How new agents may address NMIBC treatment challenges

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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 orchietomy.

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 Monitor patients for symptoms and signs of AI, particularly if patients are withdrawn from corticosteroids, have corticosteroid dose reductions, or experience unusual stress.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 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

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


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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.

DOSSAGE 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 adrenal cortical 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.

Manufactured for:
Sun Pharma Global FZE

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APRIL 2020
Infectious diseases are the second-leading cause of death in patients with cancer, whose immune systems are often compromised. By itself, that fact likely comes as no surprise to the readers of a publication for health professionals caring for patients with urologic malignancies. But the unprecedented pandemic of COVID-19 has made it essential for cancer providers to keep abreast of the latest developments related to the deadly coronavirus, which causes COVID-19.

“We’ve been finding that individuals with underlying medical conditions such as cancer might be immunocompromised and at a higher risk for complications associated with the virus that causes COVID-19,” Christina Tan, MD, MPH, assistant commissioner of the New Jersey Department of Health, told our sister publication, OncLive.

Of course, the pandemic continues to have far-reaching effects not only on the management of cancer, but all aspects of medicine, including patient and clinician safety, the use of telemedicine, elective surgery, and research, to name a few.

In the management of prostate cancer, urologist Neal Shore, MD, points out that the COVID-19 pandemic amplifies the potential value biomarker tests help in identifying which patients’ follow-up appointments might be postponed and which patients benefit from more immediate care. (For articles on these topics, see www.urologytimes.com/coronavirus.)

On a lighter note, this issue of Urologists in Cancer Care introduces a refresh of our content and redesign of our pages. Articles focus primarily on three common genitourinary malignancies: prostate, bladder, and kidney cancer. Each issue will bring you practical review articles by key opinion leaders, How I Do It features on how to operationalize aspects of cancer care, Technology Updates, a Case of the Month, and expert commentary by Editor-in-Chief Raoul Concepcion, MD.

The pandemic has had far-reaching effects not only on the management of cancer, but all aspects of medicine.
Over the past decade, a couple of themes have dominated much of the discussion about the management of our urologic cancer patients. Clinically, the first topic has been the concept of precision medicine. Next-generation sequencing (NGS) and the endless work being conducted worldwide by so many researchers have given us deeper insight into the genetic signatures associated with prostate cancer, whether it be in patients with localized disease or the unfortunate ones who are progressing and will eventually succumb.

Testing for both germline/hereditary and somatic mutations will allow more precise therapeutic recommendations based on tumor expression for each patient. We will no longer assume that all patients with a Gleason 3+4 cancer will have the same tumor biology. The correct treatment will be chosen for the appropriate patient, whether it is surgery, active surveillance, or the most suitable agent for the next line of therapy. Additionally, identification of these alterations may have consequences for the patient’s family to determine who may potentially be at risk for future tumor development.

Second, but equally important, is the transition of our delivery model away from fee-for-service to value-based care. The working definition of value-based care is outcomes divided by costs; a must-read for all was published in 2013 by the Harvard Business Review, “The Strategy That Will Fix Health Care.” Costs are hard to control and even more difficult to understand.

Outcomes depend on whom you ask. For payers and insurance companies, it is how much was spent on a particular patient or disease. As urologists, we will be more interested in clinical and pathologic metrics. What was our surgical margin, incontinence, and sexual dysfunction incidence after prostatectomy? What is the time to biochemical or radiographic progression?

For the patient, outcomes may be “how long will I be in the hospital and when can I return to work and be back to ‘normal’”? So, even defining value, which inherently depends on outcome, becomes elusive, depending on the respondent.

The continued development of targeted agents and immunotherapies has resulted in our ability to practice and offer precision medical therapies. But the associated ticket price has been astronomical. The National Cancer Institute has estimated that the cost of cancer care will increase 27% from 2010 to 2020 and reach annual spending of $158 billion. Furthermore, from 2009 to 2014, the yearly costs for most oncolytic therapies was more than $100,000 per year. Recently, some CAR T-cell therapies will be well north of $400,000. This is an unsustainable financial model.

At the 2020 Genitourinary Cancers Symposium in San Francisco, there were no less than 25 posters and presentations specifically looking at patient-reported outcomes and quality-of-life metrics in prostate cancer management. My friend, colleague, and fellow Nashvillian, Dr. David F. Penson, of Vanderbilt University Medical Center, delivered the keynote address, “Financial Toxicity and Quality of Life: Understanding and Improving Patient-Centered Outcomes in Genitourinary Malignancies.” As providers, we want our patients with cancer to live longer and enjoy a life that allows more time to spend with family and celebrate milestones. We have gravitated to more targeted and oral therapies that

We need to remain focused on a more patient-centered model where the goal is prolonging life, but not at the expense of quality of life where the therapies may result in performance, emotional, or financial toxicity.

—RAOUL S. CONCEPCION, MD, FACS
potentially facilitate ease of delivery and require less supportive agents to mitigate the side effect profile of our more traditional cytotoxic drugs. But the financial burden, toxicity, and costs of therapy can have a significant impact on patients’ quality of life and their ability to enjoy that life.

This topic has gone underappreciated, and not discussed, as we continue to drive toward the cure for cancer. These concerns should be discussed as potential adverse events no different than asthenia, neutropenia, or cardiovascular risk.5

With more and more data at our disposal, we begin this new decade facing new clinical challenges, which will include interpretation of NGS, molecular imaging, and how this ultimately has an impact on the therapeutic plan for patient management. We need to remain focused on a more patient-centered model where the goal is prolonging life, but not at the expense of quality of life where the therapies may result in performance, emotional, or financial toxicity.

Before any of us became technical wizards in robotic surgery or renowned researchers, we all stood as graduating medical students and recited some form of the Hippocratic Oath, in which a revised, 1964 version clearly states:

“I will remember that I do not treat a fever chart, a cancerous growth, but a sick human being, whose illness may affect the person’s family and economic stability. My responsibility includes these related problems, if I am to care adequately for the sick.”6

REFERENCES


**NEWS BRIEFS**

**Data show high unmet need for novel therapies in NMIBC**

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

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

“Available treatments are not doing a fair job in terms of slowing progression. What these data are calling for is better treatment,” Dr. Yang said.

**Combination therapy shows promise in advanced PCa**

A phase 1b trial of cabozantinib (CA-BOMETYX) in combination with atezolizumab (TECENTRIQ) in patients with locally advanced or metastatic solid prostate tumors showed encouraging results, including a 32% objective response rate.

Patients in the study, known as COSMIC-021, had to have measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST v. 1.1) and had progressed on prior novel hormone therapy and could have received prior docetaxel for hormone-sensitive disease. Forty-four patients were included in this interim analysis. The median follow-up was 12.6 months.

The objective response rate (ORR) per RECIST v. 1.1, the trial’s primary endpoint, was 32%, including two complete responses and 12 partial responses. Disease control rate was 80%. Among the 36 patients with high-risk clinical features including visceral metastases and/or extra-pelvic lymph node metastases, the ORR was 33%. Median duration of response for all responding patients was 8.3 months.

