American Urological Association

AUA NEWS

| THE OFFICIAL NEWSMAGAZINE OF THE AMERICAN UROLOGICAL ASSOCIATION |

AUA NEWS

2018 ANNUAL MEETING HIGHLIGHTS

Immunotherapy in GU Cancer

Course #005IC
Chemotherapy and Immunotherapy Options for Genitourinary Malignancies: A Primer for the Advanced Practice Provider

Course #019IC
Immunotherapy for the Urologist: Basic Principles, Adverse Effects & Drug Delivery

Course #055IC
Genetic Testing in Prostate Cancer: Understanding Clinical Implications for Early Detection, Localized Disease & CRPC

Course #058IC
Management of Common Dilemmas in Prostate Cancer Diagnosis, Staging & Treatment

Presentation
Urologic Care for the Advanced Practice Provider: Bladder Cancer: New Diagnostic Tools, Intravesical Therapies and Management of Intravesical Drug Toxicities

Presentation
Tumor Board: Bladder Cancer

***AUANews* Editor**
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Publisher
American Urological Association
1000 Corporate Boulevard
Linthicum, MD 21090

AUA2018 ANNUAL MEETING HIGHLIGHTS

Immunotherapy in GU Cancer

Independent educational grant support provided by:

- AstraZeneca
- Genentech
- Merck & Co., Inc.

CME Credit

CME INFORMATION

2018 AUA Annual Meeting Highlights: Immunotherapy in GU Cancer

Method of Participation

To claim CME credit/hours of participation, the learner must read the overview of courses 005IC, 019IC, 055IC, 058IC, Urologic Care for the Advanced Practice Provider: Bladder Cancer: New Diagnostic Tools, Intravesical Therapies, and Management of Intravesical Drug Toxicities, and Tumor Board: Bladder Cancer, complete the posttest, passing with 80% accuracy, and submit the evaluation and credit request form by visiting AUAU.AUAnet.org/18HLIO.

Estimated time to complete this activity:	1.25 hours
Release Date:	October 2018
Expiration Date:	October 31, 2019

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Content

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Statement of Need

An AUA survey indicated that urologists see an average of 17 patients a month with bladder cancer. While 84% of respondents felt very knowledgeable about the surgical treatment options, only 44% of them felt very knowledgeable about chemotherapy and immunotherapy options. When asked about increasing their knowledge in the area of bladder cancer 75.4% stated it was necessary to extremely necessary.

Target Audience

Urologists, urologists in training and non-physician providers involved in urology.

Course 005IC: Chemotherapy and Immunotherapy Options for Genitourinary Malignancies: A Primer for the Advanced Practice Provider

Learning Objectives

At the conclusion of this CME activity, participants should be able to:

- Describe the standard of care chemotherapy regimens for genitourinary malignancies
- Recognize newer immunotherapy options in the treatment of genitourinary malignancies
- Identify and manage the toxicities with relation to these agents
- Identify the survivorship issues surrounding patients on systemic treatments for genitourinary malignancies

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Course 019IC: Immunotherapy for the Urologist: Basic Principles, Adverse Effects & Drug Delivery

Learning Objectives

At the conclusion of this CME activity, participants should be able to:

- Describe the new innovations in tumor immunology and new immunotherapies in order to identify the right drug for the right patient
- Summarize the major findings in bladder and kidney cancer trials using immunotherapy
- Define the non-immune and the immune related side effects and manage the common side effects of immunotherapy
- Discuss the implementation of a systemic immunotherapy program in your practice, including regulatory, billing and coding for immunotherapy treatment
- Identify predictive biomarkers of immuno-oncology treatment

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Course 055IC: Genetic Testing in Prostate Cancer: Understanding Clinical Implications for Early Detection, Localized Disease & CRPC

Learning Objectives

At the conclusion of this CME activity, participants should be able to:

- Counsel men with BRCA1/2 mutations, Lynch syndrome and other key inherited syndromes regarding their prostate cancer risk and appropriate strategies for cancer screening
- Understand the criteria for genetic testing of patients with prostate cancer, the gene panels available, and options for testing these men
- Interpret results of genetic testing and relay this information to patients in order to facilitate shared decision making based on the test results
- Utilize the results of genetic testing to improve outcomes among patients with metastatic prostate cancer, including recommendations regarding PARP-inhibition, chemotherapy and immunotherapy

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Course 058IC: Management of Common Dilemmas in Prostate Cancer Diagnosis, Staging & Treatment

Learning Objectives

At the conclusion of this CME activity, participants should be able to:

- Use shared decision making to test men with prostate specific antigen, to decide whom to biopsy and how to biopsy
- Understand the pros and cons of different types of biopsy and how to select men for surveillance, surgery or external beam radiation therapy
- Determine the new therapies for advanced and metastatic cancer with androgen deprivation therapy, chemotherapy and immunotherapies
- Identify the roles of new staging positron emission tomography scans

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Urologic Care for the Advanced Practice Provider: Bladder Cancer: New Diagnostic Tools, Intravesical Therapies, and Management of Intravesical Drug Toxicities

Learning Objectives

At the conclusion of this CME activity, participants should be able to:

- Recognize new tools for diagnosing and surveilling patients with non-muscle invasive bladder cancer
- Examine intravesical therapy options pre and post bacillus Calmette-Guérin failure
- Identify and treat toxicities associated with intravesical therapy

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CME Information

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Tumor Board: Bladder Cancer

Learning Objectives

At the conclusion of this CME activity, participants should be able to:

- Identify novel immunotherapies for urothelial cancer
- Discuss the mechanism of action of PD-1 immunotherapy
- Identify current trials of perioperative immunotherapy
- Explain the rationale for trials of PD-1 immunotherapy for patients with non-muscle invasive bladder cancer

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Acknowledgements

The AUA Office of Education would like to thank the companies who support continuing education of physicians. The AUA recognizes the following companies for providing educational grant support:
AstraZeneca
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- Limit content to evidence with no recommendations
- Introduction of a debate format with an unbiased moderator (point-counterpoint)
- Inclusion of moderated panel discussion
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COURSE #005IC

Chemotherapy and Immunotherapy Options for Genitourinary Malignancies: A Primer for the Advanced Practice Provider

Costas D. Lallas, MD, FACS, Course Director; Anne E. Calvaresi, DNP, CRNP and Edouard J. Trabulsi, MD, FACS, Faculty

The next generation of management of genitourinary (GU) malignancies is marked by multidisciplinary care, interdisciplinary conferences and collaborative efforts. Long gone are the days when these patients were treated by clinicians operating out of separate silos with outcomes often determined by 1 person making the majority of the decisions surrounding care. Concurrently, urologists nationwide are facing a profound workforce shortage. It is conceivable that office urology, including the diagnosis and behavioral or medical treatment of straightforward urological maladies, can be off-loaded to primary care physicians. However, the treatment of patients with genitourinary malignancies should never occur far from the input of a urologic oncologist.

Therefore, with the emergence of multidisciplinary management of genitourinary malignancies and the impending workforce shortage in urology, a position expanding in scope has been created in the advanced practice provider (APP) with directed formal training in urologic oncology. These physician extenders (nurse practitioners and physician assistants) may work independently to increase the bandwidth of a urologic oncologist but make decisions ultimately dictated, directly or indirectly, by the physician.

