American Urological Association

AUA NEWS

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AUA NEWS

2019 ANNUAL MEETING HIGHLIGHTS

Prostate Cancer

Course #013IC
Genetic Testing in Prostate Cancer: Understanding Clinical Implications for Early Detection, Localized Disease and CRPC

Course #027IC
AUA CRPC Guidelines and Therapeutic Advances in Metastatic Prostate Cancer

Course #037IC
Using Shared Decision Making to Help Patients Decide on Prostate Cancer Screening and Treatment

Course #048IC
Novel Agents and Concepts in the Management of Hormone Naïve and CRPC

Course #065IC
Prostate Cancer Update

Urologic Care for the Advanced Practice Provider

Developing a Prostate Cancer Survivorship Program

Patients Receiving Androgen Deprivation Treatment for Prostate Cancer: Managing Side Effects

Panel Discussion

Biomarkers in Prostate Cancer

AUANews Editor

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AUA 2019 chicago MAY 3–6

AUA2019 ANNUAL MEETING HIGHLIGHTS

Prostate Cancer

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CME INFORMATION

2019 AUA Annual Meeting Highlights: Prostate Cancer

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Statement of Need

To better understand urologists' educational needs for treating castrate resistant prostate cancer (CRPC), the AUA conducted an in-depth educational needs assessment of its domestic membership representing >90% of U.S. Board Certified urologists in 2013 (Phase I). The AUA reassessed its members' educational needs after releasing the updated CRPC Guideline and targeted CRPC educational activities in 2015 (Phase II) and again in 2017 (Phase III). Areas identified as an educational need with regard to managing CRPC center on sequencing of agents, managing side effects of treatments and comorbid conditions, and identifying potential interactions between immunosuppressive agents and other medications. Urologists continue to indicate a strong educational need for a thorough review of the AUA CRPC Guideline.

Target Audience

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

013IC: Genetic Testing in Prostate Cancer: Understanding Clinical Implications for Early Detection, Localized Disease and 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
- Identify 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 poly (ADP-ribose) polymerase inhibition, chemotherapy and immunotherapy

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Course 027IC: AUA CRPC Guidelines and Therapeutic Advances in Metastatic Prostate Cancer

Learning Objectives

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

- Identify the active agents and their mechanism of action in the management of nonmetastatic (nm) CRPC and metastatic (m) CRPC
- Explain the sequencing and indications for active treatment with approved agents in the management of nmCRPC
- Analyze the evidence and outcomes on the treatment of M0 and M1 CRPC as outlined in the newly updated AUA CRPC guidelines
- Improve diagnostic and therapeutic decision making processes by illustrating the application of these guidelines in urological practice
- Describe breakthrough treatments in the management of advanced and metastatic hormone naïve prostate cancer

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Course 037IC: Using Shared Decision Making to Help Patients Decide on Prostate Cancer Screening and Treatment

Learning Objectives

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

- Explain shared decision making
- Discuss the impact of shared decision making on patients and on patient-clinician communication
- Describe at least one implementation strategy for using shared decision making in clinical practice

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Course 048IC: Novel Agents and Concepts in the Management of Hormone Naïve and CRPC

Learning Objectives

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

- Diagnose both nonmetastatic and metastatic castrate resistant prostate cancer, and outline the treatments and the proper order for administration
- Manage nmCRPC and mCRPC with systemic agents by learning the proper candidates for treatment, and counsel patients on the pros and cons of therapy
- Analyze the mechanism of action and risks/benefits of using systemic agents in the treatment of nmCRPC and mCRPC
- Describe the bone-targeted, radiopharmaceutical agent and its sequencing
- Review the newer generation antiandrogen agents and their use in nmCRPC and mCRPC

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Course 065IC: Prostate Cancer Update

Learning Objectives

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

- Cite important new publications in this field during the past year
- Identify the relative strengths and weaknesses of the reports
- Evaluate how new studies relate to the existing state-of-the-art in clinical practice
- Analyze whether they and their colleagues should consider changing their practice based on the new information

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COURSE #013IC

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 management of localized or metastatic prostate cancer. Although guideline bodies are increasingly providing guidance to aid the prostate cancer community in navigating the complexities of genetic testing, 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 those without a family history of prostate cancer.[1] For men who have first-degree relatives diagnosed with prostate cancer, the risk of the disease increases roughly twofold compared to the general population. An additional familial risk factor is a history of breast, ovarian, pancreatic and/or colon cancers.