Data were reported at the Genitourinary Cancers Symposium in San Francisco.
How new agents may address NMIBC treatment challenges

Bladder cancer is traditionally thought of as almost two distinct cancers, with nearly 80% of newly diagnosed cases being nonmuscle-invasive disease (NMIBC). The challenge of managing patients with NMIBC is predicting which patients are at risk for progression to muscle-invasive bladder cancer (MIBC), where treatment is much more aggressive and life altering, versus those that are at a much lower risk and potentially the surveillance can be altered with a concomitant reduction in costs.

For patients with higher risk NMIBC, the mainstay of therapy has historically been bacillus Calmette–Guérin (BCG). However, because of the ongoing BCG shortage in addition to the lack of effective alternative drug therapies for patients with BCG-unresponsive disease, a large unmet need exists for these patients and providers. Newer agents are addressing these challenges. Matthew Galsky, MD, discusses these therapies, their specific indications, how they are administered, dosing, and side effects.

Dr. Galsky was interviewed by Raoul S. Concepcion, MD, chief clinical urologic officer, Integra Connect, West Palm Beach, FL, and clinical associate professor of urology, Vanderbilt University School of Medicine, Nashville, TN.

Q: What are the current challenges associated with the treatment of NMIBC?

A: There are two major challenges. One is in patients who are treatment naive, and that challenge is that there’s a shortage of the standard-of-care treatment for patients with high-risk nonmuscle-invasive disease, which is BCG. That creates some challenges in terms of clinical management, but it also creates challenges in terms of clinical trials in that if you don’t have the standard of care as a control treatment, then it’s difficult to run clinical trials that are randomized or with combination therapies, etc.

The second major challenge has existed for a bit longer, and that’s how we optimally manage patients who have BCG-unresponsive carcinoma in situ, ie, patients who have not adequately responded to treatment with BCG. We know that the standard of care in that context is radical cystectomy, but that’s a treatment many patients would like to avoid if possible. That’s led to a long history of studies seeking to determine whether or not there are medical treatments that can be used to avoid cystectomy, ideally, or at the very least, delay it.

Q: Please discuss develop-
State-of-the-art technology is helping urologists better manage non-muscle invasive bladder cancer.

Bladder image from White Light Cystoscopy

Same image from Blue Light Cystoscopy with Cysview®

Visit Cysview.com to learn what makes tumors glow bright pink under blue light.

Product Indication

Cysview® is an optical imaging agent indicated for use in the cystoscopic detection of carcinoma of the bladder, including carcinoma in situ (CIS), among patients suspected or known to have lesion(s) on the basis of a prior cystoscopy, or in patients undergoing surveillance cystoscopy for carcinoma of the bladder. Cysview is used with the KARL STORZ D/uni2010Light C Photodynamic Diagnostic (PDD) system to perform Blue Light Cystoscopy (BLC®) as an adjunct to White Light Cystoscopy.

Important Risk & Safety Information

Cysview® is not a replacement for random bladder biopsies or other procedures used in the detection of bladder cancer. Anaphylactoid shock, hypersensitivity reactions, bladder pain, cystitis, and abnormal urinalysis have been reported after administration of Cysview. The most common adverse reactions seen in clinical trials were bladder spasm, dysuria, hematuria, and bladder pain.

Cysview should not be used in patients with porphyria, gross hematuria, or with known hypersensitivity to hexaminolevulinate or any derivative of aminolevulinic acid. Cysview may fail to detect some malignant lesions. False positive fluorescence may occur due to inflammation, cystoscopic trauma, scar tissue, previous bladder biopsy and recent BCG therapy or intravesical chemotherapy.

No specific drug interaction studies have been performed. Safety and effectiveness have not been established in pediatric patients. There are no available data on Cysview use in pregnant women. Adequate reproductive and developmental toxicity studies in animals have not been performed. Systemic absorption following administration of Cysview is expected to be minimal. There are no data on the presence of hexaminolevulinate in human or animal milk, the effects on a breastfed infant, or the effects on milk production. The development and health benefits of breastfeeding should be considered along with the mother’s clinical need for Cysview and any potential adverse effects on the breastfed infant from Cysview or from the underlying maternal condition.

Cysview is approved for use with the KARL STORZ D-Light C Photodynamic Diagnostic (PDD) system. For system setup and general information for the safe use of the PDD system, please refer to the KARL STORZ instruction manuals for each of the components. Prior to Cysview administration, read the Full Prescribing Information at Cysview.com and follow the preparation and reconstitution instructions.

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Opinions that will address one or both of those challenges. What do you anticipate will be approved for the management of NMIBC over the next 12 months, especially in the BCG non-responsive patient?

A: Pembrolizumab (KEYTRUDA), the PD-1 inhibitor, has already been approved for the treatment of BCG-unresponsive disease. That approval was based on a single-arm study that involved two cohorts. We only have the results of one of those cohorts—patients with BCG-unresponsive disease who had carcinoma in situ with or without papillary disease—and that was the basis for the approval of pembrolizumab.

Incidentally, another systemic therapy, atezolizumab, which is a PD-L1 inhibitor, was being studied in a similar context in SWOG-1605, and that trial closed prematurely. We don’t fully understand the results of that study yet and the nuances of pembrolizumab versus atezolizumab in this setting.

There are also two intravesical treatments that are being reviewed by the FDA, and the expectation is that one or both of these drugs will likely become available as well. These agents include nadofaragene firadenovec (Instiladrin), which is an interferon-alpha expressing-adeno-virus, and that has been studied in nonmuscle-invasive BCG-unresponsive disease and led to a 12-month complete response rate of 24%, which is encouraging in this context, particularly based on the route and frequency of administration.

A second intravesically administered drug is called Vicinium, which is a fusion protein consisting of an epithelial cell adhesion molecule (Ep-CAM) that is fused to a Pseudomonas exotoxin, essentially delivering this exotoxin to Ep-CAM-expressing cells. Vicinium has been studied in a single-arm study with a 12-month complete response rate of 17%.

The 12 month-complete response rates with pembrolizumab, nadofaragene, and Vicinium—even though these cohorts are not exactly the same and there are some nuances in terms of study eligibility—line up fairly well at between 17% and 24%.

Q: How are these three therapies administered?

A: Pembrolizumab is administered intravenously every 3 weeks. In the clinical trial that led to its approval, it was administered for up to 2 years as long as there wasn’t evidence of recurrence or progression. Nadofaragene is administered intravesically every 3 months for up to 4 years. Vicinium is administered intravesically one to two times a week for 12 weeks, and then every 2 weeks for 2 years.

Q: Will the approvals be for high-grade TA, T1 disease, and carcinoma in situ?

A: As I mentioned, the approval for pembrolizumab was based on one of the two cohorts that were explored in that study, and that was a cohort of patients with carcinoma in situ with or without papillary disease (Ta or T1 disease). Results for Cohort B, which was in patients with papillary disease, are not available yet. So far, the approval of pembrolizumab is in patients with carcinoma in situ, and
we’ll have to see if that’s extended based on the initial results.

In the nadofaragene and the Vicinium trials, if these therapies are indeed approved, it will be interesting to how restricted the label might be with regard to the type of NMIBC.