By serving as the eyes and ears of the physicians with whom they work, APPs in urologic oncology must familiarize themselves with the newest cancer therapies. One such area that has emerged during the last 5 years is immunotherapy.

The concept of immunotherapy for bladder cancer is not new. Bacillus Calmette-Guérin (BCG) was FDA (Food and Drug Administration) approved for the treatment of superficial bladder cancer in 1990 and is still considered standard of care for noninvasive, high grade urothelial carcinoma of the bladder.[1] However, despite its relative success the mechanism of action of BCG has not been fully elucidated.

It is generally believed to elicit an immune response much like native tuberculosis, for which BCG was first created as a potential vaccine. Additionally, the relatively muted response of BCG in an immune deficient state suggests its foundation in immunotherapy. Finally, although BCG is associated with ease of administration and tolerability, it can cause particularly toxic side effects including dysuria, fevers, arthralgia and (thankfully rarely) BCG induced sepsis. Therefore, it should never be administered in the setting of active infection or gross hematuria.

Like BCG, another immunotherapy that has shown efficacy against high risk nonmuscle invasive bladder cancer (NMIBC) is interferon (IFN). This treatment is often used in conjunction with a reduced dose of BCG as a second line treatment for BCG refractory NMIBC. An APP working with a urologic oncologist is typically responsible for administering these intravesical therapies, and must be up to date on agents, including dosing schedules, side effects and when to switch to another agent because of intolerability or lack of efficacy.

Most of the recent excitement surrounding immunotherapy and bladder cancer lies in the introduction of the checkpoint inhibitors (CPIs). The astounding efficacy of this class of medications against urothelial cancer prompted a well-known and established genitourinary oncologist to state at an international meeting that he had "not seen such dramatic responses in my 30 years of treating these cancers."

The checkpoint proteins are molecules that impede immune function (namely T-cell immunity). In a normal individual this immune regulation helps the body recognize self and prevent autoimmunity and immune overactivity. However, malignant cells can hijack this mechanism and mimic the signals released by healthy cells. In so doing, the immune system remains inactive against the malignant cells, allowing them to grow and proliferate unregulated. A checkpoint inhibitor takes the proverbial foot off of the brake and activates the cellular response, allowing the immune system to attack the malignant cells.

The 3 checkpoint targets PD-1 and CTLA-4 (on the T-cell) and PD-L1 (on the tumor cell) are currently the focus of investigation. Atezolizumab is a monoclonal antibody, the first described PD-L1 inhibitor found to be active in bladder cancer. It received accelerated approval by the FDA for the treatment of urothelial cancer after failed platinum based chemotherapy, the first such agent in this disease space in more than 2 decades. The phase 2 IMvigor trial was the basis for the FDA approval as it demonstrated an objective response rate of 16% in 310 patients with platinum treated inoperable, locally advanced or metastatic urothelial carcinoma.[2]

Pembrolizumab is a humanized monoclonal antibody against PD-1 that was studied in KEYNOTE-045, a large open label, international, phase III trial evaluating its efficacy in the platinum refractory setting.[3] The positive results of this trial led to FDA approval of pembrolizumab for platinum refractory advanced urothelial carcinoma. Additional checkpoint inhibitors that are FDA approved for this disease are nivolumab (anti-PD-1), durvalumab and

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avelumab (both anti-PD-L1). Furthermore, atezolizumab and pembrolizumab have gained approval in the first line cisplatin ineligible population.

Like bladder cancer, renal cell carcinoma (RCC) is not a stranger to immunotherapy, particularly for the treatment of metastatic disease. From the 1990s to the early 2000s the only agents considered effective for patients with advanced RCC were high dose interleukin-2 and interferon. In fact, much of the data concerning cytoreductive nephrectomy, which is still commonly practiced today, were based on patients receiving adjuvant IFN.[4] However, harsh toxicities and relatively poor response rates associated with these older immunotherapy agents in part led to the quick conversion to the targeted therapy era in advanced RCC. These medications (eg sunitinib) were considered standard of care for approximately 10 to 15 years.

With the arrival of the CPIs came a new immunotherapy era for RCC. The CheckMate trial was published in 2018 and demonstrated improved overall survival in the intermediate to poor risk metastatic RCC group treated with ipilimumab (anti-CTLA-4) and nivolumab (anti-PD-1) combination vs sunitinib monotherapy. Additionally, the combination CPI regimen was better tolerated.[5] These results led to FDA approval of this regimen as first line treatment for intermediate to poor risk metastatic RCC. Additionally, results from other trials evaluating immunotherapy as adjuvant therapy or in the cytoreductive space are anxiously awaited.

Unlike other GU malignancies, prostate cancer has not demonstrated a clear benefit from CPIs and most of the recent strides for advanced prostate cancer surround the androgen receptor targeted agents. The only immunotherapy currently FDA approved for prostate cancer is sipuleucel-T, which is used in nonvisceral, asymptomatic or minimally symptomatic M1 castration resistant prostate cancer.[6] It involves 3 separate cycles of leukapheresis, ex vivo cell activation and reinfusion of the activated immune cells into the patient. Each cycle occurs during 1 week. Counterintuitively, efficacy does not necessarily correlate with a biochemical response and prostate specific antigen is not a reliable surrogate marker in patients being treated with this immunotherapy. Also, the labor-intensive mechanism of administration of sipuleucel-T has limited its use in many outpatient settings, particularly that of the urologic oncologist. As a result, familiarity with this medication, its regimen and side effects is important for the urologic oncology APP, although logistical issues surrounding drug administration may not be as applicable.

Immunotherapy in GU oncology, although not necessarily novel, has certainly had a resurgence with the introduction of newer classes of medications. Patients with advanced disease are more functional because of better survival and tolerability and, thus, are more often being seen in the outpatient setting. Because of increased collaboration of care for these patients, they are being evaluated more frequently in the clinic of a urologic oncologist. These appointments are often managed by the physician extender, who must be familiar with these newer treatments. Thus, these exciting times in GU cancer treatment are paralleled by a growing role for the APP in urologic oncology.

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4. Flanigan RC, Mickisch G, Sylvester R et al: Cytoreductive nephrectomy in patients with metastatic renal cancer: a combined analysis. J Urol 2004; **171:** 1071.
5. Motzer RJ, Tannir NM, McDermott DF et al: Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. N Engl J Med 2018; **378:** 1277.
6. Kantoff PW, Higano CS, Shore ND et al: Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010; **363:** 411.

COURSE #019IC

Immunotherapy for the Urologist: Basic Principles, Adverse Effects & Drug Delivery

Joshua Meeks, MD, PhD, Course Director; Peter Black, MD, FACS, FRCSC, Terence Friedlander, MD, Neal Shore, MD, FACS, Brian Shuch, MD, Kelly Stratton, MD and Robert Svatek, MD, Faculty

At the AUA2018 in San Francisco we presented a multidisciplinary course on immunotherapy for the urologist, based on the escalating role of immunotherapy in genitourinary (GU) malignancies. Urologists have been delivering immunotherapy since the 1970s, when Alberto Morales first published the response to bacillus Calmette-Guérin (BCG) in patients with nonmuscle invasive bladder cancer (NMIBC). While most trials of immunotherapy were started by medical oncologists in metastatic cancer, urologists treating kidney and bladder cancer have witnessed the rapid shift of immunotherapy trials for patients with localized cancer, sequenced as neoadjuvant and adjuvant therapy.