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, which can greatly increase lifetime risk. Familial prostate cancer is a broader term that encompasses 15% to 20% of cases and can include 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 (SNPs) which may or may not have a functional role in increasing the risk of prostate cancer. A number of polygenic risk scores for prostate cancer risk have been developed which could be useful clinically to help guide prostate cancer early detection strategies.

Germline Alterations

Multiple higher penetrance genes have been implicated in heritable prostate cancer, most of which have important roles in the DNA damage repair machinery. They 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 time than those with sporadic prostate cancers.[3, 4] Recently, Nicolosi et al showed that in a cohort of 3,607 patients with localized and metastatic prostate cancer multigene panel testing revealed that 620 (17%) had a germline variant present.[5]

Several options for germline genetic testing are now available for men with prostate cancer at high risk for harboring a genetic alteration. While single gene testing, such as for BRCA1 or BRCA2, can be performed, 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 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 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 the 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. While these variants are reclassified as benign the majority of time, patients must be educated regarding the possibility of variant reclassification as a pathogenic variant and there should be a clear line of communication for them to receive any updated information.

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Guideline Statements on Testing and Early Detection

Recognizing the importance of germline mutations, particularly BRCA1/2, the NCCN Genetic/Familial High-Risk Assessment: Breast and Ovarian Guideline recommends that men who have a personal history of Gleason score 7 or greater prostate cancer with at least 1 close blood relative (1st, 2nd or 3rd degree) and ovarian cancer, pancreatic cancer, metastatic prostate cancer or breast cancer diagnosed at age 50 years or less; or 2 relatives with breast or prostate cancer; 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.

While the NCCN guidelines for early detection of breast and ovarian cancer 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 a known or suspected cancer susceptibility gene undergo prostate cancer screening by age 45 years after a risk and benefit discussion. These guidelines recommend biopsy for prostate specific antigen (PSA) greater than 3 ng/ml or for suspicious exam in these high risk men. Furthermore, the guidelines suggest followup based on initial PSA level for those whose initial screening does not trigger a biopsy. Particularly in light of the population-wide decrease in PSA screening in the last decade, however, there is a need to better define the early detection approach for these high risk men.

The role for dedicated and early screening of men with known or potential germline mutations predisposing to prostate cancer is being evaluated in a number of settings, including the IMPACT and PROFILE trials in the United Kingdom.[6,7] 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 exam starting at age 35 years, with a low PSA threshold for biopsy. This protocol is combined with additional urine biomarker testing (SelectMDx®) with the objective of better defining the role for intensified risk based prostate cancer screening in the United States.

Treatment Implications

Men with BRCA1/2 mutations have been shown in multiple studies to potentially have more aggressive prostate cancer and decreased survival compared to patients with sporadic prostate cancer. Key questions regarding eligibility of active surveillance for 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-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 breakthrough designation by the FDA (U.S. Food and Drug Administration) for olaparib for metastatic castration resistant prostate cancer, having a DNA damage repair alteration appeared to predict response to olaparib.[8] This finding 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.[9] There is also evidence of increased sensitivity to platinum based chemotherapy for metastatic prostate cancer in patients with germline DNA repair mutations, likely related to the mechanism of platinum action through DNA damage.[10] Due to the treatment implications, potential relevance for family members along with inconsistent insurance coverage and access to services, studies are ongoing to explore novel methods of delivering cancer genetic testing and counseling to men with metastatic prostate cancer, including the University of Washington/Fred Hutch Cancer Center web-based GENTleMEN study (www.clinicaltrials.gov, NCT03503097).