Q: Will these agents be approved for primary therapy, given the current BCG shortage?
A: I don’t suspect they’ll be approved as primary therapy in the near term, even with the BCG shortage. I think the question, though, is will they be used in the absence of BCG? When there are drug shortages in other disease states, we see some extrapolations of data, so it wouldn’t be a surprise to me if we start to see some of these drugs being used in that context if BCG can’t be obtained.

In the longer term, whether or not these therapies have the potential to be compared to BCG in randomized studies and ultimately replace BCG remains to be seen. We know there are studies with immune checkpoint blockade in combination with BCG aimed at potentially finding a drug to replace maintenance BCG, which could certainly lighten the load in terms of the need to source BCG. Those studies are probably coming in the future, but I don’t suspect the approvals will be for that use in the short term.

Q: For the immunologic agents, will there be both induction and maintenance dosing?
A: There isn’t induction and maintenance dosing per se, but there is long-term treatment, at least based on the initial study. With pembrolizumab, the treatment is administered for up to 2 years in the absence of recurrence or progression. The dosing, though, is the same, and the schedule is the same. Unlike with BCG, where the schedule changes with maintenance, pembrolizumab is administered potentially for a long term, but with the same dosing schedule. The optimal duration of immune checkpoint inhibitors, even in the metastatic setting, remains unclear.

Q: How do you anticipate that medical oncologists, who have historically not managed non-muscle-invasive bladder cancer patients, and urologists will use these newer agents?
A: That’s going to be an evolving question, at least in part based on longer term follow-up data from these studies and, of course, the pending approvals of Vicinium and nadofaragene. The reason I say that is, if you look across the studies with those three agents—and again, it’s somewhat dangerous to do that because they’re not randomized and the eligibility doesn’t exactly line up—the proportion of patients who have a complete response at 12 months is pretty similar.

Then you need to think about other factors to help make the decision about choice of treatment, which include the potential side effects of treatment, the mode of administration, the frequency of administration, and potentially the cost. One can develop a scorecard of those items for each of these individual therapies. If there’s an intravesical treatment that works potentially just as well, spares systemic side effects, and is administered less frequently, then that may be a preferable treatment from the standpoint of patient and physician.

However, one also need to consider the long-term follow-up data from these trials. The goal of giving these treatments is really to avoid cystectomy ideally more so than delay cystectomy. If our goal is to avoid cystectomy, then we are looking for treatments that are potentially curative in at least a subset of patients. If there is a subset of patients who are cured with these treatments, rather than just experiencing a delay in recurrence or progression, then the value proposition of that treatment changes a bit. So if immune checkpoint blockade given for a fixed period of time, say 2 years, leads to eradication of cancer and durable remission in a subset of patients, that might balance against the inconvenience of intravenous administration and the risk for systemic side effects. So, treatment paradigms are in evolution based on all of these considerations.

Q: What are the side effects of the three agents you discussed?
A: The side effect profile of pembrolizumab is pretty well defined based on its approval in metastatic cancers. Pembrolizumab and other immune checkpoint inhibitors are widely approved in various solid tumors and hematologic malignancies as well, so we have a pretty good understanding of the potential side effects, which don’t seem to differ in the NMIBC patient population. Based on the KEYNOTE study that led to the approval of pembrolizumab, there was a 13% likelihood of having treatment-related moderate to severe (grade 3 to 5) side effects. Those side effects include the potential for inflammation of various parts of the body: colitis, pneumonitis, dermatitis, hepatitis, etc.

When those side effects occur, they often resolve with simply stopping the medication. Sometimes steroid
Role and rationale for molecular testing in advanced prostate cancer

Advances in genomic testing will help determine lines of therapy in men with mCSPC, mCRPC

BY RAOUl S. CONCEPCION, MD

Prostate cancer is a clinically heterogenous disease with variability in progression once diagnosed, ranging from the very indolent cases that may require no therapy to patients who present with de novo metastasis. In 2019, there were approximately 174,650 newly diagnosed prostate cancer cases in the United States and a cancer-specific mortality of 31,620 directly attributable to the disease or 5.2% of all cancer deaths.1

A number of newer therapies (all mechanistically different) and treatment regimens have been approved for the management of both patients with metastatic castration-sensitive prostate cancer (mCSPC) and metastatic castration-resistant prostate cancer (mCRPC). A unique dynamic progressive model estimates the incidence of these two subsets may approach 42,970 patients in 2020.2

Unfortunately, despite the availability of superior agents, optimal sequences or a combination of these oncolytics have yet to determined, as there are no predictive biomarkers to inform the provider what is the most ideal initial line of therapy (LOT) and as patients progress, what will be the most appropriate next LOT. What makes this situation even more challenging is that these newer therapies, as well as those that we anticipate will be approved in 2020 and beyond, are targeted for molecular drivers of prostate cancer. For the patient with mCSPC or mCRPC, how can we best determine the initial and subsequent LOTs, given the limitations of the monotherapy registration trials?

A number of key genomic mutations have been consistently identified in patients with prostate cancer (hormone naive and mCRPC). These mutations include gene fusion/chromosomal rearrangements (TMPRSS2-ERG), androgen receptor (AR) amplification, inactivation of tumor suppressor genes (PTEN/PI3-K/AKT/mTOR, TP53, Rb1), and oncogene activation (c-myc, RAS-RAF).3 More significantly, defects in DNA repair appear to be central in increasing one’s susceptibility to malignant transformation.

Germline vs. somatic mutations

It is critical to patient management that we determine whether these mutations are inherited (germline) or acquired (somatic). Germline mutations are changes in DNA that are present in the patient’s reproductive cells (sperm or ovum) and are thus passed from generation to generation and will be identified in every cell of the body. Therefore, germline testing can be conducted with just a swab from the mouth, saliva, or blood from the patient. There are many companies in the United States that currently offer germline testing.

It is paramount that in order to obtain the most comprehensive analysis and report, genetic testing through next-generation sequencing in a diagnostic laboratory is mandatory. This type of testing should be compared with many of the direct-to-consumer tests that are currently marketed to patients. The testing platforms deployed by many of these companies are much less robust and often include a very limited number of known genetic mutations in their panels.

For example, thousands of identified BRCA mutations have been identified, but only a handful may be tested in some of these direct-to-
consumer testing kits. This situation can lead to an unacceptable number of studies with false-negative results and should not be used for clinical decision-making.

Acquired or somatic mutations can be defined as any alteration in DNA that occurs after conception. These can occur in any cell of the body (except the reproductive cells) and usually arise as a result of exogenous or environmental exposures, such as tobacco smoking or UV radiation. Therefore, somatic testing requires next-generation sequencing of cells extracted from the tumor itself and cannot be performed by using a sample of saliva or blood.

Pritchard and colleagues were among the first to demonstrate the value of assessing inherited genetic changes in prostate cancer. Among 692 patients with metastatic prostate cancer, they examined the prevalence of mutations in 20 DNA repair genes. Mutations were identified in 1.74% of their study cohort (82 men) with significant geographic heterogeneity, even among these recognized cancer centers (prevalence of 8.8% in patients treated at the University of Washington and 18.5% in those treated at Memorial Sloan Kettering), potentially reflecting referral biases. Subsequently, Castro et al found a prevalence of germline DNA damage repair gene mutations of 16.2% in patients with mCRPC. Unlike other disease states in which commonly identified germline mutations may be actionable, actionable germline mutations are relatively uncommon in patients with prostate cancer. Nicolosi and colleagues found that actionable mutations were identified in 1.74% of their study cohort with a diverse patient population. In previous analyses, Robinson et al reported clinically actionable pathogenic germline mutations in 8% of 150 patients with mCRPC, in contrast to clinically actionable aberrations in the AR in 63% and aberrations in other cancer-related genes in 65% of patients. It is likely not surprising that actionable underlying germline mutations would be more common in a cohort with more advanced prostate cancer.