For BCG refractory bladder cancer, a cohort completely treated by the urologist, multiple trials now use systemic

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Course #019IC

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therapies and urologists continue to have an important role. Therefore, our course included urologists and medical oncologists with firsthand experience with immunotherapy. The course was directed toward the urologist with an interest, but no prior experience, in the delivery of immunotherapy to patients with bladder and kidney cancer (with possible application to prostate cancer in the future). Starting with innovative breakthroughs, new therapies and their side effects, the course also covered common side effects and biomarkers to risk stratify cases.

While urologists are comfortable delivering intravesical chemotherapy and immunotherapy, there are several programmatic and organizational challenges in the delivery of systemic immunotherapy. Even if urologists do not deliver immunotherapy, learning about new therapies, their application to urological cancers and their common side effects will be important for treating cancers in the future.

The course began with Robert Svatek, MD, MSCI (UT San Antonio) covering the basic mechanisms of immune activation in cancer and the scientific rationale of checkpoint inhibitors. Dr. Svatek reviewed the rapidly changing field of immuno-oncology. Importantly, he compared and contrasted the old paradigm of immunotherapy that involved vaccine strategies and adoptive transfer of immune cells, with the new paradigm addressing self-tolerance. He described how new investigations of checkpoint blockade revolutionized how we treat cancer and how these may be applied in new and/or combination strategies.

Peter Black, MD (University of British Columbia) then updated us on current trials in bladder cancer. He summarized the current approval for all 5 PD-1/PD-L1 therapies including results of first and second line metastatic bladder cancer. Of direct interest to urologists was a discussion of the rapid use of checkpoint inhibitors in the neoadjuvant and BCG refractory bladder cancer space. Dr. Black is the co-principal investigator of SWOG 1605 (phase II trial of atezolizumab in BCG unresponsive high risk NMIBC), and he highlighted the future of immunotherapy trials involving checkpoint combinations such as DANUBE, BISCAY and CheckMate 032.

The role of immunotherapy in the treatment of renal cancer was comprehensively reviewed by our third speaker, Brian Schuch, MD, PhD (Yale). Dr. Schuch contrasted historical trials of immunotherapy, including the use of interferon and high dose interleukin-2, with current trials combining the CTLA-4 inhibitor (ipilimumab) and PD-1 inhibitor (nivolumab) compared to sunitinib (CheckMate 214). While these trials are quickly changing the management of metastatic renal cancer, Dr. Schuch conveyed his excitement about recent trials investigating checkpoint therapy in the adjuvant and neoadjuvant settings. He highlighted PROSPER (EA8143), a neoadjuvant trial of 2 doses of nivolumab before nephrectomy. In particular, this trial requires enthusiastic participation from urologists to recruit patients before nephrectomy.

We were fortunate to have medical oncologist Terence Friedlander, MD (UCSF) present how to identify and manage complications of immunotherapy. He discussed the common (pneumonitis and colitis) and rare (myocarditis) side effects of checkpoint therapy and how medical oncologists balance treating side effects while still delivering optimal oncologic care. Understanding and recognizing the side effect profile of checkpoint therapy will be a major educational effort if urologists consider providing immunotherapy in the future.

This presentation transitioned nicely to Kelly Stratton, MD (University of Oklahoma), one of the few urologists at an academic center delivering immunotherapy. Dr. Stratton charted his course starting in 2016 involving a team approach to the delivery of immunotherapy and described how a urologist can champion this effort in the NMIBC setting. He discussed the barriers of malpractice insurance, credentialing and weekend coverage for urologists considering providing immunotherapy.

This environment could be contrasted with the experience of LUGPA (Large Urology Group Practice Association) practices as described by Neal Shore, MD (Carolina Urologic Research Center/Atlantic Urology Clinics), in which 50% of practices have the resources necessary for immunotherapy. Dr. Shore provided a look at the real-world experience of urologists, including key billing and coding notation required for urologist reimbursement. LUGPA has had a critical role in the education of its members with its annual curriculum at the "Bladder Cancer Academy" led by medical oncologists and urologists, aiming to give urologists the tools necessary to handle all aspects of bladder cancer care.

Finally, we concluded with a discussion of biomarkers of immunotherapy that may define a precision approach in the near future. While many of us had reservations about PD-L1 expression, on the day of the course the Food and Drug Administration issued information that first line patients with metastatic bladder cancer should be PD-L1 high-expressing to receive checkpoint blockade as chemotherapy appeared to be more effective in PD-L1 low-expressing cases. Further promising molecular biomarkers include total mutation burden and markers of DNA damage repair and immune signatures.

We hope this course provided a foundation for urologists to consider playing a key role in immunotherapy for patients with GU malignancy. While delivery of systemic therapy may require infrastructure and educational resources for urological practices, many urologists may continue to champion the care of patients with GU cancers and provide this important therapy.

COURSE #055IC

Genetic Testing in Prostate Cancer: Understanding Clinical Implications for Early Detection, Localized Disease and CRPC

Todd M. Morgan, MD, Course Director; Leonard G. Gomella, MD, FACS and Heather H. Cheng, MD, PhD, Faculty

Introduction

During the last several years our understanding of germline mutations as an important cause of aggressive prostate cancer has dramatically increased. Urologists treating men with prostate cancer are incorporating germline genetics into routine prostate cancer care, from early detection to the treatment of men with localized or metastatic prostate cancer. Multiple organizations now provide guidance to aid the prostate cancer community in navigating the complexities of genetic testing, but significant work remains to optimize and refine the field of germline genetics in prostate cancer.

Hereditary and Familial Prostate Cancer

Family history is a critical consideration for prostate cancer risk. Men with a family history of prostate cancer have a higher incidence of prostate cancer and higher prostate cancer specific mortality compared to men without a family history of prostate cancer.[1] For men who have first-degree relatives diagnosed with prostate cancer, their risk increases by roughly twofold compared to the general population. It is important to distinguish between hereditary prostate cancer (HPC) and familial prostate cancer. HPC is estimated to account for 5% to 10% of prostate cancer cases. These are generally considered to be due to higher penetrance inherited genetic variants, such as mutations in *BRCA1* or *BRCA2*, and these variants can greatly increase lifetime risk.

Familial prostate cancer is a broader term that encompasses 15% to 20% of cases and can include those patients with a strong family history of prostate cancer but no detectable genetic mutations.[2] More common polygenic variants with smaller effect sizes likely factor into many of these familial cases. These are often recognized as single nucleotide polymorphisms which may or may not themselves have a functional role in increasing the risk of prostate cancer.

