strict FDA review and approval process.

Q: Are there data to suggest a protective effect against bladder cancer in patients who have been vaccinated with BCG?  
A: I'm not sure how well that's been studied. We won't be able to answer that question in our trial, because previous vaccination is one of the exclusion criteria. The trial design was based upon Matthew Albert's, [MD, PhD] work from the Institut Pasteur. 4 He and his colleagues compared induction BCG in patients who were previously vaccinated and those who were not, and the vaccinated patients seemed to do better. 5

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BCG SHORTAGE
continued from page 13

a lot better but that was with induction only and no maintenance BCG. Conceptually, the idea is that you prime the immune system with vaccination 3 weeks prior to intravesical BCG, so that, where it normally takes between 4 to 6 intravesical instillations during induction to reach peak cytokine induction, we think that that would happen much earlier, and by virtue of that, yield better outcomes in terms of failure-free survival.

Q: You mentioned a couple of ways to potentially relieve the stress on urologists who can’t obtain BCG. Is there a role for thiопeta, adriamycin, valubicin, and some of the other agents that have been used in the past?
A: I think most urologists should be comfortable using mitomycin and gemcitabine. Here in Houston and the surrounding area, we’ve been very happy to guide clinicians in the use of intravesical chemotherapy drugs that they may not have a lot of experience with, particularly these combinations. I would say that if you don’t have experience, then simply reach out to your nearest academic urology department for guidance. These are really easy to use. We’re available for consultation, guidance, and treatment, if needed. I think most of us are in a situation where we currently have adequate BCG supply, but I’m still getting referrals for patients in my community from physicians who don’t have access to BCG.

Q: You mentioned boosting the immune system. I understand that you are involved with a trial evaluating BCG vaccinations for coronavirus disease 2019 (COVID-19).
A: Yes, this is something that a number of us have become involved with. Infectious disease experts here in the US, the Netherlands, and Australia have done a lot of work in this space, conducting research on BCG vaccination for tuberculosis globally. They observed that, epidemiologically, countries that had programmatic vaccination for tuberculosis from birth had about a 10-fold lower incidence of COVID-19 and about a 10-fold reduction in mortality rate compared with countries that did not have programmatic vaccination from birth. There is a fair amount of laboratory and experimental evidence to support why that might be. There are nonspecific immune effects of BCG vaccination that have been shown to reduce the risk of bacterial and viral respiratory infections, particularly yellow fever, which is another virally transmitted disease. The experimental evidence suggests that BCG causes epigenetic modification of immune cells that make them perhaps more alert to other foreign viruses; in this particular case, the novel coronavirus causing COVID-19.

As a result, the infectious disease community has put together randomized clinical trials comparing BCG vaccination to placebo, initially focusing on the highest risk health care workers, first responders, and the elderly. The trial that I am involved with is a collaboration with Baylor College of Medicine, The University of Texas MD Anderson Cancer Center (Ashish Kamat, MD, is 1 of the principal investigators), Texas A&M University, Cedars-Sinai Medical Center, and Harvard University (NCT04348370). This was largely conceived of and led by the infectious disease community, but they logically tapped into the urologic community because we have experience with BCG. The primary outcome measure is incidence of COVID-19, and the secondary outcome measure is disease severity. We do not feel these trials will have a material negative impact on BCG supply as a single vial that is used for 1 treatment of BCG in a patient with bladder cancer can vaccinate up to 500 patients.

Q: Is there anything else you’d like to add?
A: I serve on the board of directors for the Bladder Cancer Advocacy Network (BCAN). They have been very active in calling attention to the BCG shortage and trying to develop strategies for patients who face many challenges navigating this complex situation.

As a community, we must always be sensitive to the needs of patients, and work very closely with them. Consider a patient who is out 12 or 18 months and never returned, receiving their maintenance BCG and surveillance cystoscopies. Then their doctor tells them that, in order to manage this shortage, their treatment is being stopped. That can come as a big shock to patients, and it can create a lot of concern and anxiety. We can reassure them that they have already received most of the benefit and will continue close surveillance. In addition, we need to use BCG only for the highest risk patients. That will go a long way towards helping manage the shortage. Finally, we need to support clinical trials that could lead to getting new strains into the market as well as clinical trials evaluating other drugs that could be used to treat patients with alternative agents if shown to be as effective as BCG.

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Disclosures: Lerner has conducted clinical trials for Endo, FKI Therapies, JBL Science, Roche/Genentech, UroGen Pharma, Vexlion Therapeutics, Viventia Bio Inc; is a consultant/adviser for FerGene, Genentech, Merck, Pfizer/EMD Serono, QED Therapeutics, UroGen Pharma, Vexlion Therapeutics, and Verity Pharmaceuticals; has received honoraria from Grand Rounds in Urology and UroToday; and holds a patent for The Cancer Genome Atlas Classifier.
Final Analysis of SPARTAN Study Includes Overall Survival Data on ERLEADA® (apalutamide) in Patients With Non-Metastatic Castration-Resistant Prostate Cancer: What Does This Mean for Treatment?

In American men, prostate cancer is the most common form of cancer, other than skin cancer, and the second-leading cause of cancer death. One in 9 men will be diagnosed with the disease in his lifetime. Some will be diagnosed with a particular form of the disease known as non-metastatic castration-resistant prostate cancer (nmCRPC), which is disease that has not spread to other parts of the body, but no longer responds to medical or surgical treatment that lowers testosterone. 2

Within recent years, the US Food & Drug Administration (FDA) has approved multiple treatment options for patients with nmCRPC. These treatment options help delay metastasis, which is critical2 because the relative 5-year survival rate for patients diagnosed at distant-stage prostate cancer is 31%.4 In 90% of men, once prostate cancer metastasizes, it will spread to the bone, increasing the likelihood of pain, pathologic fractures, bone marrow failure, and spinal cord compression.3

One treatment option is ERLEADA® (apalutamide), the first FDA-approved therapy to treat nmCRPC, based on results from the Phase 3 SPARTAN clinical trial.6,7 ERLEADA® is also approved for the treatment of patients with metastatic castration-sensitive prostate cancer (mCSPC) based on results from the Phase 3 TITAN study.8,9

The SPARTAN trial was a Phase 3, randomized, double-blind, placebo-controlled, multicenter study that evaluated ERLEADA® plus androgen-deprivation therapy (ADT) in patients with nmCRPC who had a prostate-specific antigen (PSA) doubling time less than or equal to 10 months.7,9 The SPARTAN study enrolled 1207 patients who were randomized 2:1 to receive either ERLEADA® orally at a dose of 240 mg once daily plus ADT (n=806) or placebo once daily plus ADT (n=401).8 Results from the primary analysis showed that, compared with placebo plus ADT, ERLEADA® plus ADT met the trial’s primary endpoint of metastasis-free survival (MFS), prolonging median MFS by more than 2 years (difference of 24.3 months) and reduced the risk of metastasis by 72% (HR=0.28; 95% CI, 0.23-0.35; P<0.0001).9 The SPARTAN primary analysis was first presented at the 2018 American Society of Clinical Oncology Genitourinary Cancers Symposium (ASCO GU) and simultaneously published in The New England Journal of Medicine.

While MFS is the primary endpoint in the SPARTAN trial, overall survival (OS), a secondary endpoint in the SPARTAN trial, may provide the most objective and clear measure of survival benefit.10 OS data from the SPARTAN trial were not mature at the time of the final MFS analysis (24% of the required number of events).11 The final analysis, which was presented at the ASCO 2020 Virtual Scientific Program, included OS data, a secondary endpoint.11 These data, published in European Urology, are not included in the ERLEADA® Full Prescribing Information.

The SPARTAN final analysis demonstrated that ERLEADA® plus ADT significantly improved OS, compared with ADT alone, in patients with nmCRPC who were at high risk of developing metastases.12,13 Specifically, ERLEADA® plus ADT demonstrated a median OS that was significantly longer than seen for placebo plus ADT: 73.9 months compared with 59.9 months [HR=0.78; 95% CI; P=0.016 (the P value for OS confirmed a statistically significant improvement of OS, crossing the prespecified O’Brien-Fleming boundary of 0.046)].11 Median treatment duration was 21.4 months longer for patients treated with ERLEADA® plus ADT (32.9 months) compared with those treated with placebo plus ADT (11.5 months).11

Treatment with ERLEADA® plus ADT significantly delayed patients’ time to cytotoxic chemotherapy by 37%, a secondary endpoint, compared with placebo plus ADT (HR=0.63; 95% CI [0.49-0.81]; P=0.0002).11

Grade 3/4 treatment-emergent adverse events of special interest for ERLEADA® plus ADT were rash (5.2%), fractures (4.9%), falls (2.7%), hypothyroidism (0%) and seizures (0%).11 Safety and tolerability of ERLEADA® is consistent and as reported previously. The most common adverse reactions (≥10%) in ERLEADA*-treated patients (≥2% over placebo) from the randomized placebo-controlled clinical trials (SPARTAN and TITAN) were fatigue, arthralgia, rash, decreased appetite, fall, decreased weight, hypertension, hot flush, diarrhea, and fracture.10

The final analysis of SPARTAN demonstrated that, in addition to improved MFS and time to symptomatic progression reported previously, ERLEADA® plus ADT improved OS and lengthened time to initiation of cytotoxic chemotherapy in patients with nmCRPC. With additional Phase 3 registrational trials underway, SPARTAN has the longest follow-up period (52 months) of the registrational trials that supported indications for the treatment of nmCRPC.10,12,13,14,15,16

ERLEADA® IMPORTANT SAFETY INFORMATION6

WARNINGS AND PRECAUTIONS

Ischemic Cardiovascular Events — In a randomized study (SPARTAN) of patients with nmCRPC, ischemic cardiovascular events occurred in 4% of patients treated with ERLEADA® and 3% of patients treated with placebo. In a randomized study (TITAN) in patients with mCSPC, ischemic cardiovascular events occurred in 4% of patients treated with ERLEADA® and 2% of patients treated with placebo. Across the SPARTAN and TITAN studies, 6 patients (0.5%) treated with ERLEADA® and 2 patients (0.2%) treated with placebo died from an ischemic cardiovascular event. Patients with current evidence of unstable angina, myocardial infarction, or congestive heart failure within 6 months of randomization were excluded from the SPARTAN and TITAN studies. Ischemic cardiovascular events, including events leading to death, occurred in patients receiving ERLEADA®. Monitor for signs and symptoms of ischemic heart disease. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Consider discontinuation of ERLEADA® for Grade 3 and 4 events.

Fractures — In a randomized study (SPARTAN) of patients with nmCRPC, fractures occurred in 12% of patients treated with ERLEADA® and in 7% of patients treated with placebo. In a randomized study (TITAN) of patients with mCSPC, fractures occurred in 9% of patients treated with ERLEADA® and in 6% of patients treated with placebo. Evaluate patients for fracture risk. Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone-targeted agents.

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

Seizure — In 2 randomized studies (SPARTAN and TITAN), 5 patients (0.4%) treated with ERLEADA® and 1 patient treated with placebo (0.1%) experienced a seizure. Permanently discontinue ERLEADA® in patients who develop a seizure during treatment. It is unknown whether anti-epileptic medications will prevent seizures with ERLEADA®. Advise patients of the risk of developing a seizure while receiving ERLEADA® and of engaging in any activity where sudden loss of consciousness could cause harm to themselves or others.

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

ADVERSE REACTIONS

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

This supplement is sponsored by Janssen Biotech, Inc.

6 ERLEADA® Full Prescribing Information.
Concomitant use of ERLEADA® with medications that are substrates of P-gp, BCRP, or OATP1B1 can result in lower exposure of these medications. Use caution if substrates of P-gp, BCRP or OATP1B1 must be co-administered with ERLEADA® and evaluate for loss of activity if medication is continued.

Please see the full Prescribing Information for ERLEADA®.

REFERENCES:

This supplement is sponsored by Janssen Biotech, Inc.
Adjuvant RT after prostatectomy does not improve recurrence rate

PSA monitoring, early salvage therapy appears to be safest in these patients

Despite previous randomized controlled studies demonstrating a benefit from post-prostatectomy adjuvant radiation therapy (RT), urologists have been slow to adopt this approach. This may be related to inconsistencies in the reported outcomes as well as the timing of salvage RT, which was thought to have been initiated much later than the contemporary clinical practice. Consequently, 3 randomized controlled trials (RADICALS-RT, GETUG-AFU 17, and RAVES) were initiated nearly a decade ago to evaluate the oncologic outcomes after adjuvant RT or early-salvage RT in post-prostatectomy patients with high-risk and/or locally advanced pathology. Recently, a combined analysis of these 3 trials was reported, which did not demonstrate any advantage to adjuvant RT when compared to early-salvage RT; that is, following rise in prostate-specific antigen (PSA) level after prostatectomy.

Vale and colleagues prospectively planned a systematic review and meta-analysis of the combined data from the 3 trials before the final results were available to assess whether adjuvant RT was superior to early-salvage RT. Individually, the 3 trials were powered for different primary outcomes such as time free of metastases (RADICALS-RT), event-free survival (GETUG-AFU 176), and biochemical progression (RAVES). Inclusion criteria for the trials varied slightly but included the following: postoperative PSA less than 0.2 ng/mL, and one or more high-risk features including stage pT3 or 4, Gleason score 7–10, or positive surgical margins.