In patients with regional or metastatic prostate cancer, somatic tumor testing may also be considered on the basis of the observation that nearly 90% of men have potentially actionable mutations at the tumor level, whereas only a relatively small proportion of men would have actionable germline mutations (approximately 9% of patients with mCRPC, according to the National Comprehensive Cancer Network). In these patients, testing may be undertaken for somatic homologous recombination repair (HRR) gene mutations (eg, BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, and CHEK2) and for microsatellite instability (MSI) or mismatch repair (MMR). In patients with advanced prostate cancer, identification of underlying germline mutations may guide treatment selection to determine the most appropriate next LOT, especially in those who have progressed through multiple lines of prior therapy, including AR signaling agents. Patients with identified MSI-high status, defects in DNA MMR genes, or CDK12 biallelic loss may respond to checkpoint inhibition therapy.

Somatic testing requires next-generation sequencing of cells extracted from the tumor itself and cannot be performed by using a sample of saliva or blood.

Pembrolizumab (KEYTRUDA), an FDA-approved PD-1 inhibitor, is the first immunotherapy to win approval in a tumor-agnostic manner and not based on organ type. Further, patients with mutations in HRR genes (including BRCA1/2, CHEK2, and genes that cause Fanconi anemia) may be better suited for treatment with PARP inhibitors, many of which are in ongoing phase III trials with expected approval in 2020.

Finally, patients with DNA repair defects may have increased sensitivity to platinum-based chemotherapeutics. Given the uncertainty regarding optimal treatment selection and pending approval of current agents in trial, the National Comprehensive Cancer Network prostate cancer guideline panel recommends clinical trial enrollment for all men with prostate cancer and identified DNA repair gene mutations. In addition, somatic testing for specific gene variants may be undertaken.

For the most part, this approach is used in patients with advanced disease with the goal of identifying specific actionable targets. For example, mutations in HRR or MMR genes and identification of MSI-high versus MSI-low status may suggest certain treatments are more likely to be beneficial.

In addition to genetic testing of tumor tissue, assessing circulating tumor cells may offer important information. For example, testing of AR variant status can be performed us-
A recent analysis looking at various commercially available multigene panels shows that the average number of genes tested is 12.

...
Management of UTUC using a kidney-sparing approach

Advances in endourology have made kidney-sparing treatments a viable treatment option

BY BRETT WATSON, MD; JASON HAFRON, MD

THE CASE

An 84-year-old man presented to the urology department following an episode of painless gross hematuria. His medical history was significant for atrial fibrillation (for which he takes warfarin), coronary artery disease, and BPH. He had a significant smoking history with one to two packs of cigarettes per day for 75 years. His glomerular filtration rate was estimated at 60 mL/min/m².

CT urogram revealed a 1.2-cm enhancing lesion within the left lower pole infundibulum (figure). Urine cytology was suspicious for a low-grade lesion.

The patient was taken to the operating room to undergo cystoscopy and flexible ureteroscopy. No lesions were seen in the urethra or bladder. On pyeloscopy, a large pedunculated soft tissue mass was seen filling the lower pole of the kidney.

The surgeon biopsied the mass with a 3F Piranha Ureteroscopic Forceps and placed a ureteral stent. Pathologic analysis revealed low-grade papillary transitional cell carcinoma without muscular invasion (pT1, stage 1).

After a discussion of the various treatment options, the patient elected to undergo endoscopic management. He was taken back to the operating room for ureteroscopy fulguration using a 3F monopolar Bugbee electrode. Fulguration was continued until no visible tumor was seen and margins appeared clear.

The patient was then started on a surveillance protocol with urine cytology, CT urography, and cystoscopy with ureteroscopy.

During the first surveillance ureteroscopy at 3 months, a small recurrence of low-grade UTUC was seen in the kidney and was treated endoscopically. The ureteroscopy interval was then increased to every 6 months for 1 year and then to every 12 months. CT urography (CTU) is performed annually, and there have been no further recurrences 39 months after the initial treatment.

FIGURE Excretory phase of CT urogram in the coronal and axial planes shows a 1.2-cm filling defect (arrow) within the lower pole calyx and infundibulum of the right kidney.

TURN TO PAGE 18
FOR PRESENTATION AND DIAGNOSIS

APRIL 2020

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Presentation and diagnosis
UTUC is an uncommon malignancy, accounting for just 5% to 10% of all urothelial carcinomas (UCs). UC tends to be a multifocal disease, and approximately 17% of those with UTUC will have concurrent UC of the bladder. The majority of patients with UTUC present with hematuria. Ureteral obstruction with flank pain occurs in 20% to 40% of patients.

The European Association of Urology (EAU) and National Comprehensive Cancer Network (NCCN) have similar guidelines for the diagnostic workup of suspected UTUC. In addition to the testing noted in the information to follow, the NCCN guidelines recommend renal function testing and chest x-ray for all patients. The AUA does not currently have guidelines specific to UTUC.

CTU is the preferred imaging modality for diagnosis of UTUC. An enhancing mass or thickening of the urothelium should prompt further evaluation. Hydronephrosis may be seen and is an independent predictor of muscle invasion and high-grade disease. For patients who cannot undergo CTU due to iodinated contrast allergy or impaired renal function, magnetic resonance urography with gadolinium-based contrast is an alternative.

Cystoscopy should be performed to rule out UC of the bladder. Retrograde pyelography may be performed at the time of cystoscopy, and solitary filling defects and hydronephrosis are the most common abnormal findings. Urine cytology should be obtained as well. Cytology has a lower sensitivity for UTUC than for UC of the bladder and should be obtained in situ from the renal pelvis. Diagnostic flexible ureteroscopy is mandatory and allows for direct visualization of the entire upper urinary tract. Biopsy samples should be taken to confirm the diagnosis and stage the tumor.

Ureteroscopic biopsy specimens can make accurate staging difficult. In our case, we used ureteroscopic biopsy forceps, but many have reported improved yield with an endoscopic stone basket. Several novel imaging techniques to be used in conjunction with ureteroscopy such as narrow band imaging (NBI), photodynamic imaging (PDI), and optical coherence tomography (OCT) are under investigation. NBI for the upper tract is commercially available as an extension of the currently available systems used for NBI cystoscopy, PDI systems are commercially available and currently used primarily for bladder lesions, and OCT is investigational for urologic purposes (current systems are for ophthalmologic diagnostics).

Risk stratification
Proper risk stratification is critical when considering patients for a kidney-sparing approach. UTUC that invades the muscular wall (pT2) carries a poor prognosis with a 5-year survival rate <50%. Given the available diagnostic tools and challenges with obtaining an adequate biopsy, accurate assessment of tumor stage remains a challenge. Therefore, the EAU proposes a classification in which tumors are stratified as low or high risk based on a number of tumor-related factors.