Germline Alterations

A number of genes have been implicated in heritable prostate cancer, most of which have important roles in the DNA damage repair machinery. These include *BRCA1, BRCA2, CHEK2, ATM* and *PALB2*, along with mismatch repair mutations responsible for Lynch syndrome (*MLH1, MSH2, MSH6* and *PMS2*). *BRCA1* and *BRCA2* are critical proteins in the process of homologous recombination, and pathogenic mutations in these genes have long been known to increase the risk of breast and ovarian cancers in women. Germline *BRCA1* and *BRCA2* mutations in men are associated with a significant increase in the risk of prostate cancer, and men with pathogenic *BRCA2* mutations are typically diagnosed at a younger age, have higher Gleason grade tumors and have a shorter median survival than men with sporadic prostate cancers.[3,4]

Several options for germline genetic testing are now available for those men with prostate cancer with a high risk of harboring a genetic alteration. While single gene testing can be performed, such as for *BRCA1* or *BRCA2*, multigene panel testing has become more commonplace in the absence of a known familial mutation. These tests typically include a panel of genes associated with the disease of interest. For prostate cancer these panels usually include *BRCA1, BRCA2, ATM, CHEK2, MLH1, MSH2, MSH6, PMS2, EPCAM* and *TP53* among others specific to the individual commercial platform. Importantly, while many of the genes included in these panels have a clear association with prostate cancer risk, others carry a still unknown clinical significance with poorly defined cancer risk. Furthermore, given that NCCN® (National Comprehensive Cancer Network®) recommendations focus on BRCA testing, gaps in insurance coverage may limit the accessibility and use of multigene panel testing.

Many variants identified on multigene panel testing may not be clinically relevant. Some are known to be nonpathogenic, while others are indeterminate and classified as variants of uncertain significance. This occurs when a genetic change is present that differs from a normal control but there is insufficient information to classify it as deleterious or benign with respect to cancer risk.

Guideline Statements on Testing and Early Detection

In recognizing the importance of germline mutations, particularly *BRCA1/2*, the NCCN Genetic/Familial High-Risk Assessment: Breast and Ovarian Guideline recommends that men with a personal history of Gleason score 7 or greater prostate cancer with at least 1 close blood relative (first, second or third-degree) with ovarian cancer, pancreatic cancer, metastatic prostate cancer, or breast cancer diagnosed at age 50 years or younger, or 2 relatives with breast, pancreatic or prostate cancer (any grade), or individuals with Ashkenazi Jewish ancestry, should be considered for germline genetic testing. Men who have metastatic prostate cancer also meet NCCN criteria for *BRCA1/2* genetic testing. Additionally, these guidelines recommend that men with a pathogenic or likely pathogenic

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BRCA2 mutation should start prostate cancer screening at age 45 years. Men with *BRCA1* mutations should consider the same.

While the NCCN guidelines for breast and ovarian cancer early detection have endorsed dedicated prostate cancer screening in men with known or suspected *BRCA1/2* mutations for a number of years, only recently have the NCCN Prostate Cancer Early Detection guidelines placed *BRCA1/2* mutation status into the screening algorithm. Current prostate cancer early detection guidelines suggest that men with *BRCA1/2* mutations or family history of hereditary breast and ovarian cancer undergo prostate cancer screening by age 45 after a risk and benefit discussion. These guidelines recommend biopsy for prostate specific antigen (PSA) greater than 3 ng/ml or for suspicious examination in these high risk cases. Furthermore, the guidelines suggest followup based on initial PSA for those whose initial screening does not trigger a biopsy. However, particularly in light of the population-wide decrease in PSA screening during the last decade, there is a need to better define the early detection approach for these high risk cases.

The role for dedicated and early screening in men with known or potential germline mutations predisposing to prostate cancer is being evaluated in several settings, including the IMPACT and PROFILE trials in the UK.[5, 6] At the University of Michigan Prostate Cancer Risk Clinic, men who are known carriers of germline pathogenic mutations related to prostate cancer (eg *BRCA1/2*) are offered PSA screening and digital rectal examination starting at age 35, with a low PSA threshold for biopsy. This is combined with additional urine biomarker testing (SelectMDx) with the objective of better defining the role of intensified risk based prostate cancer screening in the United States.

Treatment Implications

In multiple studies men with *BRCA1/2* mutations have been shown to potentially have more aggressive prostate cancer and decreased survival compared to patients with sporadic prostate cancer. Key questions regarding eligibility of active surveillance in low risk disease or treatment intensification in men with high risk localized disease remain to be answered. In the metastatic setting there is emerging evidence of the efficacy of poly(ADP [adenosine diphosphate]-ribose) polymerase (PARP) inhibitors and platinum based chemotherapy in patients with germline and/or somatic biallelic defects in DNA repair genes. In the TOPARP-A trial, which led to FDA (Food and Drug Administration) breakthrough designation for olaparib in metastatic castration resistant prostate cancer, having a DNA damage repair alteration appeared to predict response to olaparib.[7] This is particularly relevant in the context of the work by Pritchard et al, who found germline DNA damage repair mutations in 11.8% of men with metastatic prostate cancer.[8]

There is also evidence of increased sensitivity to platinum based chemotherapy in patients with metastatic prostate cancer and with germline DNA repair mutations, likely related to platinum's mechanism of action through DNA damage.[9] With the treatment implications and potential relevance for family members, along with inconsistent insurance coverage and access to services, studies are ongoing to explore novel methods of providing cancer genetic testing and counseling to men with metastatic prostate cancer, including the University of Washington/Fred Hutchinson Cancer Center web based GENTleMEN study (www.clinicaltrials.gov, NCT03503097).

Finally, there is also evidence across a number of cancers that patients with an increased tumor mutational burden, such as those with DNA mismatch repair (MMR) deficient tumors, are particularly sensitive to immune checkpoint inhibition. This is most commonly seen in colorectal cancer, which is the most common malignancy associated with Lynch syndrome. However, as previously mentioned, mutations in MMR genes are also associated with prostate cancer and are likely present in approximately 5% of advanced prostate cancers.[10] Emerging data regarding MMR deficiency and checkpoint inhibition sensitivity have led to FDA approval for pembrolizumab, a PD-1 inhibitor, in solid tumors with mismatch repair deficiency such as in Lynch syndrome.[11] While there are still only limited data surrounding PD-1 sensitivity in MMR deficient prostate cancer, there are reports of extreme responses to pembrolizumab in this setting.

Conclusion

Germline mutations predisposing to prostate cancer have an increasing impact on the clinical management of prostate cancer, from pre-diagnosis genetic counseling, to screening and early detection, to newly diagnosed localized prostate cancer to metastatic disease. Using platinum based therapies, immunotherapy or PARP inhibitors in men with metastatic prostate cancer who have known germline mutations may lead to improved long-term outcomes, although additional research in these areas is needed. Given emerging evidence and guidelines, clinical pathways are now needed to facilitate germline testing in appropriately selected patients in order to inform treatment plans. Further work to improve access to genetic counseling, cancer screening and treatment options for men with relevant germline mutations is likely to yield significant long-term benefits for these patients.

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COURSE #058IC

Management of Common Dilemmas in Prostate Cancer Diagnosis, Staging and Treatment

Gerald L. Andriole, Jr., MD, Course Director; Anthony D'Amico, MD, PhD, Adam Kibel, MD and Oliver Sartor, MD, Faculty; Eric H. Kim, MD, Highlight Coauthor

Urologists have been familiar with the use of immunotherapy in cancer treatment for many years, including interleukin-2 and interferon-α for metastatic kidney cancer, and bacillus Calmette-Guérin for nonmuscle invasive bladder cancer. More recently, sipuleucel-T received FDA (Food and Drug Administration) approval for the treatment of asymptomatic or minimally symptomatic metastatic castration resistant prostate cancer (CRPC).[1] Based on its mechanism of action, sipuleucel-T is referred to as an anticancer vaccine, but may be more accurately classified as an immunostimulant.