After randomization, adjuvant RT was to be initiated within 6 months after surgery while early-salvage RT for biochemical recurrence was to be initiated at PSA level of 0.2 ng/mL (0.1 ng/mL for RADICALS-RT). The RT dose was quite similar in all 3 trials; that is, 64 to 66 Gy in 32 to 33 fractions. The concurrent use of hormone therapy was variable across the 3 trials. For this meta-analysis, the agreed-upon primary outcome measure was event-free survival. An event after randomization was defined as the first evidence of any of the following: biochemical progression (PSA ≥ 0.4 ng/mL), clinical or radiological progression, initiation of additional treatment, and PSA level of at least 2.0 ng/mL at any time after randomization.

In the 3 trials combined, 2153 patients were recruited between November 2007 and December 2016. Of these, 1075 patients were randomly assigned to receive adjuvant RT and 1078 were assigned to early-salvage RT. Median age was 64 to 65 years. A majority of patients had either stage pT3a/b disease (79.8%), positive surgical margins (70.9%), and extracapsular extension (76.9%). The median follow-up ranged from 60 to 78 months.

There were 270 (12.5%) events recorded out of the 2153 randomized patients. The pooled event-free survival analysis yielded an overall hazard ratio of 0.95 (95% CI, 0.75–1.21; P = 0.70) which translates into an overall 5% absolute difference between adjuvant RT and early-salvage RT groups. Further, there was no advantage to adjuvant RT on event-free survival when analyzed based on pre-specified subgroups including pre-surgical PSA, Gleason score, seminal vesicle involvement, surgical margins, or CAPRA-S risk group. In the group assigned to early-salvage RT, only 421 (39.1%) had required RT at the time of this analysis. A majority of the men remained free of biochemical progression at 5 years (87% in RAVES, 88% in RADICALS-RT, and 94% in GETUG-AFU 17). It seems clear from this meta-analysis that adjuvant RT for men with high-risk, localized, or locally advanced prostate cancer after prostatectomy does not improve event-free survival. These results are in contrast to the previous trials (from EORTC and SWOG), which had demonstrated improved biochemical recurrence rates following adjuvant RT in these men. However, the enthusiasm for adjuvant RT remained limited due to the timing of salvage RT in previous trials (which was initiated much later than the contemporary practice), and concerns about the risks of over-treatment and adverse events of adjuvant RT (such as urinary, bowel, and sexual dysfunction).

The unique design of current meta-analysis can remove some of the biases associated with retrospective meta-analyses and provides an increased number of subjects to allow for sufficiently powered analysis of longer-term survival outcomes. The authors were able to include up-to-date, event-free survival results from 100% of patients randomized in all 3 trials. However, it should be noted that the recurrence events were dominated by biochemical recurrence and not clinical or radiological recurrence, and the overall event (recurrence) rates were low.

The results of additional analyses (which are pre-planned by the authors), of the effects of adjuvant vs early-salvage RT on metastases-free survival, prostate-cancer specific survival, and overall survival are awaited. It’s possible that after longer follow up, the timing of RT and the use of hormone therapy may yield different results in a subgroup with multiple high-risk features. For now, avoiding adjuvant RT (and associated adverse events) in favor of PSA monitoring and early-salvage therapy appears to be the safest initial option for post-prostatectomy patients with adverse pathology.

REFERENCE
Prostate Cancer / CLINICAL UPDATES

CDC warns incidence of metastatic prostate cancer on the rise

Rate of localized cases saw decrease over same period of time, researchers report

Jason M. Broderick
Associate Editorial Director, Urology Times®

Over the past decade, the incidence of metastatic prostate cancer in the United States has been on the rise, according to an analysis published in the Centers for Disease Control and Prevention Morbidity and Mortality Weekly Report.1

Between 2003 and 2017, the percentage of patients diagnosed with metastatic prostate cancer increased from 4% to 8%. This increase occurred even though the overall age-adjusted incidence of prostate cancer in the United States went down from 155 per 100,000 in 2003, to 105 per 100,000 in 2017.

“Although approximately three-fourths of US men with prostate cancer have localized stage at diagnosis, an increasing number and percentage of men have received diagnoses of distant stage prostate cancer. Survival with distant stage prostate cancer has improved, but fewer than one-third of men survive 5 years after diagnosis,” the investigators wrote.

The CDC analysis examined data from the population-based cancer registries that are used for the official US Cancer Statistics (USCS) composite. Overall, there were 3,087,800 new prostate cancer cases diagnosed in the United States between 2003 and 2017. The incidence was highest among men aged 70-74 years and African American men. The vast majority of these cases were localized (77%), followed by regional (11%), metastatic (5%), and unknown (7%). Compared to all other races/ethnicities, Caucasian men had the lowest rates of metastatic (5%) and unknown stage (6%) disease at diagnosis.

Although the rate of patients diagnosed with metastatic disease increased between 2003 and 2017, in that same period, the rate of localized cases decreased from 78% to 70%, respectively. Survival data available for 3,104,380 men across all disease stages showed that between 2001 and 2016, the 5-year relative survival rate was 97.6% and the 10-year relative survival rate was 97.2%. The 10-year relative survival rates for men with localized versus metastatic disease were 100% versus 18.3%, respectively. The 10-year rates were 96.1% for patients with regional disease and 78.1% for patients whose disease status was unknown.

Of note, when comparing 5-year relative survival for the periods of 2001-2005 and 2011-2016, the rate improved from 28.7% to 32.3% in patients with metastatic disease. The authors suggested that the improvement might be attributed to recent advances in the prostate cancer armamentarium, including novel antibody and hormone treatments.

Although the 5-year survival rate was higher for Caucasian versus African American or Latin American men when combining all stages of prostate cancer, the 5-year survival rate for patients with metastatic disease was higher for African American and Latin American men compared with Caucasian men. The 5-year survival rates by race for men diagnosed with metastatic cancer between 2001 and 2016 were 42% for Asian/Pacific Islander; 37.2% for Latin Americans; 32.2% for American Indian/Alaska Native; 31.6% for African American men; and 29.1% for Caucasian men.

The investigators wrote that 1 explanation for the recent uptick in the incidence of metastatic disease was the US Preventive Services Task Force (USPSTF) issuing a grade D recommendation in 2012 against the use of PSA screening in the general US population, regardless of age.

“This recommendation likely contributed to a decrease in overall reported prostate cancer incidence and might have contributed to an increase in the percentage and incidence of distant stage prostate cancer,” they wrote.

The current USPSTF PSA screening policy is slightly changed, with a grade C recommendation for men aged 55 to 69 years, meaning in this population, an individual decision on screening should be made based on a physician-clinician discussion of the potential benefits and risks. However, many urologists still find this recommendation lacking.

In their concluding remarks, the CDC investigators wrote, “Understanding incidence and long-term survival by stage, race/ethnicity, and age could inform messaging related to the possible benefits and harms of prostate cancer screening and could guide public health planning related to treatment and survivor care. Further research is needed to examine how social determinants of health affect prostate cancer diagnosis and treatment; findings should inform interventions to decrease disparities in outcomes.”

REFERENCE

HIFU is a safe and effective ablation option in prostate cancer

Jason M. Broderick
Associate Editorial Director, Urology Times®

Use of focal high-intensity focused ultrasound (HIFU) was shown to be effective and safe in patients with localized prostate cancer, according to findings published in the Journal of Urology.1

At a minimum follow-up of 12 months, 83% of patients receiving HIFU had negative in-field biopsy results. Thirteen percent of patients had de novo positive out-of-field biopsy. There were no complications above grade 3, and only 5 total grade 3 events occurred. Within 3 to 6 months of treatment, questionnaire scores returned to baseline levels for urinary symptoms, and sexual function scores returned to baseline levels by 12 months.

HIFU demonstrated “acceptable short-term oncologic and functional outcomes. The complications are minimal and patient selection is essential. Short-term oncologic outcomes are promising but longer follow-up is required to establish long-term oncologic outcomes,” the investigators wrote.

The single-center, prospective study assessed data for 52 patients who received primary focal HIFU between January 2016 and July 2018. The median patient age was 67 years (range, 49-88), the median patient PSA level at baseline was 5.5 ng/mL (range, 1.6-25.9), and the median prostate volume on TRUS was 34 (range, 14-84).

Overall, 67% of patients had tumors that were grade group (GG) 2 or greater. At baseline, there were 17 patients in GG1 (Gleason, 3+3); 24 in...
Short-term outcomes suggest feasibility of active surveillance for these patients

Cheryl Guttmann Krader, BSPharm
Urology Times® Contributing Editor

Findings from an analysis of short-term oncologic outcomes suggest that active surveillance may be a feasible strategy for management of low-risk prostate cancer in men carrying germline DNA repair gene mutations, concluded Israeli urologists who reported their experience in the Journal of Urology.1 However, the authors emphasized as a caveat the need for close monitoring and cautious discussion of this option with patients, pending more outcomes data from larger patient cohorts with longer follow-up.

The paper reported on 15 men with germline DNA repair gene mutations who initiated active surveillance at the Rabin Medical Center in Petah Tikva, Israel, after receiving a diagnosis of low-risk (Gleason grade group 1) prostate cancer. Fourteen men (93.3%) were fully adherent to the active surveillance protocol, which included prostate-specific antigen (PSA) level measurement every 3 months and multiparametric MRI (mpMRI) and MRI-ultrasound fusion biopsy within 1 year and annually thereafter. During a median follow-up of 28 months, 3 men (20%) had upgrading at confirmatory biopsy and underwent definitive treatment, whereas the remaining 12 men (80%) continued on active surveillance without upgrading or treatment.

David Margel, MD, PhD, professor of urology at the Sackler Faculty of Medicine at Tel Aviv University in Israel and senior author of the paper, told Urology Times®, “This is the first prospective study that shows it is feasible to perform active surveillance among men with BRCA2 and other DNA repair gene mutations. Most physicians and patients are afraid to lose the window of curability in this situation. Our study comprises a small cohort with short follow-up, but our finding that the progression rate is similar to that seen in other active surveillance cohorts is encouraging.”

Commenting on the study, Leonard G. Gomella, MD, noted that germline testing is slowly finding its proper place in the management of prostate cancer. “Testing for germline DNA repair gene mutations is being used to inform decisions on screening and applied to treatment decisions such as active surveillance and in the management of advanced disease,” said Gomella, the Bernard W. Godwin Professor of Prostate Cancer and chairman of the Department of Urology at Thomas Jefferson University in Philadelphia, Pennsylvania.

The study encompassed the period between May 2014 and February 2019. It included a total of 18 men who had a diagnosis of very low- or low-risk prostate cancer and who were found to have a germline DNA repair gene mutation, the most common being in BRCA1 and BRCA2. All men had stage T1c and Gleason grade group 1 disease in up to 3 cores. After receiving thorough counseling on active surveillance, 3 men chose to undergo definitive treatment. The 1 patient in active surveillance who was not fully adherent to the follow-up protocol declined to undergo fusion biopsy after being found to have normal PSA kinetics and no abnormalities in his mpMRI. Two men in active surveillance had implanted metallic devices that prevented them from having mpMRI, 1 had a confirmatory biopsy within 6 months after diagnosis because of a significant rise in PSA level, and a fourth man had not reached the 1-year follow-up.

Three men had upgrading on confirmatory biopsy to Gleason grade 2 and underwent treatment with radical prostatectomy or focal high-intensity focused ultrasound. All 3 men had organ-confined disease and were free of biochemical recurrence at last follow-up.

Margel told Urology Times® that the group’s active surveillance cohort of men with low-risk prostate cancer who are germline DNA repair gene carriers now includes 24 patients.

“The progression rate in this expanded group is approximately 30%, and all the men who progressed had organ-confined disease,” he said.

“Germline DNA repair gene carriers are rare in the [patient population with] prostate cancer, and the only way to enroll a large active surveillance cohort will be through a collaborative effort. We are now trying to coordinate that with other groups in Israel,” Margel concluded.

REFERENCE
YONSA® is the only abiraterone acetate that is micronized, a process that increases surface area and enables more rapid dissolution and absorption.¹

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**INDICATION**

YONSA® (abiraterone acetate) in combination with methylprednisolone is indicated for the treatment of patients with metastatic castration-resistant prostate cancer (CRPC).  

**Important Administration Instructions**

YONSA® may not be interchangeable with other abiraterone acetate products. To avoid substitution errors and overdose, be aware that YONSA® tablets may have different dosing and food effects than other abiraterone acetate products. Patients receiving YONSA® should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy.

**IMPORTANT SAFETY INFORMATION**

**CONTRAINDICATIONS**

YONSA® can cause fetal harm and potential loss of pregnancy.

Please see the following pages for Important Safety Information and Brief Summary of the Full Prescribing Information.
IMPORTANT SAFETY INFORMATION, CONTINUED

WARNINGS AND PRECAUTIONS

Hypertension, Hypokalemia, and Fluid Retention Due to Mineralocorticoid Excess: YONSA® may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition. Monitor patients for hypertension, hypokalemia, and fluid retention at least once a month. Control hypertension and correct hypokalemia before and during treatment with YONSA®.