Management
Radical nephroureterectomy (RNU) with bladder cuff excision is the gold-standard treatment for UTUC. More recently, advances in endourologic equipment and techniques have allowed kidney-sparing treatments to become a viable management option. These kidney-sparing surgeries should be reserved for patients with low-risk UTUC or those with imperative indications such as solitary kidney, impaired renal function, or severe comorbidities.

Endoscopic Ablation. Endoscopic ablation is most commonly performed in a retrograde fashion. A percutaneous approach can also be employed for difficult-to-reach calyceal tumors, although advances in ureteroscope maneuverability make this technique rarely necessary. Once the tumor is visualized, an energy source is used to ablate the tumor and its base. This step can be achieved with electrocautery (typically a 3F monopolar Bugbee electrode) or laser energy. There is a high rate of recurrence ranging from

<table>
<thead>
<tr>
<th>Low-risk characteristics</th>
<th>High-risk characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unifocal disease</td>
<td>Hydronephrosis</td>
</tr>
<tr>
<td>Tumor size &lt; 2 cm</td>
<td>Tumor size &gt; 2 cm</td>
</tr>
<tr>
<td>Low-grade cytology</td>
<td>High-grade cytology</td>
</tr>
<tr>
<td>Low-grade biopsy</td>
<td>High-grade biopsy</td>
</tr>
<tr>
<td>No invasion seen on imaging</td>
<td>Multifocal disease</td>
</tr>
<tr>
<td>Previous radical cystectomy for bladder cancer</td>
<td>Variant histology</td>
</tr>
</tbody>
</table>

Source: Adapted from EAU guidelines on upper tract urothelial carcinoma, 2017 (Eur Urol 2018; 73:111-22)
Learn about this unique drug-device technology at Cysview.com

Product Indication
Cysview® is an optical imaging agent indicated for use in the cystoscopic detection of carcinoma of the bladder, including carcinoma in situ (CIS), among patients suspected or known to have lesion(s) on the basis of a prior cystoscopy, or in patients undergoing surveillance cystoscopy for carcinoma of the bladder. Cysview is used with the KARL STORZ D/uni2010Light C Photodynamic Diagnostic (PDD) system to perform Blue Light Cystoscopy (BLC®) as an adjunct to White Light Cystoscopy.

Important Risk & Safety Information
Cysview® is not a replacement for random bladder biopsies or other procedures used in the detection of bladder cancer.

Anaphylactoid shock, hypersensitivity reactions, bladder pain, cystitis, and abnormal urinalysis have been reported after administration of Cysview. The most common adverse reactions seen in clinical trials were bladder spasm, dysuria, hematuria, and bladder pain.

Cysview should not be used in patients with porphyria, gross hematuria, or with known hypersensitivity to hexaminolevulinate or any derivative of aminolevulinic acid. Cysview may fail to detect some malignant lesions. False positive fluorescence may occur due to inflammation, cystoscopic trauma, scar tissue, previous bladder biopsy and recent BCG therapy or intravesical chemotherapy.

No specific drug interaction studies have been performed. Safety and effectiveness have not been established in pediatric patients. There are no available data on Cysview use in pregnant women. Adequate reproductive and developmental toxicity studies in animals have not been performed. Systemic absorption following administration of Cysview is expected to be minimal. There are no data on the presence of hexaminolevulinate in human or animal milk, the effects on a breastfed infant, or the effects on milk production. The development and health benefits of breastfeeding should be considered along with the mother’s clinical need for Cysview and any potential adverse effects on the breastfed infant from Cysview or from the underlying maternal condition.

Cysview is approved for use with the KARL STORZ D-Light C Photodynamic Diagnostic (PDD) system. For system set up and general information for the safe use of the PDD system, please refer to the KARL STORZ instruction manuals for each of the components. Prior to Cysview administration, read the Full Prescribing Information at Cysview.com and follow the preparation and reconstitution instructions.
CASE OF THE MONTH

KIDNEY CANCER

30% to 70%. Most recurrences are low grade and patients must be willing to undergo strict surveillance.

NCCN and EAU guidelines advise urine cytology and CTU at 3 months, 6 months, and then annually. Cystoscopy with ureteroscopy with selective cytology should be performed at 3 months, 6 months, every 6 months for 2 years, then annually. For low-grade, low-stage tumors, oncologic outcomes are similar between those treated with endoscopic ablation and those undergoing RNU.

INTRAURAL URETERECTOMY. RNU with bladder cuff resection is the only curative option for patients with UTUC. Patients with high-risk UTUC should be offered RNU if they have adequate renal function and are acceptable candidates for major surgery. Open, laparoscopic, and robotic approaches have been described, with no difference in oncologic outcomes among these techniques. The role of regional lymph node dissection remains controversial. Current guidelines recommend node dissection for patients with high-risk tumors. No standardized template exists for lymphadenectomy. Recurrence of UC in the bladder following RNU for UTUC is 22% to 47%, and a single postoperative dose of intravesical chemotherapy immediately following surgery reduces this risk.

There are several ongoing clinical trials evaluating the role of neoadjuvant chemotheraphy for UTUC. Although no level 1 evidence currently exists, retrospective analyses have shown improved disease-specific and overall survival with platinum-based regimens.

Conclusion
Kidney-sparing surgery is an acceptable alternative to RNU in appropriately selected patients with low-grade UTUC. Proper risk stratification including endoscopic biopsy is critical when considering a kidney-sparing approach. Due to high recurrence rates, close surveillance is also mandatory.

REFERENCES

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Operationalizing immunotherapy in urologic practice

Team-based approach is key to safely, appropriately dispensing checkpoint inhibitors

BY GAUTAM JAYRAM, MD

The impact of checkpoint inhibitors (CPIs) in oncology over the past decade cannot be overstated. These treatments are providing patients with advanced cancers the opportunity to live longer and better than ever before. Urologic oncology has been especially fortunate in this era, with a flurry of recent FDA approvals and clinical trials with CPIs in prostate, kidney, and bladder cancer.

Currently, there are three approved disease states in genitourinary oncology for CPI utilization: (1) metastatic urothelial cancer (first-line therapy with cisplatin ineligibility and PD-L1 expression; second line, post-platinum failures); (2) metastatic renal cell carcinoma; and (3) those with bacillus Calmette-Guérin (BCG)-unresponsive carcinoma in situ of the bladder (FDA approved January 2020). Many urologists are generally familiar with CPIs; however, this most recent indication has the opportunity to bring our specialty in much closer contact with these novel therapies.

Shift in practice patterns

The debate regarding whether urologists should bring CPIs into their treatment realm has been rather spirited. Provider-specific factors such as practice setting, clinical volume, and hospital affiliation will likely drive this decision. Since sipuleucel-T (Provenge) entered the prostate cancer arena in 2010, many large independent urology groups have centralized advanced prostate cancer care and have implemented infrastructure to administer systemic therapies. This move has led to a shift in practice patterns for advanced prostate cancer, with an increasing proportion of patients with castration-resistant prostate cancer in the community setting being treated primarily by urologists.