Sipuleucel-T treatment requires leukapheresis, in which patients' dendritic cells are extracted. The dendritic cells are then incubated with a fusion protein that contains prostatic acid phosphatase (PAP) and granulocyte-macrophage colony stimulating factor. Once activated against PAP, the dendritic cells are then infused into the patient, with the course of treatment consisting of 3 infusions at 2-week intervals. At this time sipuleucel-T remains the only FDA approved immunotherapy for prostate cancer (PCa).

The initial approval for sipuleucel-T was based on a randomized trial of 512 patients with metastatic CRPC who demonstrated a significant increase in median overall survival (OS) compared to placebo (26 vs 22 months, p=0.03). Interestingly, no differences were observed in progression-free survival, which was defined as progressive disease on serial imaging or new cancer related pain associated with a radiographic anatomical correlate.[2] As the field has gained experience with immunotherapy across disease sites, we now know that pseudoprogression, initial radiographic increases in the size of tumor lesions as well as development of new lesions, can be seen in patients who ultimately derive benefit from treatment.[3] Although the treatment course for sipuleucel-T is discrete rather than continuous, knowledge of this phenomenon is important for patient counseling during therapy and the accurate interpretation of radiographic findings in the absence of changes in prostate specific antigen (PSA).

Using the same randomized trial data that led to FDA approval,[2] subsequent studies have demonstrated that patients with lower PSA levels derive a greater benefit from sipuleucel-T. For patients with a PSA less than 22.2 ng/ml, median OS was 41 months for sipuleucel-T vs 28 months for placebo. For patients with a PSA greater than 134.2 ng/ml, median OS was 18 months for sipuleucel-T vs 16 months for placebo.[4] Based on these results (and in the absence of prospective trials evaluating the timing of advanced PCa therapies), many recommend that sipuleucel-T be considered early in the treatment of metastatic CRPC.[5]

We can expect to have more definitive answers as the results of numerous ongoing clinical trials evaluating the timing of sipuleucel-T with respect to other advanced PCa treatments become available. Some important trials include 1) ClinicalTrials.gov identifier NCT01981122–sipuleucel-T with concurrent vs sequential enzalutamide, 2) NCT01487863–sipuleucel-T with concurrent vs sequential abiraterone, 3) NCT02463799–sipuleucel-T with or without radium-223 in bone metastatic CRPC, 4) NCT03024216–sipuleucel-T combined with atezolizumab (a PD-L1 inhibitor with FDA approved indications in lung and bladder cancer) and 5) NCT01804465–immediate or delayed ipilimumab (a CTLA-4 inhibitor with FDA approved indications in melanoma, and kidney and colorectal cancer) after sipuleucel-T treatment.

Given the apparent relative advantage of sipuleucel-T treatment for early metastatic CRPC (greater benefit compared to placebo at lower PSA levels),[4] one may expect that the use of sipuleucel-T in metastatic hormone sensitive PCa would be beneficial as well. Unfortunately, no studies have been performed in this clinical setting and, so, the theoretical role of sipuleucel-T in hormone sensitive PCa must be based on surrogate information.

Studies have demonstrated that OS for patients with CRPC treated with sipuleucel-T can be correlated to immune activity parameters and, thus, greater

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immune activity may be viewed as an indicator of improved OS in early studies involving sipuleucel-T.[6] For patients with biochemical recurrence after prostatectomy and a relatively short PSA doubling time, sipuleucel-T before androgen deprivation therapy (ADT) demonstrated significantly greater antitumor immune responses.[7] In another study of similar patients, sipuleucel-T plus ADT increased the PSA doubling time (slowed the progression of disease) compared to placebo plus ADT.[8] Even localized PCa studies have suggested an oncologic benefit, as sipuleucel-T administration before prostatectomy demonstrated significant recruitment of activated T cells into the prostate tumor microenvironment.[9]

Although FDA approval for sipuleucel-T is currently limited to metastatic CRPC, these studies are thought-provoking in that treatment with sipuleucel-T or other immunotherapies may provide survival benefit if delivered earlier in the management of PCa, particularly if we are able to accurately predict which patients are at highest risk for metastatic disease and castration resistance.

The successful application of immunotherapy in PCa treatment will undoubtedly rely on advanced molecular profiling of patients' cancer. The recent widespread attention surrounding immunotherapy in the field of oncology has largely centered on the role of immune checkpoint inhibitors (ie PD-1, PD-L1 and CTLA-4 inhibitors), as a number of these medications have gained FDA approval in numerous cancer types (eg atezolizumab, avelumab, ipilimumab, nivolumab and pembrolizumab). Within urologic oncology, although immune checkpoint inhibitors have demonstrated a survival benefit for metastatic kidney and bladder cancer, they have not yet demonstrated a survival benefit for PCa. Although some may interpret this as discouraging, others have suggested that the underlying reason for the apparently limited benefit of immune checkpoint inhibitors is a result of the mutational heterogeneity of advanced PCa.

As advances in technology have led to improvements in molecular diagnostics, we have learned that patients with metastatic PCa are significantly more likely to harbor germline DNA repair gene mutations (approximately 12% of patients) than previously believed.[10] If we couple the studies that have demonstrated efficacy of immune checkpoint inhibitors in patients with DNA mismatch repair deficiencies,[11, 12] with the knowledge that a subset of patients with metastatic PCa have germline mutations in mismatch repair genes,[13] then we can conclude that immune checkpoint inhibitors may have a role for appropriately identified patients with metastatic PCa.

Future studies of immune checkpoint inhibitors in advanced PCa must correctly enroll patients with tumors whose molecular profiles are associated with a therapeutic response. We are seeing the same strategy with the use of small molecule inhibitors such as poly(adenosine diphosphate-ribose) polymerase inhibitors used in patients with metastatic CRPC who have mutations in DNA repair genes.[14]

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PRESENTATION

Urologic Care for the Advanced Practice Provider: Bladder Cancer: New Diagnostic Tools, Intravesical Therapies, and Management of Intravesical Drug Toxicities

Heather Schultz, RN, MSN, NP-C and Kenneth Mitchell, MPAS, PA-C, Course Co-Directors; Michael A. O'Donnell, MD, Faculty

Recognition and Management of bacillus Calmette-Guérin (BCG) Related Toxicity

Bacillus Calmette-Guérin (BCG), the live attenuated vaccine strain of cow tuberculosis (TB), remains the standard of care for patients with high risk, nonmuscle invasive bladder cancer (NMIBC) and for those with intermediate risk disease in whom conventional intravesical chemotherapy has failed.[1] Although its exact mechanism of action remains unknown, it is still the only agent that has been shown to reduce the risk of progression to muscle invasive disease.[2] Despite this clear advantage, BCG has a number of side effects, some of which can be life threatening. Proper recognition and treatment of BCG related toxicity are vital to providing the best and safest care.