Closely monitor patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalemia or fluid retention, such as those with heart failure, recent myocardial infarction, cardiovascular disease, or ventricular arrhythmia. The safety of YONSA® in patients with left ventricular ejection fraction < 50% or New York Heart Association (NYHA) Class III or IV heart failure (in Study 1) or NYHA Class II to IV heart failure (in Study 2) was not established because these patients were excluded from these randomized clinical trials.

Adrenocortical Insufficiency (AI): AI was reported in patients receiving abiraterone acetate in combination with corticosteroid, following an interruption of daily steroids and/or with concurrent infection or stress. Monitor patients for symptoms and signs of AI, particularly if patients are withdrawn from corticosteroids, have corticosteroid dose reductions, or experience unusual stress. Symptoms and signs of AI may be masked by adverse reactions associated with mineralocorticoid excess seen in patients treated with YONSA®. Perform appropriate tests, if indicated, to confirm AI. Increased dosages of corticosteroids may be used before, during, and after stressful situations.

Hepatotoxicity: In postmarketing experience, there have been abiraterone acetate-associated severe hepatic toxicity, including fulminant hepatitis, acute liver failure and deaths. Measure serum transaminases (ALT and AST) and bilirubin levels prior to starting treatment with YONSA®, every two weeks for the first three months of treatment and monthly thereafter. In patients with baseline moderate hepatic impairment receiving a reduced YONSA® dose of 125 mg, measure ALT, AST, and bilirubin prior to the start of treatment, every week for the first month, every two weeks for the following two months of treatment and monthly thereafter. Promptly measure serum total bilirubin, AST, and ALT if clinical symptoms or signs suggestive of hepatotoxicity develop. Elevations of AST, ALT, or bilirubin from the patient’s baseline should prompt more frequent monitoring. If at any time AST or ALT rise above five times the ULN, or the bilirubin rises above three times the ULN, interrupt YONSA® treatment and closely monitor liver function.

Re-treatment with YONSA® at a reduced dose level may take place only after return of liver function tests to the patient’s baseline or to AST and ALT less than or equal to 2.5X ULN and total bilirubin less than or equal to 1.5X ULN.

Permanently discontinue treatment with abiraterone acetate for patients who develop a concurrent elevation of ALT greater than 3X ULN and total bilirubin greater than 2X ULN in the absence of biliary obstruction or other causes responsible for the concurrent elevation.

The safety of YONSA® re-treatment of patients who develop AST or ALT greater than or equal to 20X ULN and/or bilirubin greater than or equal to 10X ULN is unknown.

ADVERSE REACTIONS

The most common adverse reactions (>10%) are fatigue, joint swelling or discomfort, edema, hot flush, diarrhea, vomiting, cough, hypertension, dyspnea, urinary tract infection and confusion.

The most common laboratory abnormalities (>20%) are anemia, elevated alkaline phosphatase, hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyperglycemia, elevated AST, hypophosphatemia, elevated ALT and hypokalemia.

DRUG INTERACTIONS

Based on in vitro data, YONSA® is a substrate of CYP3A4. In a drug interaction trial, co-administration of rifampin, a strong CYP3A4 inducer, decreased exposure of abiraterone by 55%. Avoid concomitant strong CYP3A4 inducers during YONSA® treatment. If a strong CYP3A4 inducer must be co-administered, increase the YONSA® dosing frequency only during the co-administration period. Abiraterone is an inhibitor of the hepatic drug-metabolizing enzymes CYP2D6 and CYP2C8. Avoid coadministration of abiraterone acetate with substrates of CYP2D6 with a narrow therapeutic index (e.g., thioridazine). If alternative treatments cannot be used, exercise caution and consider dose reduction of the concomitant CYP2D6 substrate drug.

In a CYP2C8 drug-drug interaction trial in healthy subjects, the AUC of pioglitazone (CYP2C8 substrate) was increased by 46% when pioglitazone was given together with an abiraterone acetate single dose equivalent to YONSA® 500 mg. Therefore, patients should be monitored closely for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly with abiraterone acetate.

USE IN SPECIFIC POPULATIONS

- Females and Males of Reproductive Potential: Advise male patients with female partners of reproductive potential to use effective contraception.
- Do not use YONSA® in patients with baseline severe hepatic impairment (Child-Pugh Class C).

Please see the following page for the Brief Summary of the Full Prescribing Information.

Brief Summary of Prescribing Information for YONSA® (abiraterone acetate) tablets
This Brief Summary does not include all the information needed to use YONSA safely and effectively.
See full prescribing information for YONSA.

INDICATIONS AND USAGE:
YONSA (abiraterone acetate) is indicated in combination with methylprednisolone for the treatment of patients with metastatic castration-resistant prostate cancer.

CONTRAINDICATIONS:
YONSA is contraindicated for use in pregnant women. YONSA can cause fetal harm and potential loss of pregnancy.

Dosage and Administration:
Recommended dose: YONSA 500 mg (four 125 mg tablets) administered orally once daily in combination with methylprednisolone 4 mg administered orally twice daily. Patients receiving YONSA should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy.

To avoid medication errors and overdose, be aware that YONSA tablets may have different dosing and food effects than other abiraterone acetate products.

WARNINGS AND PRECAUTIONS:
YONSA may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition. Monitor patients for hypertension, hypokalemia, and fluid retention at least once a month. Control hypertension and correct hypokalemia before and during treatment with YONSA.

Monitor for symptoms and signs of adrenocortical insufficiency. Increased dosage of corticosteroids may be indicated before, during and after stressful situations.

Hepatotoxicity can be severe and fatal. Measure serum transaminases (ALT and AST) and bilirubin levels prior to starting treatment with YONSA, every two weeks for the first three months of treatment and monthly thereafter.

ADVERSE REACTIONS:
The most common adverse reactions (≥10%) are fatigue, joint swelling or discomfort, edema, hot flush, diarrhea, vomiting, cough, hypertension, dyspnea, urinary tract infection and contusion.

The most common laboratory abnormalities (≥20%) are anemia, elevated alkaline phosphatase, hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyperglycemia, elevated AST, hypophosphatemia, elevated ALT and hypokalemia.

DRUG INTERACTIONS:
CYP3A4 Inducers: Avoid concomitant strong CYP3A4 inducers during YONSA treatment. If a strong CYP3A4 inducer must be co-administered, increase the YONSA dosing frequency.

CYP2D6 Substrates: Avoid co-administration of YONSA with CYP2D6 substrates that have a narrow therapeutic index. If an alternative treatment cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate.

USE IN SPECIFIC POPULATIONS:
Females: Women who are pregnant or women who may be pregnant should not handle YONSA tablets without protection, e.g., gloves.

Males of Reproductive Potential: Males with female partners of reproductive potential should use effective contraception.

Hepatic Impairment: Do not use YONSA in patients with baseline severe hepatic impairment (Child-Pugh Class C).

Pediatric Use: Safety and effectiveness of abiraterone acetate in pediatric patients have not been established.

To report SUSPECTED ADVERSE REACTIONS, contact Sun Pharmaceutical Industries, Inc. at 1-800-818-4555, FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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Sun Pharma Global FZE

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Sun Pharmaceutical Industries, Inc.
Cranbury, NJ 08512

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Rx ONLY
Why is rucaparib response higher in BRCA2-mutated prostate cancer?

Investigators present 2 hypotheses for variance in sensitivity to PARP inhibition

Jason M. Broderick
Associate Editorial Director, Urology Times®

The diminished clinical activity of rucaparib (Talzenna) and other poly(ADP-ribose) polymerase (PARP) inhibitors in patients with prostate cancer with BRCA1 versus BRCA2 mutations may be explained by zygosity status and additional genomic alterations, according to an editorial published in the Journal of Clinical Oncology.1

In the editorial, coauthors Mark C. Markowski, MD, PhD, and Emmanuel S. Antonarakis, MD, both from Johns Hopkins University School of Medicine, Baltimore, Maryland explained that the variance in sensitivity to PARP inhibition between BRCA1- and BRCA2-mutated tumors appears to be consistent across this class of agents. They compiled a pooled analysis of PARP inhibitors across several trials (olaparib [Lynparza]: TOPARP-A, TOPARP-B, and PROfound; rucaparib: TRITON2; and talazoparib [Talzenna]: TALAPRO-11) showing that the objective response rate (ORR) was 26.3% (5/19) in BRCA1-positive patients compared with 50% (79/158) in BRCA2-positive patients.

In their editorial, Markowski and Antonarakis provided a deeper dive into the TRITON2 data. The open-label, multicenter, international TRITON2 study, which led to the FDA approval of rucaparib in BRCA1-positive metastatic castration-resistant prostate cancer (mCRPC), enrolled male patients with mCRPC associated with 1 of 13 homologous recombination repair gene alterations. Patients had disease progression on androgen receptor–directed therapy and 1 prior taxane-based chemotherapy.

In the study, the PARP inhibitor induced a confirmed ORR per independent review of 43.5% in heavily pretreated patients with mCRPC and a deleterious BRCA1 alteration.2 The ORR was 45.3% in patients with BRCA2 mutations compared with 33.3% in patients with BRCA1 mutations. Further, the PSA response rate was 59.8% versus 15.4%, respectively.

The authors generated several potential hypotheses explaining the variation in response, and considered 2 to have the most potential. The first hypothesis was that BRCA1 alterations are less commonly biallelic mutations compared to BRCA2 alterations. In TRITON2, biallelic mutations were associated with a higher PSA response rate versus mononucleic mutations, at 75% versus 11%, respectively. Among patients in TRITON2 evaluable for zygosity status, only 40% (2/5) of patients with BRCA1 mutations had biallelic alterations, as compared with 85% (34/40) of BRCA2 mutations. The authors wrote that other recent research yielded similar findings.

The second hypothesis Markowski and Antonarakis determined to be likely was that tumors with BRCA1 mutations are more likely than BRCA2-mutated tumors to have additional genomic alterations, such as TP53 or PTEN, associated with a poor prognosis. Having such mutations could lead to these patients showing a reduced sensitivity to PARP inhibitors. Along this line, it was shown in TRITON2 that coalterations in TP53 and PTEN were more common in patients with BRCA1 versus BRCA2 mutations at 62% versus 42% and 69% versus 29%, respectively.

The investigators corroborated these findings using data from the cBioPortal for Cancer Genomics. In their concluding remarks, Markowski and Antonarakis urged caution when extrapolating their findings to the population at large.

“Ultimately, because of the relative rarity of both germline and somatic BRCA1 mutations compared with BRCA2 mutations in prostate cancer (unlike the situation in breast or ovarian cancers, where the prevalence of 2 genes is roughly equal), our conclusions related to PARP inhibitor sensitivity should be interpreted with caution,” the authors wrote.

“Additional studies and meta-analyses will be required to gain clearer insights on the potential differential efficacy of PARP inhibitors in prostate cancers with BRCA1 versus BRCA2 mutations and to understand the biologic mechanisms underpinning this phenomenon,” added Markowski and Antonarakis.

REFERENCES

Most men receive darolutamid at full, planned dose in pivotal nmCRPC trial

Jason M. Broderick
Associate Editorial Director, Urology Times®

Over 97% of men with nonmetastatic castration-resistant prostate cancer (CRPC) received the full, planned dose of darolutamide (Nubeqa) in the pivotal phase 3 ARAMIS trial, according to an ad hoc analysis presented during the 2020 European Society for Medical Oncology Virtual Congress.3

The ARAMIS trial randomized patients to androgen-deprivation therapy (ADT) plus either darolutamide at a dose of 600 mg twice daily, or placebo. At the time of the ad hoc analysis, the median time on treatment was 16.5 versus 11.6 months in the darolutamide versus control arms, respectively. At a median follow-up of 14.8 months, 97.2% of patients had been treated with the full, planned dose of darolutamide/ADT compared with 98.4% who received the full ADT dose in the control arm.

Dose modifications were required in 15.2% versus 9.7% of the darolutamide versus control arms, respectively; however, 91.7% and 88.9% of these patients, respectively, were eventually able to return to the full, planned dose.

“In clinical practice, ability to maintain planned dose and schedule are important considerations,” Matthew Smith, MD, PhD, director of the Genitourinary Malignancies Program, Massachusetts General Hospital Cancer Center, Boston, said in a press release. “These data support darolutamide’s value as a treatment option in men with nonmetastatic CRPC.”

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Report adds insight on prostate MRI for monitoring during active surveillance

Cheryl Guttmann Krader, BPharm
Urology Times® Contributing Editor

Findings from analyses of data collected in the multicenter prospective Canary Prostate Cancer Active Surveillance Study are adding to the body of literature regarding the utility and shortcomings of prostate magnetic resonance imaging (MRI) in active surveillance of men with low-grade prostate cancer.1

Describing their study as the largest cohort data on this topic, the investigators concluded its evidence suggests that a negative MRI in a patient on active surveillance does not ensure a lack of tumor upgrading. Furthermore, based on the findings, they recommended that systematic biopsy be performed in patients with negative MRI and in addition to targeted biopsies in men with a positive MRI.