This has brought with it opportunities for large groups to participate in clinical trials, in-office dispensing, multidisciplinary treatments, and other high-value resources for patients with cancer. Immuno-oncology, specifically CPIs, likely represent the next step in this cascade.

Similar to other large groups, our practice has a dedicated cancer facility with an infusion suite, in-office dispensary, and full research staff. Over the years, our program has evolved to include cancer navigation, bone health and nutrition clinics, and clinical trials across multiple tumor types. We began administering CPIs for patients with advanced urothelial cancers in 2017 after significant internal discussion. Through the success of our advanced prostate cancer program and patient feedback, we have learned that patients want to stay in a familiar environment, even in the setting of advanced disease. Patients with bladder cancer are unique in that they have special urologic needs ranging from ostomy/diversion care to treatment of bladder symptoms and unique cancer surveillance protocols.

Centralizing these patients’ needs, improving continuity of care, and providing low-cost, convenient, and efficient cancer care was our main rationale to start offering this service to our patients.

We use two urologic oncology–focused physicians as champions of our immuno-oncology program. Our program has been bolstered by the implementation of an advanced bladder cancer clinic, where patients with metastatic disease, BCG-unresponsive bladder cancer, or complex (atypical histology) cases are sent for secondary consultation. Furthermore, all requests for BCG throughout the practice are centrally reviewed, providing quality-control measures during the BCG shortage and also appropriately escalating care for patients who do not respond to BCG treatment. These measures along with cancer navigation have allowed us to identify a large pool of patients who could potentially benefit from CPIs.

At our center, the champion pro-
provider meets with all potential patients and has a thorough discussion of indications, treatment protocol, adverse events (AEs), and alternative treatments for the patient’s cancer, including clinical trials or referral to a medical oncologist. Before starting CPIs, each patient undergoes a baseline laboratory panel of tests including those for complete blood count, a comprehensive metabolic panel, thyroid-stimulating hormone, and cortisol levels.

Patients who demonstrate endocrine abnormalities or have pre-existing thyroid or adrenal disease are required to obtain a referral from the endocrinology department before starting therapy. Similarly, appropriate specialists are consulted for patients with significant cardiac or pulmonary disease at baseline. Patients meeting all criteria are precertified for treatment and given a treatment schedule.

### Treatment considerations

On the day of treatment, patients are seen by the physician before their infusion, and their lab test results and clinical responses are reviewed. The patient completes a validated adverse event (AE) questionnaire, which is indicative of ongoing morbidity from therapy. Vital signs are obtained before and after the infusion, which takes about 30 minutes, and the patient is then allowed to leave with a companion. Depending on the agent, CPIs are given on a fixed schedule every 2 to 6 weeks, with treatment discontinued for drug intolerance or radiographic disease progression and lasting a total of up to 2 years. While on treatment, patients are routinely monitored for disease progression with cross-sectional imaging with or without cystoscopy and cytology given their disease process and clinical stage.

Managing treatment-related AEs has been cited in numerous surveys as the biggest obstacle for urologists in embracing CPI administration. In our experience, administering PD-1 and PD-L1 inhibitors for patients with advanced cancer has been safe and manageable with a team-based approach and appropriate practice awareness. On the group level, it is important that all physicians (not just the champions) who may come in contact with patients be made aware of the potential systemic AEs from CPIs and their basic management.

Group physicians and treatment team members need to understand that seemingly small AEs from treatment (rash, cough, diarrhea) may blossom into severe issues if not monitored and treated appropriately. Physician- and patient-specific resources (pamphlets, hotlines, and treatment expectations) have been made avail-

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### TABLE Management of adverse events caused by CPIs

<table>
<thead>
<tr>
<th>Severity (CTCAE grade)</th>
<th>Ambulatory vs. inpatient care</th>
<th>Corticosteroids</th>
<th>Other immunosuppressive drugs</th>
<th>CPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ambulatory</td>
<td>Not recommended</td>
<td>Not recommended</td>
<td>Continue</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory</td>
<td>Topical or systemic steroids oral 0.5-1 mg/kg/day</td>
<td>Not recommended</td>
<td>Suspend temporarily</td>
</tr>
<tr>
<td>3</td>
<td>Hospitalization</td>
<td>Systemic steroids oral or IV 1-2 mg/kg/day for 3 days then reduce to 1 mg/kg/day</td>
<td>To be considered for patients with unresolved symptoms after 3-5 days of steroid course; multidisciplinary consultation advised</td>
<td>Suspend and discuss with patient based on risk/benefit ratio</td>
</tr>
<tr>
<td>4</td>
<td>Hospitalization; consider intensive care unit</td>
<td>Systemic steroids IV methylprednisolone 1-2 mg/kg/day for 3 days then reduce to 1 mg/kg/day</td>
<td>To be considered for patients with unresolved symptoms after 3-5 days of steroid course; multidisciplinary consultation advised</td>
<td>Discontinue permanently</td>
</tr>
</tbody>
</table>

Source: Gautam Jayram, MD
able by most immune-oncology manufacturers and are valuable educational tools. Although most non-treating urologists fear the isolated late-night call concerning CPI AEs, in our experience, with good patient selection and education, it has not been a frequent occurrence.

**Patient monitoring**
On the day-to-day level, establishing a protocol of monitoring (laboratory and telephone) and setting triggers for evaluation and treatment is necessary. In our practice, clinical questionnaires and laboratory values are reviewed before each treatment. Patients with any AEs are clinically and radiographically evaluated to determine severity.

The table shows the management of AEs caused by CPIs. Low-grade AEs are managed by withholding the next infusion and active monitoring. The hallmark of management for significant AEs is corticosteroid administration, which can usually be managed as an outpatient. This treatment usually entails a 3- to 4-week steroid taper, during which our clinical staff is in contact with the patient to ensure clinical improvement.

Providers administering CPIs need to understand patients can develop toxicity immediately after the first dose and/or months after completing treatment. As reflected by the literature, the majority of patients can return to CPIs after steroid treatment for mild to moderate AEs. Patients with severe, life-threatening issues are rare but need urgent hospitalization, intravenous steroids, and medical consultation. CPIs should not be restarted in these patients even after a full recovery.

**Patient selection**
Patient selection is important for success, especially in the early stages of a new program with systemic therapy. Patients with more severe comorbidities, a higher disease burden (when treating in the metastatic setting), and prior chemotherapy will have a higher risk of both disease-specific and treatment-specific morbidity early on during therapy. As these therapies move into localized disease processes (such as for high-risk nonmuscle-invasive bladder cancer), the hope is that the treatment morbidity will be even less, and this has been supported by safety data in the KEYNOTE-057 trial. Our experience has told us that although patients will certainly develop AEs necessitating treatment, severe toxicity is very rare, and the majority of patients do quite well on treatment.

From an operational standpoint, the burden on the busy group practice is fairly low, especially on those with advanced therapeutic capabilities. Obtaining the medication already compounded helps avoid concerns about USP <800> and bypasses the need for special facilities (storage, hood, etc). We have one infusion nurse who performs the infusions, calls the patient post-treatment, and triages messages of concern to the physicians.

Although there is valid debate concerning the financial toxicity of these treatments, our experience with billing and payers has been straightforward, and the therapies seem to be reimbursed on a schedule and scale consistent with other cancer medicines in urologic oncology.