Local Toxicity Associated with BCG

For patients previously naïve to BCG or TB, it is unusual to have much in the way of local toxicity or bladder irritability during the first few weekly doses of BCG. Thereafter, patients commonly begin to experience frequency, urgency and dysuria beginning shortly after the first 2-hour void that escalates during the ensuing 6 to 12 hours. These symptoms usually resolve by 24 hours initially but with increasing re-treatment, tend to become more intense sooner with a longer time (2 to 7 days) to completely dissipate.

The local toxicity situation with BCG/TB exposed patients is more accelerated. Using a validated questionnaire Bohle et al addressed the symptoms among German patients (most BCG vaccinated) during the course of 6-week instillations of BCG for NMIBC.[3] Even after the first instillation, 50% of the patients complained of dysuric episodes. During subsequent instillations there was an increase up to 80% of patients with dysuric complaints. In a study by Saint et al cystitis lasting 2 to 48 hours was noted in 46%, 48 hours to 7 days in 38% and more than 7 days in 12%.[4] Increased duration was seen after the fourth induction treatment. Along with this increased intensity of irritable symptoms, the likelihood of gross hematuria also increased such that up to a third of patients suffered from this side effect.

The recorded incidence of these varied symptoms is listed in the table and is notably greater for BCG than for any of the cytotoxic chemotherapeutics. Lamm et al reported that only 16% of patients randomized to a miniseries of 3-weekly maintenance treatment actually received all their scheduled doses, presumably due to toxicity.[5] Saint et al reported a similar 19% completion rate for all maintenance doses in a smaller trial of similar design.[4] Furthermore, 57% had dose reduction for toxicity and 39% had treatment discontinued. Even if maintenance therapy is associated with higher local toxicity, its benefit is largely offset by enhanced efficacy, as most local side effects are mild to moderate and reversible.

The histological changes found in the bladder after BCG therapy imply a generalized inflammatory process with pronounced mononuclear inflammatory infiltrate and epithelial sloughing.[6] Granulomas are present in roughly a quarter of the cases. Visual abatement of most bladder inflammation occurs after 6 weeks but full resolution of granulomatous changes may take 6 months or longer.[7]

After irritative symptoms the most common side effect is asymptomatic prostatitis, which is estimated to occur in up to 40% of male patients. It is often associated with an abnormal digital rectal examination (DRE) that typically does not require specific therapy.[8] However, because it may be difficult to distinguish the abnormal DRE from the nodularity associated with prostate cancer, irregularity persisting for 3 months may require biopsy.[9] Prolonged symptomatic BCG cystitis and/or prostatitis (estimated incidence less than 5%) can be troublesome during therapy and in the post-BCG observation period.[1] This is particularly more likely to occur during re-treatment or prolonged maintenance therapy. This situation is best avoided by withholding BCG treatment until all significant symptoms from the prior instillation have subsided. A 1 to 2-week delay has not been shown to reduce BCG efficacy in such a setting.[10, 11] Reinstitution of BCG at a lower dose or premature termination of further treatment for this cycle may also be appropriate. Dose reduction may reduce local symptoms without compromising treatment efficacy, especially during the maintenance phase.[11, 12] If localized severe cystitis does occur and conservative symptomatic treatment measures fail, this condition can be treated with oral fluoroquinolones (3 to 12 weeks) or oral isoniazid (INH). An oral steroid taper sandwiched between TB specific antibiotic coverage is usually

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needed in refractory cases because of the risk of causing BCG dissemination. These patients may require a taper of oral prednisone over 3 to 12 weeks. Successful tapers for refractory BCG cystitis have been described with doses starting at 20 mg daily for 3 weeks with a 3-week taper to 0 mg. Higher dose tapers have been described for more difficult to treat cases.[12, 13]

Systemic Side Effects of BCG

Systemic side effects of BCG occur in 1 of 2 major forms, infectious and noninfectious. Fever/chills and a flu-like illness are reported in about a quarter of patients receiving BCG and have actually been associated with an improved cancer prognosis (see table).[14] In roughly 3% of patients, body temperature exceeds 39.5C.[15] However, not all fevers are a sign of BCG infection, but rather may be the result of spillover of BCG induced pyogenic inflammatory cytokines from the bladder into the bloodstream.[16] Unfortunately in the acute setting it is difficult to distinguish an infectious event from a noninfectious event. Fevers that persist more than 48 hours or relapse in a diurnal pattern (usually in the early evenings) following the ebb in the cortisol cycle are indicative of BCG infection. At a minimum those patients with high fevers after BCG instillation should be evaluated, and many will require hospitalization for observation and an infectious disease consultation. A fluoroquinolone antibiotic should be considered immediately since it will treat the majority of non-BCG bacterial urinary tract infections and has reasonable antimycobacterial activity until the patient declares him/herself. Patients with self-limiting fevers less than 48 hours may be re-treated with nonsteroidal anti-inflammatory drug prophylaxis before the next BCG treatment (eg 600 mg ibuprofen every 6 hours × 3 beginning 2 hours before therapy) and a reduced dose of BCG.[17]

Clinical signs that suggest BCGosis (systemic BCG infection) include exaggerated manifestations of the previously mentioned systemic effects, particularly if they occur within 2 hours after BCG instillation, in the setting of traumatic catheterization or too soon after transurethral bladder resection (TURB). In the extreme case a picture resembling gram-negative bacterial sepsis may emerge with rapid and sequential appearance of skin mottling, chills, rigors, high temperatures (often higher than 39.5C) and hypotension, likely as a result of high levels of cytokines released directly into the bloodstream (the so-called cytokine storm).[18, 19] The estimated incidence of this life threatening event may be as high as 0.4% and several deaths have been reported.[16, 20, 21]

Prompt fluid resuscitation measures should be instituted as well as antipyretics. Anti-tuberculosis antibiotics and systemic steroids have been shown to be lifesaving in such instances.[19, 22] These patients should undergo treatment with 600 mg rifampin PO daily, 300 mg isoniazid PO daily, 50 mg pyridoxine PO daily, 1,200 mg ethambutol PO daily and 40 mg prednisolone intravenously daily that is tapered during a 2 to 3-week period after the sepsis has resolved. Ethambutol is continued for 2 months, and rifampin, isoniazid and pyridoxine are continued for at least 6 months.

Organ specific manifestations of BCG infection outside the bladder are uncommon but potentially serious.[23] These include pneumonitis (in a characteristic military pattern), granulomatous hepatitis, osteomyelitis (Pott's disease), granulomatous pyelonephritis, psoas abscess and epididymo-orchitis. Even more rare are BCG infections affecting heart valves, prosthetic devices, grafts, bone marrow (leading to cytopenia) and the vitreous humor of the eye. Sometimes these may occur even years after BCG therapy, representing a release of dormant BCG sequestered organisms, particularly in the bladder, causing sterile pyuria due to chronic BCG cystitis. Thus, there must be a high index of suspicion for any unusual infections occurring with or after prior BCG treatment.

In cases of BCG infection that are not life threatening, tuberculosis drugs should be continued for 3 to 12 months depending on the severity of the presenting illness. Double drug therapy, eg INH plus rifampin, is continued until the acute effects are controlled and acid-fast bacilli cultures show no growth. Then single drug INH therapy may suffice during the latter half of therapy. Liver enzyme monitoring is required for INH and rifampin. Vitamin B6 (pyridoxine), 50 mg PO daily, is added whenever INH is used as this depletes endogenous supplies.