The follow-up protocol for men enrolled in the Canary study included quarterly PSA testing, semiannual digital rectal examination, and surveillance prostate biopsies at 1 and 2 years after initial diagnosis and biennially thereafter. The performance of prostate MRI was left to the clinician’s discretion as was the technique used for prostate biopsy (cognitive or MRI/ultrasound fusion image guidance and amount of systematic sampling added to targeted biopsy cores). MRI images were graded based on PI-RADS.

To evaluate the diagnostic performance of MRI in active surveillance, the investigators identified men who had Gleason grade group less than 2 and a prostate biopsy with 12 months of multiparametric MRI. Their study included a total of 361 men who had 395 MRI studies and a median follow-up of 4.1 years. Of the 395 imaging studies, 284 were classified as positive based on the presence of a PI-RADS 3-5 lesion.

Biopsy reclassification to Gleason grade group 2 or greater on post-MRI biopsy was evaluated as the primary outcome, and 108 (27%) of the biopsies met the criterion for reclassification. The evaluation of MRI diagnostic performance showed that it had a positive predictive value of 31% and a negative predictive value of 83%, indicating that a negative MRI would miss a substantial proportion of patients with higher grade cancer. The negative predictive value of MRI was 82% if the definition of a positive MRI was changed to include only PI-RADS 4 or 5 lesions.

The investigators also created multivariable logistic regression models to assess the value of MRI for predicting biopsy reclassification. A base model incorporated only clinical factors (age, body mass index, number of negative biopsies after diagnosis, percent of total biopsy cores containing cancer from the previous biopsy, log-transformed prostate size, and log-transformed serum PSA), and a second model incorporated PI-RADS score.

Although presence of a PI-RADS 5 lesion versus a PI-RADS 1 or 2 lesion was found to be significantly associated with cancer reclassification to Gleason grade group 2 or greater, results of receiver operating curve analyses showed that discrimination between patients with and without biopsy reclassification improved only minimally by adding the PI-RADS score to the base model.

Another analysis evaluated the utility of MRI fusion biopsy by comparing the detection of high grade cancer in targeted versus systematic biopsies. It included data from 194 fusion biopsies and showed that the systematic biopsies detected a similar number of unique Gleason grade group 2 or higher cancers as the targeted biopsies (23 vs 21).

Commenting on these results, the investigators noted they are consistent with other research showing that targeted biopsies in men undergoing active surveillance may add little for predicting upgrading or reclassification. They stated, “if the goal of surveillance biopsy is to identify higher grade disease, systematic and targeted biopsies should be obtained for men with a region of interest identified on MRI.”

REFERENCE

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The ad hoc analysis also examined PSA response, defined as a 50% or greater decrease in PSA level from baseline. Overall, a PSA response was reached in 83.6% of the darolutamide arm compared with 7.6% of the control arm. The median PSA decrease from baseline was 91.7% versus 31.9%, respectively. Of note, around 95% of the patients who had a greater than 90% decrease in PSA from baseline were metastasis free at 12 months.

The double-blind ARAMIS trial included 1509 patients with nonmetastatic CRPC. Patients were randomized in a 2:1 ratio to receive oral darolutamide plus ADT (n = 955) or placebo plus ADT (n = 554). Patients had an ECOG performance status of 0 to 1. The primary end point of the trial was metastasis-free survival (MFS), with overall survival (OS) as a key secondary end point.

Previously reported findings from the primary analysis of the trial showed a highly significant MFS benefit with darolutamide. The darolutamide regimen reduced the risk of metastases or death by 59% versus ADT alone, with a median MFS of 40.4 months versus 18.4 months, respectively (HR, 0.41; <.001).2

In addition to improving OS, the darolutamide regimen also led to statistically significant delays in the time to first symptomatic skeletal event (HR, 0.48; P = .005), time to pain progression (HR, 0.65; P <.001), and time to initiation of chemotherapy (HR, 0.58; P <.001).2

REFERENCES
BiTE immuno-oncology therapy appears safe with preliminary efficacy in mCRPC

More than 25% of patients show confirmed PSA response to investigational treatment

Kristie L. Kahl
Editorial Director, Urology Times®

A novel BiTE immuno-oncology therapy, AMG 160, demonstrated a manageable safety profile, with preliminary evidence of efficacy in men with metastatic castration-resistant prostate cancer (mCRPC) who were heavily pretreated, according to preliminary results from a phase 1 study (NCT03792841) presented at the 2020 European Society for Medical Oncology Virtual Congress.1

“Despite the long list of agents now approved for the treatment of metastatic castration-resistant prostate cancer, there remains an urgent need for treatments that can overcome resistance to hormonal therapies, chemotherapies, and radiation therapies. And despite impressive activity in other cancers, novel immune-based therapies have offered limited efficacy in mCRPC,” Ben Tran, MBBS, FRACP, Peter MacCallum Cancer Centre, Melbourne, Australia, explained during a presentation at the virtual congress.

“The study is nearing completion of the dose exploration phase 1b, followed by those expansion phase armory objectives to evaluate the safety and tolerability of AMG 160 and to determine its recommended phase 2 dose and secondary objectives to characterize pharmacokinetics and evaluate preliminary antitumor activity,” Tran said.

AMG 160 was administered as a short IV infusion every 2 weeks at doses of 0.003 mg to 0.9 mg. Patients were a median age of 66 years (range, 49-78). The majority of patients were Caucasian (79.1%) and had 4 or more prior lines of therapy (60.5%). Median PSA at baseline was 79.2 μg/L (range, 0.1-4035.0 μg/L). Forty-three patients received 1 or more doses of AMG 160 monotherapy, of which 41 (95.3%) experienced treatment-emergent adverse events (TEAEs). In addition, 19 patients remained on treatment at the time of data analysis.

Forty-one patients experienced treatment-related AE (TRAEs), including cytokine release syndrome (CRS; 90.7%), fatigue (44.2%), vomiting (44.2%), nausea (39.5%), pyrexia (17.2%), headache (34.9%), diarrhea (32.6%), dry mouth (30.2%), rash (27.9%), hypophosphatemia (25.6%), hypotension (23.3%), chills (23.3%), dysgeusia (23.3%), and decreased appetite (20.9%). Of note, no grade 5 events occurred and none resulted in treatment discontinuation. In total, 3 reversible dose-limiting toxicities occurred (grade 3 rash, n = 2; grade 3 gastrointestinal hemorrhage, n = 1).

Cytokine release syndrome was reversible and manageable

CRS observed in patients was reversible and manageable. The AE was most severe in cycle 2 and was associated with fever, hypotension, transient transaminisits, nausea/vomiting, and/or diarrhea. There were no grade 4/5 CRS events or treatment discontinuations. Grade 2 CRS occurred in 26 patients (60.5%) and grade 3 in 11 patients (25.6%). Of the 30 patients assessed for antidrug antibodies (ADAs), 6 (20.0%) had ADAs affecting drug exposure between cycles 1 and 10; however, no AEs associated with ADAs occurred.

“A number of mitigation strategies were used to improve the CRS profile of AMG 160,” Tran said. “Prophylactic mitigation was step dosing or dose priming, in which lower running doses were given prior to the maintenance target dose, which is administered every 2 weeks. Free medication with dexamethasone and prophylactic hydration with IV normal saline were also administered. These mitigation strategies appear to be effective in minimizing the risk of grade 3 serious events and serious adverse events.”

In total, 27.6% of patients had a confirmed PSA response to AMG 160. Overall, 68.6% of patients showed any PSA decline across all monotherapy dose cohorts and 34.3% of patients showed ≥ PSA50 reduction.

Among the 15 patients with measurable disease, 3 patients experienced a partial response (2 confirmed) and 8 patients had stable disease. Moreover, 44.2% of patients remained on AMG 160 at the time of data analysis, with 6 (14.0%) patients continuing treatment for 6 months or longer.

Maximum tolerated dose has not been reached and dosing optimization of AMG 160 continues. Meanwhile, the investigation of AMG 160 in combination with pembrolizumab is in progress.

REFERENCE

Research suggests potential gaps in ED care delivered by nonurologists

Primary care providers are less likely to order advanced pharmacologic therapies

Cheryl Guttmann Krader, BSPharm
Contributing Editor, Urology Times®

Men who receive care for erectile dysfunction (ED) from their primary care provider (PCP) are much less likely than those treated by urologists to receive advanced pharmacologic therapies for management of their condition, according to the findings of a recently published study.1

The investigators sought to evaluate the epidemiology, diagnosis, and outpatient treatment of ED by extracting data for a nationally representative sample of men using the National Ambulatory Medical Care Survey. Their search for male visits recorded between 2016 and 2016 showed that 1.2% of a total of 170,499 visits were associated with a diagnosis of ED, translating into approximately 3.4 million weighted visits annually.

The majority of visits for ED were to urologists (58%), but visits to a family practitioner or internist accounted for most of the remaining encounters (36.6%). The review of pharmacologic treatments for ED showed that a phosphodiesterase-5 inhibitor was ordered or reordered significantly more often by nonurologists than urologists (66.62% vs 50.77%, P < .05). Ordering of advanced pharmacologic therapies; eg, intracavernosal injections and intraurethral injections, was done almost entirely by urologists versus nonurologists (2.72% vs 0.25%, P < .05).

Joshua A. Halpern, MD, assistant professor of urology, Northwestern Medicine, Chicago, Illinois, is corresponding author for the published paper. He said, “Our study reinforces that ED is a very common problem for men in the United States, and it generates a high volume of visits to physicians. We hope that both PCPs and specialists will continue to be proactive in both asking their male patients about sexual health and function and in helping them to pursue the wide array of treatments that are available to help men achieve a fulfilling sex life.”

He continued, “We believe there is great opportunity for collaboration between PCPs and urologists when it comes to the treatment of ED. On a broad scale, increasing the dialogue and partnership between professional societies in creating guidelines and educational materials for both physicians and patients could be quite helpful. Locally, it is important to create and foster close relationships between PCPs, urologists and cardiologists in order to optimize care for men suffering from ED.”

Halpern told Urology Times® that the motivation for undertaking the study stemmed from the observation that many men who were being seen for ED after being previously diagnosed by a non-urologist had been prescribed medication for their problem without receiving appropriate counseling on its use. In addition, few men had received counseling about nonoral or nonpharmacologic approaches to ED treatment.

“Our observations were consistent with previous reports and led us to study the inherent differences between the management of ED between urologists and non-urologist physicians,” Halpern said.

Analyses comparing differences in the characteristics of men treated by urologists and non-urologists showed that a significantly higher percentage of men who saw urologists were older than 65 years of age compared with the group seen by a nonurologist (47.1% vs 22.6%, P < .05). Discussing the difference, the investigators postulated that it might be partially due to established physician relationships such that older men are more likely to have other urologic issues, and therefore may already have an established urologist. In contrast, younger men are less likely to have an established urologist but may have an established PCP.

Corresponding with the explanation, the investigators also found that nearly one-fourth of men seen by a urologist had an active cancer diagnosis compared with only 2.8% of men visiting a nonurologist (P < .05).

The investigators reviewed several limitations of their study. Of particular importance, they noted that the study only sheds light on differences between urologists and nonurologists in prescribing patterns for pharmacologic therapy for ED.

“A strength of our study is that the database we used provides generalizable data for ambulatory visits. However, it does not capture non-pharmacologic therapies, such as vacuum erection devices, psychotherapy, and surgery,” Halpern said.

He told Urology Times® that the study has been a catalyst for the Northwestern Medicine urologists to work more closely with nonurology colleagues locally to optimize treatment for men with ED.

“We hope that these efforts will ultimately lead to broader initiatives in both patient care and research,” he said.2

REFERENCE

CCH treatment found safe, efficacious for acute-phase Peyronie disease

Lisette Hilton
Urology Times® Correspondent

Collagenase clostridium histolyticum (CCH; Xiaflex) is not indicated to treat acute-phase Peyronie disease (PD), but it should be, according to a study published in Urology.1 Researchers have reported that CCH reduces penile curvature by an average of 35% in men with stable-phase PD. However, 2 large, randomized, phase 3 studies did not include patients in the acute phase of the disease, often defined as patients who have had PD for fewer than 12 months.

Urologists typically do not treat PD aggressively, including surgically, for 1 year, according to the study’s senior author, Wayne J.G. Hellstrom, MD, professor of urology and chief of andrology at Tulane University School of Medicine in New Orleans, Louisiana.

“The original Xiaflex collagenase studies evaluated patients after 12 months and found there was a substantial improvement in these patients. What was different about this study is we studied the acute phase of the disease, often defined as patients who have had PD for fewer than 12 months. Urologists typically do not treat PD aggressively, including surgically, for 1 year, according to the study’s senior author, Wayne J.G. Hellstrom, MD, professor of urology and chief of andrology at Tulane University School of Medicine in New Orleans, Louisiana.