**Conclusion**
In summary, CPIs have emerged as a therapeutic option in multiple urologic cancers and continue to move earlier in treatment algorithms, evidenced by the recent approval of pembrolizumab (KEYTRUDA) in patients with BCG-unresponsive bladder carcinoma in situ. This new indication will push all urologists to gain a deeper understanding of the risks and benefits of these treatments. Nontreating urologists should prioritize understanding disease indications, treatment morbidity, and a general approach to AE management. A centralized, team-based approach is key to safely and appropriately dispensing these therapies. The AE profile and management is new to urologists but can be simplified via structured monitoring and treatment protocols.

Although not all urologists are equipped to administer these medications, urology groups active and experienced in cancer treatment with dedicated facilities and staff will be well positioned to incorporate these therapies into their clinical armamentarium.

**About the Author**

**Dr. Jayram**
is a urologist at Urology Associates, Nashville, TN.

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Centralizing these patients’ needs, improving continuity of care, and providing low-cost, convenient and efficient cancer care was our main rationale to start offering this service line to our patients.
Robotics in GU oncology: Current status, future directions
Breadth of applications will widen as number of new platforms grows

BY JOSHUA CALVERT, MD, MPH

Leonardo da Vinci is credited with having drawn the world’s first robot in 1495. This device was a complex suit of armor with flexible joints controlled by a series of pulleys and is the same basic concept used by the current iteration of Intuitive Surgical’s da Vinci robotic surgical system.

Urology, as a field, has been at the forefront of the utilization of this technology since its inception. Robot-assisted laparoscopic prostatectomy is almost synonymous with robotic technology. Nearly every hospital system with a robotic platform has at least one high-volume genitourinary oncologist recording the most time on the console.

The most familiar robots used in genitourinary oncologic surgery are known as online robotic systems. These devices were designed to replicate, in real time, a surgeon’s hand movements. Interestingly, the first non-microscopic surgical robots were designed for use by the U.S. Department of Defense. The concept was a mobile armored operative suite that could be manned by surgeons at the rear of the battle. This setup would keep them out of harm’s way, with the hope of minimizing casualties and protecting surgeons. Although we now associate robotics with safe, sterile operative suites, this could not have come to fruition without the U.S. military.

Thanks to urologic pioneers and an ongoing push for a minimally invasive approach in an ever-growing breadth of surgical applications, the future looks bright for robotics in genitourinary oncology.

As laparoscopy and robotic surgery continue to gain popularity, a continued push to develop laparoendoscopic single-port surgery has followed.

Shift in practice patterns
Mani Menon, MD, is an American surgeon whose pioneering work laid the foundation for modern robotic cancer surgery. In 1997, Dr. Menon was recruited to become chairman of urology at Henry Ford Hospital. This transition of power led to Henry Ford Hospital’s urology department receiving a $20 million donation from the Vattikuti Foundation, effectively establishing the Vattikuti Urology Institute.

This financial backing freed Dr. Menon to explore minimally invasive techniques and establish robotic prostatectomy. He has performed nearly 4,000 robotic prostatectomies and is considered a world authority on the use of robotic surgery for prostate cancer.

Current technology
Intuitive was founded in 1995. World-renowned experts in telerobotic technology, human-machine interfaces, and minimally invasive surgical techniques laid the groundwork for surgical robots. Intuitive launched the first da Vinci surgical system in 1999; it became the first robot-assisted surgical system for laparoscopic surgery cleared by the FDA in 2000.

As of 2018, there was an installed base of 4,986 units worldwide—close to 3,000 in the United States. Per the company website, more than six million minimally invasive surgeries have been completed using da Vinci technology as of 2018. Additionally, more than 18,000 scientific articles on Intuitive surgical products and procedures have been published.

The da Vinci Si System was launched in 2009 and is the first model to offer dual-surgeon console capability, thus supporting training and collaboration during minimally
Invasive surgery. Additionally, this model also incorporated high-definition 3D vision.

In 2014, the da Vinci Xi System had broader capabilities than earlier generations. These included the ability to perform multi-quadrant surgeries or procedures where instruments must be able to reach up and down across the abdomen or chest. The Xi was the first system to have an overhead instrument arm configuration, allowing anatomic access from virtually any position. It also incorporated the ability to attach the endoscope to any arm, as well as the greatest range of motion with a longer instrument shaft designed to give surgeons greater operative reach.

Announced in 2017, the da Vinci X is the newest Intuitive product on the scene. It is advertised as a cost-conscious option with arm architecture similar to that of the Xi, with the goal of placing even more units into hospitals where price had previously precluded purchase.

The da Vinci SP is a new member of the family, designed for the narrowest access surgery. With the SP, a single arm delivers three multijointed instruments and a fully wristed 3-D high-definition camera for visibility and control in narrow surgical spaces. At present, the potential benefits of laparoendoscopic single-port surgery include improved cosmesis, reductions in wound infection rates, quicker recovery, and reduced postoperative hernia. However, these benefits cannot be fully evaluated until the size of single-site trocar incisions and tools is optimally miniaturized.

General limitations for robotic surgical platforms include high start-up costs and setup times involved with individual surgeries. The da Vinci system uses proprietary software that cannot be modified by physicians, thereby limiting the freedom to adjust the operation system. Furthermore, a $2 million cost places it beyond the reach of many institutions. For example, the Si version costs on average slightly under $2 million, in addition to several hundred thousand dollars of annual maintenance fees.

Another large drawback is the lack of haptic feedback, requiring the use of visual cues compared with more traditional attention and texture techniques. This can be dangerous and has also led to a reported steep learning curve for robotic surgery.

One of the greatest strengths of robotic technologies is increased manual dexterity along with tremor-filtering functions. Additionally, benefits include the ergonomic control stations and the ability to perform complex surgery in a solo fashion by using more than two arms at once.

Developments and competitors

As laparoscopy and robotic surgery continue to gain popularity, a continued push to develop laparoendoscopic single-port surgery has followed. Engineers and medical technology companies continue to develop products with the ultimate goal of natural orifice transluminal endoscopic surgery—a transvaginal cystectomy/neobladder with no abdominal incisions. Although Intuitive continues to dominate the field, there are several competing systems worth noting.

The Senhance Surgical System (TransEnterix) currently used in some gynecologic procedures has multiple manipulator arms controlled from a remote station. One main feature of this platform is that it provides actual tactile haptic feedback so surgeons can feel the tension they are applying at the distal end of their endoscopic instruments. Interestingly, the Senhance system also employs eye-tracking software that allows the surgeon to naturally focus on tissue of interest without having to redirect the endoscopic camera.

Competing in the single-port surgical space is the Flex Robotic System (Medrobotics Corp.). This is not currently approved for urologic procedures but is used in oral and head and neck surgery. Flex allows surgeons the freedom to manipulate around target anatomy by defining a nonlinear path to surgical sites. The operator is able to perform this technique by advancing a flexible outer sheath through which the inner channel instruments are deployed.

Although not currently FDA ap-
TECHNOLOGY UPDATE

proved, SPORT (Single-Port Orifice Robotic Technology, Titan Medical Inc.) features a design with a collapsible system that can be inserted through a 25-mm incision. In preclinical testing, it has been used to successfully complete a nephrectomy in animal models.