Other noninfectious systemic side effects of BCG may be related to an immune hypersensitivity state. Minor examples include arthralgias and skin rashes in 5% to 6% of patients.[1] These are typically self-limiting and provider judgment should be used regarding whether BCG treatments should continue. However, more severe cases involve polyarthritis, Reiter's syndrome (urethritis, arthritis, conjunctivitis) and frank anaphylactic reactions.[16, 24, 25] These cases require immediate and permanent cessation of further therapy, typically along with steroid therapy.

Methods to Prevent or Minimize BCG Complications

The serious infectious side effects of BCG are best prevented by careful adherence to prescribed technique. Several mechanisms to reduce the risk of BCG complications are well-known. Most importantly, catheter placement must be atraumatic and treatment should be withheld in the event of any gross blood or significant pain. At least 1 week but preferably 2 to 3 weeks should elapse after TURB before initiation of BCG. Instrumentation, such as urethral dilation or cystoscopy, should not be performed immediately before BCG instillation. BCG should never be administered under high pressure but ideally should be dripped into the bladder under gravity. Caution should be exercised in treating immunosuppressed patients with BCG. Patients on low dose oral or inhaled steroids have been

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treated successfully as have a few transplant patients on stronger antirejection medications.[26, 27] However, there have been documented cases of reactivated TB or BCG sepsis in immunocompromised patients.[28, 29] Patients with cystitis symptoms should be evaluated with urinalysis and/or culture. BCG should be delayed if bacteriuria is present or if symptoms are moderately severe from the prior instillation to reduce the risk of inducing sustained BCG cystitis.[30]

Adjustments to the BCG regimen may help reduce its local and systemic toxicity. Dose reduction of BCG has been studied to various levels down to 1/6 of the standard dose and the results are mixed. In some studies a 50% to 75% reduction in BCG dose resulted in a 30% to 50% drop in serious morbidity without a significant impact on anticancer efficacy.[31-33] However, with further dose reduction to 1/6, reduced cancer control without further reduction in side effects was reported.[34] Some studies have shown a lack of reduction in morbidity with dose reduction.[35, 36] However, these studies mainly represent patients during initial therapy for high grade papillary disease or carcinoma in situ in BCG naïve populations in North America. Dose reduction may be useful during re-induction and/or maintenance therapy when dropout rates from toxicity are higher. Validation studies have not yet been performed but small studies have been published regarding reduced dwell time to 30 minutes or spreading out treatments to every other week.[37, 38] Prophylactic INH has not been shown to diminish the associated symptomatology or the incidence of serious BCG infection, but it has been shown to transiently elevate liver function enzymes.[39] Therefore, prophylactic INH is not recommended. However, administration of 200 mg ofloxacin 6 and 18 hours after each BCG treatment significantly decreased by 18.5% the incidence of moderate and severe adverse events resulting in better compliance with full BCG treatment.[40] The long-term effect on BCG efficacy as well as the long-term safety of recurrent doses of prophylactic ofloxacin are unclear.

Treating BCG Intolerant Cases with Reduced Dose BCG Plus Interferon

Approximately 5% to 10% of patients experience sufficiently severe BCG non-infectious reactions during the 6-week induction phase and, so, clinicians are appropriately reluctant to continue further treatments. Known as BCG intolerance, this diagnosis is greatly understudied. Steinberg et al have proposed a practical definition of BCG intolerance that includes any of the characteristics of debilitating cystitis for more than 2 weeks, 2 or more episodes of gross hematuria requiring intervention, inability to hold BCG for more than 30 minutes, repeated severe but limited (less than 2 weeks) reactions to BCG or other serious BCG related symptoms excluding actual BCG infection.[41] Using this definition the authors were able to successfully treat 37 BCG intolerant cases with a markedly reduced dose of 1/10 of the standard BCG dose combined with 50 million units of interferon (IFN)-α-2B and achieve a 2-year disease-free rate of 54%. Importantly, this was not statistically different than the 59% achieved by full dose BCG in BCG naïve patients. Furthermore, while BCG intolerant patients treated in this manner did experience more cystitis and bladder pain/spasm, and required more symptomatic medication with more treatment delay or dose reduction, all patients but 1 were able to complete the full 6-week induction course. Furthermore, quality of life was not significantly affected.

Another trial looked at tolerability and toxicity data of 490 patients comparing the half who were BCG naïve who received standard dose BCG plus IFN-α (50 MU) to those with prior BCG failure who received 1/3 dose BCG plus IFN-α (50 MU).[42] This trial revealed a low rate of treatment delay (4%) and dropout (3%). Oncologic outcomes did not seem to be compromised. One-third standard dose of BCG with the addition of IFN seems to be an acceptable treatment strategy for patients in whom BCG initially fails and who are re-treated with another full 6-week induction cycle. It may allow some patients to receive maintenance therapy who would otherwise not tolerate it.

Summary

BCG is a major therapeutic approach to NMIBC that is more effective than conventional intravesical chemotherapy. However, most patients experience local toxicity and in some it is severe enough to require treatment interruption or even discontinuation. Infectious complications, while rare, can be life threatening and pleomorphic, requiring prompt recognition and appropriate antibiotic and steroid therapy. Fortunately, methods exist to reduce or prevent many of these untoward reactions while still permitting the majority of patients to complete effective therapy.

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Table. Summary of toxicity reported for common intravesical agents

	Mitomycin C	Doxorubicin	BCG
Local			
Frequency/nocturia	42 (26-59)	27 (23-32)	63 (48-76)
Dysuria	35 (30-41)	20 (8-39)	75 (64-84)
Irritative symptoms	18 (12-26)	21 (13-30)	Extremely variable
Pain/cramps	10 (6-14)	12 (4-25)	12 (7-18)
Hematuria	16 (7-28)	19 (12-29)	29 (22-36)
Incontinence	1 (0.4-4)	9 (3-18)	4 (3-6)
Bladder contracture	5 (2-11)	3 (0.8-6)	3 (2-5)
Systemic			
Flu-like	11 (4-23)	7 (3-13)	24 (18-31)
Fever/chills	4 (1-10)	4 (2-9)	27 (22-32)
Arthralgias	Not reported	1 (0.1-5)	5 (1-13)
Myelosuppression	13 (8-19)	0.8 (0.2-2)	1 (0.1-4)
Nausea/vomiting	9 (0.8-31)	8 (4-13)	9 (6-14)
Skin rash	2 (0.4-4)	2 (0.5-6)	6 (3-10)
Infectious			
Bacterial cystitis	20 (17-23)	6 (2-12)	20 (13-28)
Epididymitis, prostatitis, urethritis	4 (2-9)	2 (0.1-7)	5 (4-8)
Pneumonia	0.2 (0-2)	Not reported	1 (0.2-3)

Adapted from the AUA Bladder Cancer Guidelines Panel summary report on the management of nonmuscle invasive bladder cancer.[1]

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PRESENTATION

Tumor Board: Bladder Cancer

Eila Skinner, MD, Moderator; Yair Lotan, MD, Seth Lerner, MD, FACS, Neha Vapiwala, MD and Terence W. Friedlander, MD, Panelists

Locally advanced and metastatic (m) urothelial cancer (UC) has historically been a challenging disease to treat for many reasons. Patients are generally older and frequently have multiple comorbidities, including renal insufficiency, neuropathy, hearing loss and poor performance status, which create challenges in selecting therapies that are efficacious and tolerable.