The original Xiaflex collagenase studies evaluated patients after 12 months and found there was a substantial improvement in these patients. What was different about this study is we studied...
5-year data sustain water vapor thermal therapy benefit in BPH-related LUTS

Treatment yields durable improvements in lower urinary tract symptoms, QOL, and flow rate

Jason M. Broderick
Associate Editorial Director, Urology Times

The benefit of Rezum water vapor thermal therapy was sustained at 5 years in men with moderate-to-severe lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH), according to data from a phase 2 trial shared in an abstract during the 2020 European Association of Urology Virtual Congress.

“Preliminary results show that the minimally invasive water vapor thermal therapy offers rapid improvements in LUTS, quality of life (QOL), and flow rate that remain durable to 5 years,” co-principal investigators Kevin T. McVary, MD, Loyola University Medical Center, and Claus G. Roehrborn, MD, UT Southwestern Medical Center, wrote in their abstract conclusion.

The study included patients aged 50 years or older with a prostate volume of 30 to 80 cc, an International Prostate Symptom Score (IPSS) of 13 or higher, and a maximum flow rate (Qmax) of 15 ml/s or less. Patients were not allowed to enroll if they had a PSA higher than 2.5 ng/mL with a free PSA less than 25%, except those patients for whom biopsy had ruled out prostate cancer. Patients with an active urinary tract infection were also excluded from enrollment.

Investigators randomized patients in a 2:1 ratio to thermal therapy (Rezum System; n = 136) or sham control (rigid cystoscopy; n = 61). The study design allowed for crossover of some patients from the control arm to active treatment.

Patients received 1 treatment and were followed for 5 years. According to the investigators, “The water vapor thermal therapy procedure can be performed under local anesthesia in an office setting and is used to ablate obstructing prostate tissue including the median lobe/enlarged central zone.”

Data for the primary study analysis showed that at 3 months, the mean IPSS reduction from baseline was 11.2 points with water vapor thermal therapy and 4.3 points with sham control (P < .0001). At 5 years, the reduction in IPSS was sustained in the water vapor thermal therapy cohort with a 10.4-point (48%) mean reduction from baseline.

The change from baseline in maximum urinary flow rate was 6.4 ml/sec (69%) and 4.3 ml/sec (49%) at 3 months and 5 years, respectively.

Also of note, there was a strong correlation (Spearman’s rho = 0.72; P < .001) between improvements in IPSS and QOL scores. The investigators reported that the estimated mean change in IPSS from baseline corresponding to 1-point QOL improvement for mild (IPSS 13–19), moderate (IPSS 20–26), and severe (IPSS 27–35) LUTS was −4.9, −7.8, and −10.0 points, respectively.

The investigators consider these data to be preliminary, as 5-year data are not yet available for the patients who crossed over from the control arm to receive active treatment. They did note, however, that the available 4-year fol-

CCH TREATMENT

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patients with these intralesional injections before the 12-month period of time and what we found was there were similar improvements in penile curvature. There was no increase in [adverse] effects from treating patients earlier,” Hellstrom said. “It makes sense to offer Xiaflex to patients in the early stages of PD because afflicted men are really psychologically affected and can benefit.”

In Peyronie’s Disease: American Urological Association Guideline, investigators reported that many men with penile curvature experience emotional distress, depressive symptoms, and relationship difficulties. More than half of men report that the stress of PD negatively impacts their relationships. Many have said their concerns about how their penis looks harms their self-image and sexual satisfaction. Many also suffer in isolation, finding it difficult to talk with their doctors and partners about the condition.

Hellstrom and colleagues at 5 US institutions retrospectively collected data from 918 consecutive PD patients treated with CCH between April 2014 and March 2018. Of those patients, 134 (14.6%) had acute-phase disease with PD duration of up to 6 months, and 784 (85.4%) had longer-term stable disease.

The investigators found that treating PD in the early acute-phase with CCH is as safe and effective as treating it in the stable, chronic phase. Final change in curvature in the acute group was 13.5 degrees versus 15.6 degrees in the stable group. They found a similar frequency between groups of patients with at least 20% curvature improvement and low proportions of men needing eventual surgical correction for residual curvature.

Overall, 10.1% of the men studied had moderate-to-severe complications, including penile hematomas, corporal rupture, and severe penile swelling. Of patients in the acute and stable groups, respectively, 16 (11.9%) and 77 (9.8%) experienced treatment-related adverse events. The difference was not statistically significant, according to the authors.

Men with any kind of curvature greater than 30 degrees are candidates for early intralesional CCH therapy.

However, “if patients have calcification of the plaque that prevents insertion of a needle, or if they’re on anticoaguulants where they would be more likely to bleed, they probably would not be the best candidates for this therapy,” Hellstrom said. “The main point is that while we generally don’t perform surgery for PD in the first year, it makes sense to treat these patients earlier with intralesional collagenase clostridium histolyticum.”

Among the study’s limitations is the authors’ definition of acute-phase PD as duration of 6 months or less; that is not the only widely used definition for the condition. The American Urological Association defines it as PD characterized by dynamic and changing symptoms.

More studies are needed to confirm these results, the authors wrote.

Disclosure: Hellstrom is a speaker and consultant for Endo.

REFERENCES
Metastatic Castration-Resistant Prostate Cancer: Real-World Implications of the CARD Study

Results from the CARD study confirmed that cabazitaxel treatment should represent the standard of care for men with metastatic castration-resistant prostate cancer (mCRPC) whose disease has progressed within 12 months despite docetaxel treatment. Treatment with cabazitaxel led to longer imaging-based progression-free survival (PFS) and overall survival (OS) than treatment with an androgen-signaling (AS)–targeted inhibitor among patients with mCRPC who had previously received docetaxel and the alternative AS–targeted inhibitor (abiraterone or enzalutamide).

Background and Epidemiology
Prostate cancer is the leading cause of new cancer cases among men in the United States. Estimates suggest that 99,930 new cases of prostate cancer will be diagnosed in the United States in 2020, and that roughly 33,000 men will die from the disease. Approximately 6% of all prostate cancers are metastatic in nature; those patients with metastatic disease have a 5-year survival rate of only 31% compared with a 5-year relative survival rate of nearly 100% in patients whose disease is discovered at a local or regional stage.

The majority of metastatic prostate cancer cases are considered castration resistant, meaning that the disease has spread to other parts of the body despite androgen deprivation therapy. Although many cases of metastatic disease are initially hormone-sensitive, progression to mCRPC is almost inevitable, occurring over an average of 13.1 months in this patient population. In a retrospective analysis of a large claims database, 65% of patients with hormone-sensitive metastases progressed to mCRPC over a follow-up period of 4 years (2013–2016).

According to model-based predictions, the incidence of mCRPC will reach 42,970 cases in 2020, compared with an incidence of 36,100 cases in 2009. From 2011 to 2015, there was a decline of 7% per year in total prostate cancer incidence, which has been attributed to decreased screening after the US Preventive Services Task Force published recommendations against routine prostate-specific antigen (PSA) testing in 2008 and 2012. However, the effect of reduced screening on the incidence of advanced disease, such as mCRPC, is being studied closely. According to Negoi and colleagues, the overall decline in prostate cancer incidence marks an increase in distant-stage diagnoses across all ages and racial groups studied since 2010. Li and colleagues found that distant-stage prostate cancer incidence increased at an annual percentage change of 3.3% from 2010 to 2014, and in men 75 years or older, the incidence of metastasis at diagnosis began increasing after hitting a low point in 2011.

The overall mortality rate for prostate cancer declined significantly from 1993 to 2016, dropping from 39.3% to 19.4%. This decline was primarily due to reductions in smoking and advances in early detection and treatment. However, the mortality rate stabilized at roughly 19% from 2013 to 2017; this leveling of rates coincides with a decline in PSA testing and an increase in distant-stage diagnoses. Mortality rates are highest among patients with metastatic disease. A model-based analysis estimated that the mortality rate for mCRPC was 55.3% in 2009. Although mortality rates for mCRPC may have decreased slightly since that time because of advances in treatment, a real-world retrospective data analysis of approximately 3700 men with mCRPC from 2008 to 2018 found 50% mortality over a 1.5-year (538-day) study period.

Current Standard of Care
According to guidelines from the American Society of Clinical Oncology, the National Comprehensive Cancer Network, and Cancer Care Ontario, patients with mCRPC should continue to receive androgen deprivation therapy with a luteinizing hormone–releasing hormone agonist or antagonist regardless of additional therapies, with the goal of maintaining castrate levels of serum testosterone below 50 ng/dL.

Patients without visceral metastases have multiple options for add-on treatment. For asymptomatic patients, immune therapy with sipuleucel-T is a reasonable first option, as is therapy with an AS–targeted inhibitor (enzalutamide or abiraterone with prednisone). Another option is abiraterone with methylprednisolone. Chemotherapy with docetaxel plus concurrent steroid is the mainstay of treatment for patients with symptomatic metastases. Although not commonly used in patients without symptoms, it may be considered in those patients who rapidly progress.

Radium 223 is considered a first-line option for patients with symptomatic bone metastases without visceral extension. Additional options for these patients include clinical trial participation and other secondary hormone therapy (eg, first-generation antiandrogen, antiandrogen withdrawal, ketoconazole with or without concurrent hydrocortisone, corticosteroid, diethylstilbestrol, or other estrogens).

For patients with mCRPC and visceral metastases (defined as those occurring in the lung, liver, adrenal gland, peritoneum, or brain), docetaxel and a concurrent steroid (prednisone) is the preferred first-line treatment. Enzalutamide is another initial option, whereas abiraterone should be reserved for patients who are not candidates for docetaxel. Mitoxantrone is an option for patients who cannot tolerate docetaxel; although it has not improved survival in this clinical scenario, it has shown quality-of-life (QOL) benefit. Alternatively, patients can participate in a clinical trial, choose secondary hormone therapy (as described previously), or opt for supportive therapy. Radium 223 by itself is specifically not recommended in this scenario.

Patients who suffer disease progression with enzalutamide or abiraterone can either choose chemotherapy with docetaxel or switch to the alternative AS–targeted inhibitor (abiraterone if previously on enzalutamide; enzalutamide if previously on abiraterone). Additional options include sipuleucel-T and radium 223 in appropriate patients, and pembrolizumab in patients with microsatellite instability-high or mismatch repair–deficient tumors.

If the disease progresses despite docetaxel treatment, chemotherapy with cabazitaxel is a standard-of-care option. Abiraterone with prednisone or enzalutamide are additional next-line options, provided they were not used prior to docetaxel treatment. Previous treatment with an AS–targeted inhibitor has been shown to confer at least partial cross-resistance with docetaxel therapy, potentially because docetaxel exerts some of its antitumor activity by disrupting
Cabazitaxel improves survival in patients with mCRPC whose disease progresses on docetaxel treatment. It was the first drug to receive FDA approval for this clinical scenario and is currently considered a standard of care for patients whose disease progresses despite chemotherapy with docetaxel. Although cabazitaxel and docetaxel are both taxanes, cabazitaxel does not appear to share the same cross-resistance concerns with prior AS–targeted inhibitor therapy. Prior treatment with either enzalutamide or abiraterone did not negatively influence PSA response or OS in men with mCRPC who were subsequently treated with cabazitaxel. Additional in vivo data showed cross-resistance between enzalutamide and docetaxel, but not between enzalutamide and cabazitaxel. This is likely due to cabazitaxel exerting greater antitumor activity via androgen receptor–independent mechanisms, as well as its faster uptake into cancer cells and longer intracellular retention times compared with docetaxel.

AS–targeted inhibitors and docetaxel are both considered standard first-line treatments for patients with mCRPC, and are frequently used in earlier stages of the disease. Patients who are candidates for additional chemotherapy likely will have received both therapies. The CARD study investigated whether chemotherapy with cabazitaxel would be superior to treatment with an AS–targeted inhibitor in patients with mCRPC who had disease progression despite prior treatment with both docetaxel and the alternative AS–targeted inhibitor (enzalutamide or abiraterone).

Patients eligible for the CARD study had achieved sufficient androgen deprivation (defined as castrate levels of serum testosterone <0.5 ng/mL). They also had disease progression despite previous treatment with both docetaxel (≥ 3 cycles) and 12 months of either abiraterone or enzalutamide (given prior to or after docetaxel treatment). Progression at enrollment was classified as: (1) PSA progression only, (2) imaging-based progression only (defined as tumor growth or the presence of at least 2 new bone lesions); or (3) pain progression.

Eligible patients were randomly assigned 1:1 to receive either cabazitaxel (25 mg/m² of body surface area intravenously every 3 weeks) plus 5 mg of prednisone twice daily). Treatment was open label and was terminated if patients experienced imaging-based disease progression or unacceptable adverse effects (AEs), started different treatment, or requested the discontinuation of study drug.

The primary end point for the study was imaging-based PFS, defined as time from randomization to tumor growth, occurrence of new bone lesions, or death. Secondary end points included OS; PFS; PSA, tumor, and pain responses; first occurrence of a symptomatic skeletal event; and safety.

A total of 255 patients comprised the intention-to-treat population and were randomly assigned to treatment with either cabazitaxel (n = 129) or the alternative AS–targeted inhibitor (n = 126).