Anecdotally, one cannot discuss future robotic technologies without mentioning Verb Surgical (Verb J&J/Alphabet), a company founded in partnership with Google. Although little information is available, the prototype has been reported to combine robotics and data-driven machine learning to reduce surgical costs and expand the use to a larger array of surgeons. The company’s stated goal is to “democratize surgery,” an attempt to not just create a new surgical platform but also truly develop a new category of digital surgery.

As exciting as these newer platforms may sound, it will be some time before we see competitors in the commercial market. Regardless, the prevalence of robotic platforms will increase in smaller communities and other countries. Contemporary literature has demonstrated that the use of partial nephrectomy has increased and open radical nephrectomy has decreased since the adoption of the robot. This trend will continue not only in kidney cancer but also in other subspecialties.

**Future directions**

In tertiary referral centers, we will continue to see more and more difficult procedures performed robotically as experience continues to grow. In addition to the now standardized oncologic surgeries, we will see more complex reconstructions and vascular surgeries performed by a robot. In October 2019, a team from the Glickman Urological & Kidney Institute in Cleveland successfully performed the world’s first robotic single-port kidney transplantation. Small case series are beginning to come out presenting radical nephrectomy with inferior vena cava thrombectomy up to a level IV thrombus.

Robotic surgical platforms, as evidenced by the adoption of the da Vinci, have had a rapid and far-reaching impact on the performance of minimally invasive surgical procedures in urologic surgery as well as in other disciplines. Further developments in robotics will continue to enhance this performance and promise to improve outcomes in a wide swath of surgical fields. Urologic surgery has been a leader in robotic surgery development, and this technological revolution in the operating room continues to redefine urology and all of surgery.

All data seem to expect this trend to continue accelerating. It is projected that the global market for surgical robots will experience a compound annual growth rate of 10.4%, from $3.9 billion in 2018 to $6.5 billion by 2023.

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**In addition to the now standardized oncologic surgeries, we will see more complex reconstructions and vascular surgeries performed by a robot.**

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**REFERENCES**


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medications are required to help resolve those side effects.

With nadofaragene and Vicinium, there are side effects similar to other local therapies. Grade 3 to 5 side effects in the trials of those drugs were in the 4% range. We do see a different side effect profile when treatments are administered into the bladder versus when they’re administered systemically.

Q: What is the role of chemoradiation in chemoradiation for high-grade T1 bladder cancer?

A: That is one topic that often gets left out of the conversation. We know that chemoradiation has a role for muscle-invasive bladder cancer. Its role in T1 high-grade disease, particularly post-BCG, is not entirely well defined.

There was a fairly large study looking at chemoradiation for BCG-naïve, high-grade T1 disease that showed reasonable bladder-intact outcomes. That concept is being explored in an RTOG study in patients who have already received BCG. It is an option that we think about for T2 disease, but oftentimes we don’t think about it for T1 disease, possibly because of the absence of data in this in the post-BCG setting.

Q: What is the status of molecular markers for NMIBC?

A: The major molecular marker that’s potentially relevant is a mutation in a gene called fibroblast growth factor receptor 3, or FGFR3. We know that FGFR3 is mutated in a large subset of low-grade, nonmuscle-invasive bladder cancers, but it’s mutated in a smaller subset of high-grade cancers as well. Erdafitinib (BALVERSA) is an orally bioavailable, small-molecule inhibitors of this receptor that is now approved by the FDA for the treatment of metastatic bladder cancer.

Thus, a logical question is whether or not those treatments can be effective in patients who have FGFR3-mutated nonmuscle-invasive bladder cancer. Some pilot studies have suggested intriguing results, but there are large studies that have just been initiated with more definitive endpoints, trying to determine whether or not this could be the first “precision medicine-based” approach for nonmuscle-invasive disease.

“Will these agents be approved for primary therapy, given the current BCG shortage?”

– RAOUL S. CONCEPCION, MD, FACS

“…When there are drug shortages in other disease states, we see some extrapolations of data, so it wouldn’t be a surprise to me if we start to see some of these drugs being used in that context if BCG can’t be obtained.”

– MATTHEW GALKSY, MD


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Do you know what patient types bladder cancer experts recommend for Blue Light Cystoscopy with Cysview?

This easy reference sheet summarizes the consensus report published in *Nature Reviews Urology* April 24, 2019.

**Blue Light Flexible Cystoscopy with Hexaminolevulinate in Non-Muscle Invasive Bladder Cancer: Review of the Clinical Evidence and Consensus Statement on Optimal Use in the USA —Update 2018**

Yair Lotan, Trinity J. Bivalacqua, Tracy Downs, William Huang, Jeffrey Jones, Ashish M. Kamat, Badrinath Konety, Per-Uno Malmström, James McKiernan, Michael O'Donnell, Sanjay Patel, Kamal Pohar, Matthew Resnick, Alexander Sankin, Angela Smith, Gary Steinberg, Edouard Trabulsi, Michael Woods and SiamakDaneshmand

To get your free copy of the Consensus Publication Summary, visit rebrand.ly/ConsensusUTi or scan this code

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**Product Indication**

Cysview® is an optical imaging agent indicated for use in the cystoscopic detection of carcinoma of the bladder, including carcinoma in situ (CIS), among patients suspected or known to have lesion(s) on the basis of a prior cystoscopy, or in patients undergoing surveillance cystoscopy for carcinoma of the bladder. Cysview is used with the KARL STORZ D-Light C Photodynamic Diagnostic (PDD) system to perform Blue Light Cystoscopy (BLC®) as an adjunct to White Light Cystoscopy.

**Important Risk & Safety Information**

Cysview® is not a replacement for random bladder biopsies or other procedures used in the detection of bladder cancer. Anaphylactoid shock, hypersensitivity reactions, bladder pain, cystitis, and abnormal urinalysis have been reported after administration of Cysview. The most common adverse reactions seen in clinical trials were bladder spasm, dysuria, hematuria, and bladder pain.

Cysview should not be used in patients with porphyria, gross hematuria, or with known hypersensitivity to hexaminolevulinate or any derivative of aminolevulinic acid. Cysview may fail to detect some malignant lesions. False positive fluorescence may occur due to inflammation, cystoscopic trauma, scar tissue, previous bladder biopsy and recent BCG therapy or intravesical chemotherapy.

No specific drug interaction studies have been performed. Safety and effectiveness have not been established in pediatric patients. There are no available data on Cysview use in pregnant women. Adequate reproductive and developmental toxicity studies in animals have not been performed. Systemic absorption following administration of Cysview is expected to be minimal. There are no data on the presence of hexaminolevulinate in human or animal milk, the effects on a breastfed infant, or the effects on milk production. The development and health benefits of breastfeeding should be considered along with the mother’s clinical need for Cysview and any potential adverse effects on the breastfed infant from Cysview or from the underlying maternal condition.

Cysview is approved for use with the KARL STORZ D-Light C Photodynamic Diagnostic (PDD) system. For system set up and general information for the safe use of the PDD system, please refer to the KARL STORZ instruction manuals for each of the components.

Prior to Cysview administration, read the Full Prescribing Information at Cysview.com and follow the preparation and reconstitution instructions.