Since the development of platinum based cytotoxic chemotherapy in the late 1970s there had been no new agents approved for the treatment of mUC until recently. Indeed, cisplatin based regimens have been the mainstay of treatment for patients with good performance status. In a large randomized study the overall response rate and complete response rate were 49% and 12.2%, respectively.[1] Despite this initial activity, before the advent of novel immunotherapies the median progression-free and overall survival for patients treated with cisplatin based chemotherapy was only 7.4 and 14.8 months, respectively.

Additionally, while effective for some patients, cisplatin based therapy has significant toxicity, and the majority of patients with mUC have concurrent renal dysfunction, poor performance status and/or comorbid illnesses that preclude its use. Widely accepted consensus criteria now exist to define which patients should not be offered cisplatin.[2] While an alternative carboplatin based regimen has an overall response rate of 41.1%, median progression-free and overall survival is only 5.8 and 9.3 months, respectively, and better treatments are needed, particularly ones that do not involve cytotoxic chemotherapy.[3]

Fortunately for some patients checkpoint inhibitors (CPIs) targeting the PD-1 or PD-L1 immunologic checkpoint have shown clear activity in cisplatin naïve and cisplatin ineligible patients with mUC, as well as patients who have experienced disease progression despite a platinum regimen.[4, 5] Since 2016, 5 CPIs have been approved for the treatment of mUC, and of these 2 (pembrolizumab and nivolumab) bind to PD-1 and 3 (atezolizumab, durvalumab and avelumab) bind to PD-L1.

The study that perhaps best illustrates the efficacy of these agents is the randomized phase III KEYNOTE-045 study, in which pembrolizumab was compared to taxane or vinflunine chemotherapy in patients with platinum treated mUC.[6] In this study the overall response rate was 26%, including 11% of patients who experienced a complete response. Perhaps more exciting, more than 60% of patients who responded to therapy were still responding 1 year later. In this trial the response rates did not differ by the PD-1/PD-L1 status of the tumor. Similar results were observed in the phase II and phase III studies of the other CPIs tested. Some recent evidence suggests that patients with low PD-L1 tumor expression may not respond as well as those with high PD-L1 expression, but more data are needed.

There are major issues under exploration in the metastatic space, such as why only a minority of patients respond to CPI monotherapy, how to identify and prioritize these patients for treatment, how resistance to CPI therapy develops and which partners will pair best with CPI therapy. Additionally, whether these agents should be used for patients with localized, nonmetastatic UC is under exploration.

At tumor board a case of high grade muscle invasive bladder cancer was presented and the optimal management was discussed. Patients with T2-T4 urothelial cancer are considered curable, and it is important to maximize the chance of cure through consideration of systemic therapy that can shrink tumors and treat micrometastatic disease with the goal of consolidating therapy with radical cystectomy (RC). In the pre-CPI era in a randomized phase III study, transurethral bladder tumor resection (TURBT) plus neoadjuvant cisplatin based chemotherapy followed by RC was compared to TURBT and RC alone.[7] In this study the pathological complete response (pCR) rate at cystectomy was increased from a baseline of 15% for surgical approaches alone to 38% with the addition of neoadjuvant cisplatin based therapy. pCR was an excellent predictor of long-term outcomes and prospective data demonstrated that more than 80% of these patients achieving pCR were cured.[8]

The challenge facing many patients with muscle invasive bladder cancer is that many frequently have comorbidities similar to those of patients with mUC. Renal dysfunction due to ureteral obstruction frequently makes patients ineligible for cisplatin. However, to date no study has comprehensively evaluated neoadjuvant regimens that do not contain cisplatin. The patient presented had a creatinine of 1.3 mg/dl and a creatinine clearance of 52 ml per minute, putting her below the accepted clearance limit of 60 ml per minute to receive cisplatin. In our discussion it was emphasized that a patient like this should not be treated with neoadjuvant carboplatin chemotherapy given the lack of evidence of efficacy, and according to current guidelines should be offered up-front RC.

Given the rapid development and promising clinical activity of CPIs in the metastatic space, we discussed the usefulness of CPIs for a patient who is ineligible to receive neoadjuvant cisplatin based chemotherapy. Perioperative immunotherapy has several distinct advantages. It is generally well tolerated, with a lower frequency of overall and serious adverse events in patients treated in the metastatic setting. In addition, CPIs are safe in patients with mild

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to moderate renal impairment, offering the possibility of a tolerable therapy for patients ineligible to receive cisplatin. However, one of the concerns about neoadjuvant therapy is that in the metastatic setting only approximately 20% of patients have a partial or complete response. Thus, there is a risk that the disease could progress in a patient not responding to the preoperative CPI and decrease the chance of a cure after surgery. Similarly, it should be emphasized that while well tolerated there are some patients who experience autoimmune side effects that, while rare, could delay time to RC.

Multiple clinical trials of perioperative CPI therapy are under way and these were reviewed at the tumor board. Specifically there are 3 phase II studies of neoadjuvant CPI monotherapy, 1 at the University of California, San Francisco using atezolizumab, and 2 under way in Europe using atezolizumab and pembrolizumab, respectively. The goal of these studies is to down stage tumors and ideally provide antitumor immunity. It is hypothesized that treatment with the CPI while the tumor is still present will allow for better priming and activation of T cells, leading to durable anticancer immunity in the postoperative setting. Neoadjuvant trials additionally have the advantage of providing pretreatment and posttreatment tissue for comprehensive correlative analyses, to dissect the immunologic and genomic mechanisms of response and resistance to CPI therapy.

Similarly there are multiple randomized phase III studies under way of adjuvant (postoperative) CPI treatment, including studies of atezolizumab, pembrolizumab and nivolumab.[9-11] In these studies the patients who have undergone RC are randomly assigned to CPI therapy vs observation. The primary end point for these studies is disease-free survival, with the hope that treatment with CPIs after bladder removal will allow lymphocytes to identify and attack residual micrometastases.

Ultimately for this patient with baseline renal insufficiency it was recommended that she proceed directly to RC, but strongly consider enrollment in a neoadjuvant or adjuvant study of CPI therapy with the goal of increasing her likelihood of cure. Going forward we eagerly look forward to the presentation of the perioperative CPI trial data to better understand how to use these agents in the perioperative setting.

Lastly, while not the focus of the tumor board, it should be noted that multiple clinical trials are evaluating the use of CPIs for patients with nonmuscle invasive bladder cancer even earlier in the disease course as a means of avoiding RC and better preserving urinary function and quality of life. Specifically, in SWOG 1605, a phase II study, patients with bacillus Calmette-Guérin (BCG) resistant/refractory disease are treated systemically with atezolizumab, and undergo serial cystoscopy and TURBT to evaluate response to checkpoint therapy.[12] A separate study evaluates the use of durvalumab along with BCG compared to BCG in patients with NMIBC.[13]

While CPIs cannot be currently recommended outside of a clinical trial for nonmetastatic disease, given their activity in the metastatic setting there is optimism that some patients with localized (T1-T4) disease will respond and potentially avoid the need for RC. Therefore, results of these and other studies are eagerly awaited.

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