Of these patients, 250 received treatment: 126 with cabazitaxel, 58 with abiraterone, and 66 with enzalutamide. The median age of treated patients was 70 years, and 31% of patients were aged at least 75 years. Patients receiving cabazitaxel had a longer median duration of treatment (22 weeks vs 12.5 weeks in the comparator arm). Among patients who discontinued treatment, those who received abiraterone or enzalutamide were more likely to stop treatment because of disease progression (71.0% vs 43.7% of discontinuations with cabazitaxel). Conversely, those who received cabazitaxel were more likely to stop treatment because of an AE (19.8% vs 8.9% of discontinuations with abiraterone or enzalutamide).

After a median follow-up of 9.2 months, results for the primary end point significantly favored cabazitaxel treatment. Imaging-based disease progression or death from any cause occurred in 95 patients (73.6%) in the cabazitaxel arm and in 101 patients (80.2%) who received 1 of the 2 AS–targeted inhibitors (HR, 0.54; 95% CI, 0.40-0.73; P = .001). The median time of imaging-based PFS was 8 months with cabazitaxel and 3.7 months with abiraterone or enzalutamide. Results for the primary outcome were consistent across different ages of patients (<70 or ≥70 years), type of progression noted during the trial, as well as those with different timing of AS–targeted inhibitor (before or after docetaxel) and those with visceral metastases at randomization.

A post hoc analysis showed that cabazitaxel was superior to therapy with an AS–targeted inhibitor regardless of whether patients received abiraterone or enzalutamide in the comparator arm (imaging-based progression or death with cabazitaxel vs enzalutamide: HR, 0.57; 95% CI, 0.36-0.90; and cabazitaxel vs abiraterone: HR, 0.44; 95% CI, 0.29-0.67). In addition, post hoc multivariate Cox regression analyses employed several models (each including 3 stratification factors [eg, PSA level, age, testosterone level, and presence of visceral metastases]) to confirm the robustness of the primary outcome results from the intention-to-treat analysis.

The key secondary end point of OS also significantly favored cabazitaxel treatment. Death from any cause occurred in 54.3% of patients in the cabazitaxel group and 65.9% of patients who received an AS–targeted inhibitor (HR, 0.64; 95% CI, 0.46-0.89; P = .008). The median OS was 13.6 months with cabazitaxel compared with 11 months in the comparator arm. Other secondary end points including PFS; PSA, tumor, or pain responses; and occurrence of a symptomatic skeletal event also favored cabazitaxel.

The incidence of a serious AE of any grade was similar across treatment groups (38.9% in the cabazitaxel group compared with 38.7% of patients who received an AS–targeted inhibitor), as was the incidence of grade 3 or higher AEs (56.3% vs 52.4%, respectively). Patients in the cabazitaxel group were more likely to discontinue treatment because of a serious AE than those who received an AS–targeted inhibitor (19.8% vs 8.9%, respectively), although AEs leading to death occurred less frequently with cabazitaxel (5.6% vs 11.3%, respectively). Among AEs grade 3 or higher, those reported more commonly with cabazitaxel were peripheral neuropathy (3.2% vs 0%), asthenia or fatigue (4% vs 2.4%), nausea (3.2% vs 0%), and febrile neutropenia (3.2% vs 0%); those reported less commonly were renal disorders (3.2% vs 8.1%), cardiac disorders (0.8% vs 4.8%), spinal cord or nerve root disorders (2.4% vs 4.0%), and musculoskeletal pain or discomfort (1.6% vs 5.6%).

Quality-of-Life Impact

Results from the CARD study (NCT02485691) showed clear benefit for imaging-based PFS with the alternative AS–targeted inhibitor. PROSTATE CANCER
Although objective survival measures are of paramount importance when assessing cancer therapies, measures that affect QOL may be of equal or greater importance to patients. Thus, Fizazi and colleagues sought to further investigate changes in pain and health-related quality of life (HRQOL) among patients enrolled in the CARD study. Results of the study, by Fizazi and colleagues, were presented in abstract form at the 2020 American Society of Clinical Oncology Virtual Scientific Program. In this study, pain response was defined as a decrease of greater than 30% from baseline in Brief Pain Inventory–Short Form intensity score, without the aid of increased analgesic use. Of the 255 patients randomized in the CARD study, 172 (67.5%) had moderate to severe pain at baseline. Pain response was evaluable for 111 (86%) of patients in the cabazitaxel group and for 109 (86.5%) of patients who received an AS–targeted inhibitor. Cabazitaxel treatment was associated with both improved pain response and delayed pain progression. The probability of not experiencing pain progression after 12 months was 66.2% with cabazitaxel and 45.3% with abiraterone or enzalutamide (HR, 0.55; 95% CI, 0.32-0.97; P = .0348). These results substantiated a pain response from the original CARD study, in which de Wit and colleagues found that 45.9% of patients in the cabazitaxel group achieved a favorable pain response compared with only 19.3% of those who received an AS–targeted inhibitor (P < .001).

The Functional Assessment of Cancer Therapy–Prostate (FACT-P) questionnaire was used to assess HRQOL. To be considered evaluable, patients were required to have received at least 1 dose of study drug and to have both a baseline and at least 1 subsequent FACT-P score. A difference in score of 10 points (in either direction) from baseline was considered clinically meaningful. Of the 255 patients randomized in the CARD study, HRQOL was evaluable for 108 (83.7%) of patients in the cabazitaxel group and for 114 (90.5%) of patients who received 1 of the 2 AS–targeted inhibitors. Treatment with cabazitaxel and 1 of the 2 AS–targeted inhibitors yielded similar trends in FACT-P scores (improvement in 25% and 22.8% of patients; deterioration in 22.2% vs 24.6%, respectively). The median time to FACT-P deterioration was 14.8 months in the cabazitaxel group and 8.9 months in the AS–targeted inhibitor group, trending in favor of cabazitaxel but not reaching clinical significance (HR, 0.72; 95% CI, 0.44-1.20; P = .2072).

Conclusions

Despite advances in treatment, prostate cancer remains the second-leading cause of cancer-related deaths among men in the United States. Androgen-deprivation therapy remains the cornerstone of therapy for men with mCRPC. However, men with mCRPC require additional treatments to slow disease progression, and not all cases will be responsive to first-line therapy. The CARD study confirmed that cabazitaxel should be considered the standard of care for patients with mCRPC whose disease has progressed despite docetaxel therapy. In addition to reducing imaging-based disease progression and improving OS compared with the alternative AS–targeted inhibitor, cabazitaxel was found to improve pain response, delay pain progression, and help men with mCRPC maintain their QOL.

REFERENCES
Ureteral stent-tracking software passes performance test in feasibility study

Cheryl Guttman Krader, BSPharm
Contributing Editor, Urology Times®

Investigators at the University of Michigan have developed a cloud-based, Health Insurance Portability and Accountability Act–compliant software solution to ensure timely ureteral stent removal and validated its performance in a pilot study.

The system’s development and pilot testing are described in an article accepted for publication in the Journal of Endourology.1

John M. Hollingsworth, MD, MS, a professor of urology and health management and policy at the University of Michigan, is a senior author of the paper. He told Urology Times®, “Retained ureteral stents are common, occurring in over 12% of the patients in whom they are placed. A retained stent is bad because it can lead to substantial morbidity and increased costs of care for the patient. Moreover, a retained stent can be a source of liability for the urologist who placed it.”

He continued, “The problem faced by urologists is a lack of reliable tools to facilitate the tracking of ureteral stents to ensure their timely removal. The solution that we created to address this problem leverages data captured in the electronic health record [EHR] to automatically log and follow patients across the care continuum. Notably, the solution facilitates patient tracking without disrupting existing provider workflows.”

Hollingsworth added that the software also overcomes limitations of existing ureteral stent-tracking software.

“One stent manufacturer has a mobile application that generates reminders about device removal, but the app is manufacturer specific and necessitates activities outside the normal workflow to maintain the stent log. There are also automated systems created by other providers to capture information from the EHR, but these systems are EHR specific,” he said. “Our solution is agnostic to the device manufacturer, and we believe it can be seamlessly integrated into any EHR because it was built on Health Level Seven standards, which are common across all EHR platforms.”

For the pilot study, medical records of patients who underwent ureteral stent placement for any indication at University Hospital or 1 of its ambulatory surgery centers during a 1-month period were identified through medical record review. Information was extracted manually from the patient’s record to determine the accuracy of the software in identifying the placement procedure, scheduling follow-ups, and issuing alerts for patients without a return appointment.

The study included data from 46 patients who had a total of 51 stents placed during 49 procedures. The software captured all the procedures, correctly identified the 31 procedures in which a patient had a follow-up visit scheduled before the primary surgery, and alerted providers to the 18 procedures for which a return visit was not scheduled.

The review of the software’s performance for tracking patients who returned for stent removal showed that it registered all patients who attended their follow-up visit. Most important, it identified the ones who failed to show for their appointment.

Since submitting their manuscript, Hollingsworth and colleagues have been working to address the limitations of the initial software version tested. He explained that the initial version generated provider alerts when patients did not have a follow-up scheduled or had failed to arrive for or canceled an appointment, so an office staff member needed to contact those patients to reschedule an appointment.

“In the latest version of our software, patients receive secure text messages regarding appointment information, and we are developing the capacity for the software to be fully automated to remove the need for manual record closure, eliminating this step,” Hollingsworth said.

Further validation of the software is ongoing. The software has been deployed at another academic medical center, which uses a different EHR from the 1 used at the University of Michigan, and at the University of Michigan’s interventional radiology clinic.

“Because our software uses electronic messages that are generated during the extraction of administration and clinical tasks, which are standardized across EHRs, it is potentially compatible with all major platforms. These recent deployments of our software will demonstrate its agnosticism to the EHR vendor and show its extensibility to other temporary implantable medical devices,” Hollingsworth said.21

REFERENCE

LUTS
continued from page 27

low-up data for the crossover cohort show similar improvements as the 5-year findings in the primary randomization.

Four-year follow-up data published in the journal Urology2 previously demonstrated the durability of the benefit of Rezum water vapor thermal therapy for BPH-related LUTS.

Over 4 years, the surgical retreatment rate was 4.4%. The mean IPSS improvement (decrease means improvement) from baseline was –50.1% at 1 year, compared with –42.9% at 4 years, with a mean IPSS QOL score improvement of ~2 points (P < 0.0001).

Regarding maximum flow rate, the mean improvement in Qmax from baseline was 58.5% at 1 year compared with 49.5% at 5 years. At 4 years, the mean improvement in Qmax was 4.2 mL/sec (P < 0.0001). The mean BPH Impact Index (BPHII) improvement (decrease means improvement) from baseline was ~60.5% at 1 year and ~52.2% at 4 years. At 4 years, the mean BPHII improvement was ~3.5 (P < 0.0001).1

REFERENCES
Kidney Cancer / CLINICAL UPDATES

Nivolumab/cabozantinib combo impresses as frontline RCC treatment

Combination reduces risk of disease progression or death by 49% versus sunitinib

Gina Mauro
Editorial Director, OncologyLive®

Combination therapy with nivolumab (Opdivo) and cabozantinib (Cabometyx) significantly improved progression-free and overall survival compared with sunitinib (Sutent) as frontline treatment for patients with advanced renal cell carcinoma (RCC), according to findings from the phase 3 CheckMate 9ER trial.1

Data from the trial presented at the 2020 European Society for Medical Oncology Virtual Congress showed that the immunotherapy/TKI regimen reduced the risk of disease progression or death by 49% versus sunitinib, with a median progression-free survival (PFS) of 16.6 months versus 8.3 months, respectively (HR, 0.51; P <.0001). The median follow-up time was 18.1 months.

Additional results showed that the median overall survival (OS) was not reached in either arm, and there was a 40% reduction in the risk of death with the combination (HR, 0.60; P = .0010).

“With expanding options for patients with advanced RCC, the overall efficacy, safety, and quality of life benefits, as well as individual patient characteristics, are very important considerations when you select appropriate therapy,” lead study author Toni K. Choueiri, MD, director of the Lank Center for Genitourinary Oncology, director of the Kidney Cancer Center, senior physician with Dana-Farber Cancer Institute, and the Jerome and Nancy Kohlberg Chair and professor of medicine with Harvard Medical School, said in a press conference during the congress.

“These results, we believe, support nivolumab and cabozantinib as a potential first-line option in patients with advanced renal cell carcinoma.”

In the international, randomized, phase 3 CheckMate-9ER trial, 651 patients with advanced RCC received the combination of nivolumab and cabozantinib (n = 323) or sunitinib (n = 328) in the first-line setting. Patients must have had previously untreated advanced or metastatic disease, a clear cell component, and any International Metastatic RCC Database Consortium (IMDC) risk score.

The combination demonstrated a benefit across numerous subgroups, including age, sex, PD-L1 expression, bone metastases, IMDC risk group, and geographic region.