Finally, there is also evidence across a number of cancers that patients with 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 mentioned previously, mutations in MMR genes are also associated with prostate cancer and are likely present in approximately 5% of advanced prostate cancers.[11] The emerging data regarding MMR deficiency and checkpoint inhibition sensitivity have led to FDA approval of pembrolizumab, a PD-1 inhibitor, for solid tumors with mismatch repair deficiency as that noted in Lynch syndrome.[12] While data surrounding PD-1 sensitivity in MMR deficient prostate cancer are still limited, 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

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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 #027IC

AUA Advanced and Castration-Resistant Prostate Cancer (CRPC) Guidelines

Michael S. Cookson, MD, MMHC, Course Director; David F. Jarrard, MD, Adam S. Kibel, MD and William Lowrance, MD, Faculty

A better understanding of tumor biology and mechanisms of escape from conventional treatments has resulted in more effective therapies for men with advanced prostate cancer. In fact, the treatment of patients with newly diagnosed metastatic disease and castration resistant prostate cancer (CRPC) continues to evolve, which is important for patients who suffer from the second leading cause of cancer deaths in men.[1] Improved overall survival with a multitude of different therapeutic agents, coupled with the success of earlier use of some already approved agents and now an 8th approved therapy to delay the development of metastases, have resulted in updates of the AUA guidelines for CRPC. For the 7th consecutive year the AUA has presented these guidelines in an instructional course designed to inform clinicians of the latest changes in evidence-based recommendations for the sequencing and treatment of castration resistant disease. In addition, level 1 evidence that is being evaluated for metastatic hormone sensitive prostate cancer was reviewed.

The treatment of men with metastatic CRPC (mCRPC) continues to evolve. Almost 15 years ago once androgen deprivation therapy (ADT) failed, treatments for men with CRPC were only palliative. However, 2 landmark studies published in 2004 by Tannock[2] and Petrylak[3] et al demonstrated that docetaxel improved survival in patients with mCRPC compared to mitoxantrone. Since then the field has developed with an explosion of new therapies. In fact, 5 additional agents (abiraterone, sipuleucel-T, cabazitaxel, enzalutamide and radium-223) that have all shown a survival benefit have been approved by the U.S. FDA (Food and Drug Administration) based on randomized clinical trials.[4-9] These agents have been tested in multiple mCRPC disease states to determine the benefit from each treatment. Now some of these agents and others are being investigated in earlier stages of the disease, including the non-metastatic CRPC (M0 CRPC) setting.

At the AUA 2019 annual meeting we presented highlights of the AUA CRPC guidelines. One reason for the continued updates is the relatively rapid evolution of the field. While new agents are undergoing clinical trials, other agents are moving up in the sequencing. This year we presented data from 3 landmark trials in patients with M0 CRPC. Using androgen targeted therapy we now have data demonstrating a significant delay in metastasis-free survival (MFS) in the M0 CRPC disease state. The first published study was the SPARTAN trial, a randomized trial comparing apalutamide vs placebo in patients with M0 CRPC at high risk for metastasis.[10] The investigators reported a highly significant improvement in MFS with use of apalutamide vs placebo in men at high risk for metastasis as determined by a prostate specific antigen (PSA) doubling time of 10 months or less. These findings resulted in the FDA approval of apalutamide for use in men with M0 CRPC. Using a similar trial design, results from PROSPER also demonstrated similar improvement in MFS in men with M0 CRPC at high risk for metastasis with use of enzalutamide vs placebo.[11] A third study, ARAMIS, also demonstrated significant improvement in MFS in men with M0 CRPC using darolutamide compared to placebo in high risk men with M0 CRPC.[12] Collectively these 3 studies are considered practice changing in that for the first time we now have agents proven to delay the development of metastases in men with a rapidly rising PSA in the setting of normal conventional imaging (M0 CRPC). It is also the first time that an agent has been approved for men with CRPC based on

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this new primary end point. What is not known is the impact of these treatments on ultimate survival and this issue will require additional long-term followup. Finally, the impact of next generation positron emission tomography will continue to better identify patients with small volume metastases and should result in reclassification of patients in this disease state.