The objective response rate (ORR) was also doubled with nivolumab/cabozantinib in this setting compared with sunitinib, at 55.7% versus 27.1%, respectively (P <.0001). In the combination arm, the complete response (CR) rate was 8.0%, the partial response (PR) rate was 47.7%, and the stable disease (SD) rate was 32.2%. Additionally, 5.6% of patients had progressive disease (PD) and 6.5% were not evaluable or not assessed. In the sunitinib arm, the CR, PR, and SD rates were 4.6%, 22.6%, and 42.1%, respectively. Moreover, 13.7% of patients had PD and 17.1% of patients were not evaluable or not assessed.

Regarding safety, the incidence of the most common, any-grade and high-grade treatment-related adverse events (TRAEs) were similar in both arms. More than 50% of patients on the combination required dose reductions of cabozantinib due to adverse events (AEs). TRAEs led to treatment discontinuations in 15.3% of those in the nivolumab/cabozantinib arm and in 8.8% of those on sunitinib. Specifically, 3.1% of patients discontinued both nivolumab and cabozantinib due to AEs, 5.6% discontinued only nivolumab, and 6.6% discontinued only cabozantinib.

The overall rate of serious AEs was similar between the 2 groups; however, liver toxicity was more common with cabozantinib/nivolumab. Nineteen percent of patients on the combination required corticosteroids due to immune-related AEs, 4% of whom needed corticosteroids for at least 30 days.

Beyond improved treatment response and survival benefits, the combination was found to provide an improved HRQOL compared with sunitinib. HRQOL was maintained over time with nivolumab/cabozantinib versus sunitinib, which had a consistent deterioration per Functional Assessment of Cancer Therapy-Kidney Symptom Index (FKSI)-19 total score. The between-arm differences were significant at nearly all time points.

Disease-related symptoms (DRS) also improved with nivolumab/cabozantinib. Those who received sunitinib experienced a decline per FKSI-Disease-DRS.

“Both nivolumab and cabozantinib are currently approved in separate indications in RCC. In April 2018, the FDA approved nivolumab plus ipilimumab (Yervoy) as a frontline treatment for intermediate- and poor-risk patients with advanced RCC. Prior to that, in 2015, the PD-1 inhibitor was approved for use as a single agent in the treatment for patients with metastatic RCC following prior antiangiogenic therapy. In 2017, cabozantinib was approved by the FDA for use in previously untreated patients with advanced RCC and was initially approved as a treatment for those who had progressed on 1 prior antiangiogenic treatment.”

REFERENCE
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What are your options for billing for ureteral stent removal?

Use CPT code 52310 when dangle is within urethra and grasper is used.

Q: What is the correct coding for a patient who has a stent removed with an externally accessible dangle or if a cystoscopy is performed to remove a dangle within the urethra?

A: There are a number of CPT codes that can be used to bill the work to remove a stent from a patient depending on the situation, and there are times when no separate CPT code exists and the work for removing a stent is included in the office visit.

Let’s start with the first situation: a “dangle” attached to the stent is used for removal of the stent. There is no CPT code to describe the situation when a patient has a stent removed with an externally accessible component such as a string or dangle. The work of removing a stent in this manner is included in the evaluation and management visit.

In the situation where the dangle is still within the urethra and a cystoscope is used to perform urethroscopy and a grasper is used to grab the dangle for removal, use CPT code 52310 (Cystourethroscopy, with removal of foreign body, calculus, or ureteral stent from urethra or bladder [separate procedure]; simple).

There are some who may be tempted to use CPT code 50386 (Removal [via snare/capture] of internally dwelling ureteral stent via transurethral approach, without use of cystoscopy, including radiological supervision and interpretation) to remove a stent on a dangle that is within the urethra using an instrument to grasp the non-visualized dangle without the use of a cystoscope. However, CPT code 50386 is located in the ureter section of the CPT code book. As the full description implies through its location in the CPT manual and the description, the removal of internally indwelling stent reported with this code would require the use of a snare or capture to directly grasp and remove the stent without the use of a cystoscope. The inclusion statement “including radiological supervision and interpretation” refers to the fact that the procedure would usually require radiologic guidance for the capture or snare to guide the instrument to the stent without the use of the cystoscope. The inclusion would also prevent the separate reporting of a radiological guidance code such as fluoroscopy.

Despite the fact that anesthesia and radiologic supervision are not required within the description of the code itself, if you are snaring or capturing a dangle in the urethra and remove the stent in this manner, you have not met the definition of code 50386.

It should also be noted that the relative value units (RVUs) for 50386 were based on the average case reported for the code, which included the use of anesthesia and imaging to place a rigid biopsy forceps into the bladder to remove the stent. Understanding the average case used to develop the RVU provides some additional insight into the intention of the code and can be used by payers to determine appropriate code usage in a chart review.

Despite the fact that anesthesia and radiologic supervision are not required within the description of the code itself, if you are snaring or capturing a dangle in the urethra and remove the stent in this manner, you have not met the definition of code 50386.

Unfortunately, we do not have an accurate code to report a removal of a stent in this manner. Similar to a stent removed via an externally accessible dangle or a catheter, we would recommend including the removal of the stent via a dangle snared in the urethra in an evaluation and management code or reporting the service with an unlisted code.

Q: With the new evaluation and management changes for 2021, should I expect to be billing the same levels as before, or do you anticipate any changes due to the new Medical Decision Making section?

A: This is a great question. Although we have all heard that with the new evaluation and management (E/M) guidelines slated to start on January 1, 2021, overall, urologists will see a bit of a boost in reimbursements due to the increased relative value unit (RVU) of the majority of office E/M codes, and therefore increased payments, that would hold true if year-after-year there were the same E/M services billed (the same number of 99213s, the same number of 99214s, etc).

However, as with any new system, there are likely to be some shifts around, as the Medical Decision Making (MDM) section (which is used to determine the E/M level if time is not chosen to report the service) has changed a bit. The main changes take place in the Complexity of Problem and Amount/Complexity of Data sections. By looking through a number of charts, we do see some areas where there will be some shifts. Although not scientifically studied, when reviewing a number of charts and projecting the reported code under the new 2021 guidelines in comparison to current code levels selected, we found that the majority remained unchanged. For those codes that changed, we estimated a level neutral change, meaning the number of codes that went down in level were roughly offset by the number of codes that went up in level. That may
not be true for all urologists due to their own individual practices. Here is how we figured that out and how we anticipate some of the shifts to occur.

**Number and Complexity of Problems Addressed section of MDM.** In the 1995/1997 system, points would be added for each condition managed on that date of service, and the sum of the points would determine the level for that section. For example, the provider would get 1 point for each established stable problem, 2 points for an established worsening problem, 3 points for a new problem that does not require further workup, and 4 points for a new problem that requires further workup.

**In the 2021 system, this changes. No longer will the problems be summed to reach a final level, but rather the acuity of the illness(es) and the way that the problems affect patient management will determine patient complexity. This change was added to address the few physicians who would stack diagnoses or document in the chart diagnoses/problems that were not medically necessary to address on that day. In the new system, a patient with 1 self-limited or minor problem would still reach a level 2 in 2021, and 2 minor problems would still reach a level 3. In those encounters for which a chronic illness/problem that is worsening is addressed, a level 3 would be reached in the old system; under the 2021 guidelines, it would reach level 4 for this element of MDM. However, one can only reach level 5 if a patient has a severe exacerbation or a threat to bodily function in the 2021 system, regardless of the number of problems addressed.

**Amount and/or Complexity of Data to be Reviewed and Analyzed section of MDM.** Similarly, instead of getting 1 or 2 points for a variety of data types (review and/or order radiology tests/labs/medicine test, obtaining old records, summarizing old records or discussing with another provider, independent visualization of image or specimen), and adding them together, in the new system, again, the way the data is used and how it affect patient management determines the final data level. CPT has added a few clarifying statements as to what counts as data, when it is appropriate to use data as part of MDM and how to consider data as it pertains to each level of code. The clarifications include a specific reference to data included based on each CPT code test for specific data types and the exclusion of data for which you are separately paid for interpretation. It doesn’t necessarily take more or less data to reach certain levels, but what is more important is not the volume of data but the importance of the data, the amount of effort and expertise it takes to interpret the data, and the way that data affects patient care.

**Table of risk section of MDM.** The table itself is the section that has changed the least and is in essence the merge of the Diagnostic procedure(s) ordered and Management Options Selected subsections, with Presenting Problem(s) subsection eliminated. Therefore, those who would use the selections on the 2 subsections that remain would find the table unchanged, but those who would use the Presenting Problems subsection would not be able to use that portion on the Table of risk.

So what does this mean? Ultimately, there

See STENT REMOVAL page 36
How to use technology to manage capacity in the time of COVID-19

A poor capacity management system can lead to increased physician burnout and able to meet unique needs of all physicians in the practice, dynamic and flexible, and scalable. Digital systems comply with touch-free contactless operations and provide immediate, real-time access, as well as enable practices to run analytics and better understand their operations. Having the system centralized ensures a single source of information on all resource availability which prioritizes safety, and it enables the sharing and reallocation of resources, Miller explained.

Finding systems that meet the unique needs of the physicians in the practice will save time and improve operational efficiency for all parties and will include effort-based coding. Having a system that is dynamic and flexible allows the practice to quickly adaptable to changes in patient demand and will easily incorporate new protocols in scheduling rules, while ensuring the system is scalable limits the risk of running out of capacity when surges or crises occur and when the practice grows.

Miller identified 3 steps for using scheduling technology to adapt and manage capacity: first is identifying and centralizing resources, second is determining patient access needs and flow, and third is optimizing resources based on capacity and demand using analytics.

REFERENCE


SEND US YOUR QUESTIONS

Send coding and reimbursement questions to Jonathan Rubenstein, MD, and Mark Painter c/o Urology Times®, at urology_times@mmhgroup.com.

Questions of general interest will be chosen for publication. The information in this column is designed to be authoritative, and every effort has been made to ensure its accuracy at the time it was written. However, readers are encouraged to check with their individual carrier or private payers for updates and to confirm that this information conforms to their specific rules.

STENT REMOVAL

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will be some shifts of patients around between the levels, but it appears on a high level that the overall levels selected would remain unchanged for those who were using the MDM chart correctly. We encourage you to review the changes and seek some additional training. In the long run, these changes are good for the clinician and good for patient care, reducing the amount of clutter in the office note and the work required to add this information.

AUTHORS’ NOTE: We would like to add a note to our recent Q&A article with regard to the use of code 99072. In our discussion, we wrote, “Incident to’ services provided by staff and conforming to Medicare guidelines may also be included to assist in the collection and interpretation of data.” We based this information on information included in the proposed rule for the 2021 Medicare Physician Fee Schedule. As we also noted, the description in the CPT coding manual would imply that Physician or a Qualified Healthcare Provider time is required for inclusion in the 30 minutes spent in remote data collection and interpretation. We are going to add a note of caution here as the statement we included was in fact based on a proposed rule interpretation and not a final rule or CPT note. Medicare may not accept the medical assistant or other assistant time in the statement we included was in fact based on our experience. Miller said that this information conforms to their specific rules.
Is your practice prepared for evaluation/management coding changes in 2021?

My office manager, who used to be a biller, thinks these changes may simplify billing issues and benefit urology as a specialty overall. I have no experience with how the rules are going to change. I have an electronic medical record [EMR] I trust and that does a fantastic job of generating the right codes for me. We’ve already been alerted to an electronic update coming for the changes.

I don’t know how it will affect surgeries, but from the brief description I have, outpatient visit coding will be maximized. My reimbursement patterns are about 50-50 between surgery and office-based work. So if surgery is affected equally in the negative direction as outpatient is affected in the positive direction, it will probably be a wash for me. Again, it’s just a guess. I rely on my business person and my EMR, which we pay a hefty fee for, to keep these things running well.

We are all naturally skeptical because we are rarely rewarded for an advantage at any time when these changes are made. Urology usually seems to get the short end of the stick. The trend year after year is for a decrease in reimbursement per unit of effort. But this one seems like a potentially reasonable one.”

Victoriano Romero, MD / Redding, California

“I’m finding that hospital systems are just as clueless as most private practices are. It’s going to be a slow process for hospitals to give the proper information to their physicians so that when we’re moving on to the new coding system, we’re not doing extra work. Fortunately, I’ve been able to educate myself, but I’m finding a lot of my colleagues don’t even know there’s a change coming, and it may be to their benefit, and to their patients’, by reducing the documentation workload. Physicians simply aren’t educated enough on it.

I’m certain it’s not going to be organized by the corporate level implement an update, which is almost immediate. My understanding is that with the new codes, almost all office visits are going to fall into the same category, so what you have to do to qualify for that code will be more general. It should be a little easier for us.”

Alex M. Horchak, MD / Dubuque, Iowa

“I’m an employed physician in a large company. A team does our coding through a system-wide EMR, so when codes change, I won’t have access to deleted ones. From that standpoint, there’s not much prep.

I expect it to be ready but don’t know that I’m confident. I’m based on relative value units [RVUs], so whatever the code is, the code is. Am I convinced they’ll be 100% accurate in doing everything? No. But I’m not necessarily worried because I’m RVU based, not cash based.

The higher evaluation/management [E/M] should be helpful for me. I don’t do a lot of big open cases anymore, so I’m not a heavy surgical volume generator of my RVUs. I tend to make more in the office; it shouldn’t be a significant change.

I’m finding that hospital systems are just as clueless as most private practices are. It’s going to be a slow process for hospitals to give the proper information to their physicians so that when we’re moving on to the new coding system, we’re not doing extra work. Fortunately, I’ve been able to educate myself, but I’m finding a lot of my colleagues don’t even know there’s a change coming, and it may be to their benefit, and to their patients’, by reducing the documentation workload. Physicians simply aren’t educated enough on it.

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Jaschar Shakuri-Rad, DO / Morgantown, West Virginia

I’m pretty procedure heavy, but I also have a very busy clinical practice. There will be a drop in my production in terms of surgery and procedures, but I hope my office-based practice will make up for that.

“It’s going to be a slow process for hospitals to give the proper information to their physicians so that when we’re moving on to the new coding system, we’re not doing extra work.”

Jaschar Shakuri-Rad, DO / Morgantown, West Virginia

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Close out 2020 with these key financial planning tasks

Now is the time to assess your emergency fund, update beneficiaries

Q: What are some financial planning tasks I should focus on before year-end?
A: We are now in the final months of what has been a difficult 2020 for many. Every year, we like to present a number of year-end tasks everyone should cross off their checklist. This time of year presents the perfect opportunity to review and possibly adjust your financial planning strategies. You should update your retirement accounts and see where you stand with many of the goals you set at the beginning of the year.

Check on the status of your emergency fund. Did you need to dip into it at all this year? Have your necessary expenses changed? It’s always a good idea to review the balance of the account as well as your budget to see whether additional funds need to be added to bolster the account. The general rule of thumb for emergency funds is to have 3 months of necessary expenses if you are a dual-income household and 6 months to a year if you are a single-income household.

Max out your retirement accounts. You have until the tax filing date next spring to make a 2020 contribution to an individual retirement account (IRA), but 401(k) and 403(b) contributions are deductible only when made in the same calendar year. The 2020 contribution limit is $19,500 for 401(k)s and $6,000 for IRAs. If you are over age 50, catch-up contributions may be available as well.

Use the remaining money in your flexible spending accounts (FSAs). If you still have money set aside in an FSA for health care or dependent care expenses, try to use those funds before the end of the year, or you’ll risk forfeiting the money. Some employers offer a grace period into the spring of the following year or a $500 FSA carry-over from one year to the next, but most do not.

Make contributions to your children’s 529 accounts. College costs continue to rise, and it is important to start saving early if you hope to reach your college funding goals. Additionally, some states offer a state income tax deduction if you are a resident and contribute to their 529 plan. In some cases, the tax savings can be substantial.

Designate individuals to whom you wish to gift assets. The annual gift tax exclusion is $15,000 for 2020 ($30,000 for married couples). You can gift this amount to as many individuals as you would like without having to pay gift tax or have it count against your lifetime gift and estate tax exemption.

Make charitable donations. Giving to charity can be a very powerful tax-savings tool. Check whether you have any appreciated investment assets that you could gift instead of cash. This way, you will avoid paying capital gains tax on those investments, and you get to claim a deduction for the full value of the donated asset. When the charitable organization sells it, there’s no tax to them. Be aware, however, that under the current tax law, you may need to donate a substantial amount of assets to be eligible to claim a charitable deduction on your tax return.

Harvest investment losses. The markets have certainly fluctuated a lot this year. If you own stocks and other marketable securities that have lost money in taxable accounts like individual or joint accounts, consider selling those investments to capture the loss. The losses can be used to cancel out taxable gains elsewhere or potentially lower your 2020 tax bill. If your losses exceed your gains, you will have a net capital loss. You can deduct up to $3000 of net capital loss (or $1500 if you are married and file separately) against ordinary income, including your salary, self-employment income, and interest income. Any excess net capital loss is carried forward to future years and puts you in a position for tax savings in 2021 and beyond.

Update beneficiaries. If you have had a major change in your personal life, such as a recent marriage or divorce, the birth or adoption of a child, or a death in the family, you may need to revise the beneficiaries on your retirement accounts and life insurance policies. You may also need to update your will and power of attorney documents.

These are just a handful of financial issues to consider as you approach year-end. Your financial and legal advisers can run through a more comprehensive checklist of planning options based on your personal circumstances.

The information in this column is designed to be authoritative. The publisher is not engaged in rendering legal, investment, or tax advice. If you would like assistance with your individual investment strategy, please email witz@mediqus.com.

FINANCIAL TIPS
- You have until the tax filing date next spring to make a 2020 contribution to an individual retirement account (IRA), but 401(k) and 403(b) contributions are deductible only when made in the same calendar year.
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JEFF WITZ, CFP
Witz is an educational program director at MEDIQUS Asset Advisors, Inc. in Chicago. He welcomes readers’ questions and can be reached at 800-883-8555 or witz@mediqus.com.
How to maximize the efficiency of your clinical space

Making better use of your existing space yields numerous benefits

**Todd Shryock**

Shryock is managing editor of *Medical Economics*.²

A medical practice is often a busy place, with patients in the waiting area and physicians and nurses moving between exam rooms in narrow hallways. But have you ever stopped to think about why equipment is stored in a particular room versus another? Have you considered how doctors and patients move about the practice and if there is a better way that would save everyone time? Are you keeping excess supplies on hand because there are too many exam rooms?

These are all questions to ask when it comes to practice efficiency, said Adrienne Lloyd, MHA, PACHE, founder and CEO of Optimize Healthcare, who spoke at the 2020 Medical Group Management Association virtual conference. She said that by applying steps from both Six Sigma and Lean Manufacturing processes, a practice can eliminate bottlenecks, reduce wait times for patients, and make more efficient use of equipment.

Lloyd said to use what’s known as a “5S” event: Sort, set in order, shine, standardize, and sustain. “This is an opportunity to get the entire team involved,” Lloyd added, because each staffer’s workflow needs to be examined.

Start with a small area, such as an exam room and evaluate it. “Remove all the trash, move all unnecessary things to a holding area, then arrange everything based on how frequently it is used and label everything clearly,” Lloyd said. “Define the quantity of items you go through in a day and make sure you have enough stock for a few days or a week.”

A system should be created for alerting staff when supplies should be stored. “Identify bottlenecks and change routes or room assignments to eliminate them.”³

For the sustain step, audits should be done frequently to uncover any issues and take action to fix them. Assign an owner or champion to the system who is accountable for metrics and the regular review. This person can also monitor vendor utilization to look for bulk buying discount opportunities.

**Spaghetti mapping**

The poor flow of people and equipment through a practice can create bottlenecks and small inefficiencies that over time can cost a practice thousands of dollars in revenue, but Lloyd said a “spaghetti mapping” exercise can help identify trouble spots.

A spaghetti map exercise starts by taking a floorplan or blueprint of the practice and then drawing a line of how someone moves through the practice. Different colors are used for patients, staff, providers, paperwork, and lab specimens. By looking at where many lines intersect or where they double back on themselves, problem areas can be identified.

In 1 case, Lloyd saw a practice that had staffers going to a printer 40 times a day that was too far from their work area. This action took them enough time that it amounted to $6,000 in lost time costs, making it clear that buying a second printer and installing it in a different location was more than justified. “The same mapping can be done within a room to create better flow within it and illustrating where supplies should be stored.”

“Try to create one-way flows, evaluate the flow of each provider for each day of the week, and keep providers close to their resources,” said Lloyd. “Identify bottlenecks and change routes or room assignments to eliminate them.”

**Zero-contact intake software on the rise**

**Logan Lutton**

Assistant Editor, *Medical Economics*²

The coronavirus disease 2019 (COVID-19) pandemic has forced many practices to adapt in new ways, particularly when it comes to telehealth. One aspect of telehealth, zero-contact intake software, is becoming more popular as physicians see the benefits it provides.

Cori Beard, practice manager for child family and development, and Navin Jain, CIO of Cookeville Medical Center, led a session at the 2020 Medical Group Management Association virtual conference on their experiences with reducing in-person exposure to COVID-19 via patient intake software.

“Waiting rooms already had a negative connotation before this all began,” said Beard, whose practice specializes in outpatient pediatrics. “We tried not to use that word before the pandemic. Now, we just don’t have to.”

Instead of waiting in a cramped space to see their provider, their patients have the option to wait in their cars until it’s time for their appointment. A text message is sent when it is time to be seen, along with the room number they will be seen in. Patients are even able to store a credit card on file, which increases collections.

“We’re collecting about 98% of co-pays, Beard said. “About 95% of our clients have a card on file, and so, we’re able just to run that at each appointment.”

The software not only benefits patients, but staff as well.

“The front office has more time to talk with patients now, where before, when you have 7-10 patients to check in, you don’t really have as much time,” Jain said. “It also reduces the amount of manual work they have to do. Now we can actually focus on the other items that we have to do in the office instead of just picking up the phone.”

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¹ From “How to Maximize the Efficiency of Your Clinical Space,” *Medical Economics*, October 2020

² From “Zero-contact Intake Software on the Rise,” *Medical Economics*, October 2020

³ From “Spaghetti Mapping,” *Medical Economics*, October 2020

⁴ From “Sort, Set in Order, Shine, Standardize, and Sustain,” *Medical Economics*, October 2020
Beware the perils of friendly prescribing

Here’s how to guard against lawsuits, disciplinary actions

Nearly every physician receives requests for prescriptions from coworkers or friends. Granting these requests can take the form of “friendly prescribing,” a situation in which a prescription is provided outside a physician’s normal practice. In an attempt to be helpful, care providers can expose themselves to a risk of being sued, losing insurance coverage, and facing disciplinary investigations. Luckily, there are ways to avoid or minimize these risks while still being a helpful friend.

Imagine the following scenarios: A nurse in your office says, “Doctor, can you call in a prescription for my hypertension medicine? I’m out of refills, and my doctor charges me $100 a visit.” Or a neighbor you know well calls and says, “Doc, I have a cross-country flight coming up and a terrible fear of flying. Can you prescribe me 2 Valium for the trip? I won’t have time to schedule a visit with my doctor before my trip.”

In any variation of these situations, the pressures on the physician are the same. An acquaintance is asking for something that the physician can easily give. Refusing this type of request would surely seem like an insult. How can you say no without the implication being “I could help you, but I won’t because I just don’t care enough about you”?

Unfortunately, even setting aside adverse drug reactions that could stem from informal prescribing, providing a friendly prescription can create a variety of medico-legal risks beyond those associated with a normal patient encounter.

Claims may not be covered by malpractice insurance

If an individual who receives an informal prescription suffers an adverse outcome and a malpractice suit is filed, this claim may not be covered by malpractice insurance. The reason is simple. A friend or acquaintance provided with a prescription may not be a true “patient.”

In one tragic story involving friendly prescribing, an emergency department (ED) physician was asked by a nurse for a prescription for Zoloft for her husband, who had been struggling with depression. The ED physician wrote a prescription for 1 month of medication, just long enough for the husband to make an appointment with a psychiatrist.

Two weeks later, the nurse’s husband took his own life. The widowed nurse sued the ED physician for malpractice on the basis that the physician did not consider that increased risk of suicidal thoughts is a complication for patients starting Zoloft. Ultimately, the ED physician’s malpractice carrier refused to provide coverage for the case because the husband was not one of the physician’s patients.

Even when an informal prescription does not lead to an adverse health outcome, it can still create headaches for practitioners. “Hallway medicine” can run afoul of laws and regulations related to the requirement that an in-person evaluation be performed before a prescription is issued. Moreover, the modified or informal practices associated with writing a friendly prescription can lead to disciplinary actions from a state medical board.

In a recent case, a nurse asked a surgeon for a written prescription for an OTC medication. The nurse needed the prescription to use her health savings account for the purchase. The physician provided a partially completed handwritten prescription, leaving it to the nurse to fill in the specifics. A hospital administrator found the nearly blank prescription on a desk, and both the nurse and the surgeon were investigated by their employer and licensing authorities.

This scenario did not even involve a medication that required a prescription. Yet the physician was still subjected to an investigation by the state medical board for issuing a prescription without keeping proper records.

Best practices for friendly prescriptions

It is possible to handle requests for prescriptions without seeming rude and still protecting against exposure to lawsuits or disciplinary actions. The first step is treating the request as if it comes from a real patient. This means conducting an examination and creating a written record of the encounter. Use of an electronic medical record system can be very helpful in this regard. Creating a record that shows the friend was treated like a normal patient reduces the possibility that an insurer will deny coverage in the event of a lawsuit.

If an acquaintance needs a prescription urgently and a physical exam is not possible, physicians should create some contemporaneous record reflecting this fact. Such a record may be very useful in defusing any investigation by a licensing authority. Ultimately, failing to take these simple steps while helping a friend with a request for medication could result in proving the truth of the adage “No good deed goes unpunished.”

KENTON H. STEELE, ESQ

Steele is an attorney in the Columbus, Ohio, office of Reminger Co., LPA. He specializes in malpractice defense and insurance litigation. Please contact him at KSteele@reminger.com with any feedback or comments on this column.
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*Dr. Cohen is a paid consultant of NeoTract | Teleflex. Results may vary.
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