Enzalutamide before chemotherapy in men with asymptomatic or mildly symptomatic mCRPC was discussed in the context of the PREVAIL trial, a randomized trial of enzalutamide compared to placebo in men with mCRPC before docetaxel therapy.[9] The study demonstrated significant improvement in the 2 co-primary end points of overall survival (HR 0.706, 95% CI 0.60-0.84, p <0.001) and radiographic progression-free survival (HR 0.186, 95% CI 0.15-0.23) in patients treated with enzalutamide vs placebo. Previously abiraterone + prednisone was approved in the pre-chemotherapy setting (COU-302) as well.[4] In addition, the use of an alpha emitting radionuclide therapy was discussed relative to the FDA approved use of radium-223 dichloride in men with mCRPC who are symptomatic from bone metastases and without visceral metastatic disease.[8] These approvals and others anticipated in the not too distant future highlight the need for continuous periodic updating of the guidelines to inform clinicians regarding the rapidly changing management of this disease.

The CRPC guidelines were developed using 6 index cases intended to represent the most common scenarios encountered in clinical practice. Accordingly, cases of CRPC were categorized based on the presence or absence of metastases, degree and severity of symptoms, overall performance status and prior treatment with docetaxel. Guideline statements for each of the index cases were rated as a standard, a recommendation, an option or an expert opinion based on the grading of the strength and quality of the evidence, as well as panel assessment of the benefits and harms of treatment. The statements were also formatted into an algorithm. A summary of the revised CRPC guideline statements for each index case along with clinical case scenarios were presented for illustration.

Index patient 1 is asymptomatic with an increasing PSA and no radiographic evidence of metastases. Currently apalutamide and enzalutamide are FDA approved for patients with M0 CRPC based on data from the SPARTAN and PROSPER trials, respectively.[10,11] However, based on data from the ARAMIS trial it is highly anticipated that darolutamide will soon be approved for patients with M0 CRPC as well.[12] Accordingly the panel thought that clinicians should offer apalutamide or enzalutamide (or darolutamide pending FDA approval) with continued ADT for patients with M0 CRPC at high risk for metastasis.

Clinicians may also recommend observation with continued ADT to patients with M0 CRPC at high risk for metastasis who do not want or cannot have one of the standard therapies. Low risk patients with M0 CRPC may also be suitable for continued observation. Clinicians may offer treatment with a second-generation androgen synthesis inhibitor (eg abiraterone + prednisone) to select patients with M0 CRPC at high risk for metastasis who do not want or cannot have one of the standard therapies and are unwilling to accept observation. Currently chemotherapy or immunotherapy should not be offered to patients with nonmetastatic CRPC outside of a clinical trial.

Index patient 2 is asymptomatic or has minimal symptoms with metastases and no prior docetaxel treatment. In this setting clinicians should offer abiraterone + prednisone, enzalutamide, docetaxel or sipuleucel-T. Clinicians may offer first-generation antiandrogen therapy, first-generation androgen synthesis inhibitors or observation to index 2 patients who do not want or cannot have standard therapy. Finally, some patients may not wish to pursue any therapy and may wait for the onset of symptoms to pursue treatment.

Index patient 3 is symptomatic, has metastases and a good performance status, and has not previously received docetaxel. Clinicians should offer abiraterone + prednisone, enzalutamide or docetaxel chemotherapy in this setting. Ketoconazole + steroid, mitoxantrone or radionuclide therapy may be offered to patients who do not want or cannot have standard therapy. For patients with symptomatic bone metastases and no visceral metastases, clinicians should offer radium-223. Clinicians should not offer estramustine or sipuleucel-T to index 3 patients.

Index patient 4 is symptomatic with metastases, a poor performance status and no prior docetaxel treatment. Clinicians may offer treatment with abiraterone + prednisone or enzalutamide to these patients and ketoconazole + steroid or radionuclide therapy to those who are unable or unwilling to receive abiraterone + prednisone or enzalutamide. When performance status is directly related to the cancer, clinicians may offer docetaxel or mitoxantrone chemotherapy. Radium-223 may be offered to select patients with symptomatic bone metastases and without known visceral disease, specifically when performance status is directly related to symptoms of bone metastases.

Index patient 5 is symptomatic with metastases, a good performance status and a history of docetaxel use. Clinicians should offer treatment with abiraterone + prednisone, cabazitaxel or enzalutamide. If the patient received abiraterone + prednisone or enzalutamide before docetaxel chemotherapy, he should be offered cabazitaxel. Ketoconazole + steroid may be offered if abiraterone + prednisone, cabazitaxel or enzalutamide is unavailable. Re-treatment with docetaxel may be suggested for patients who were benefitting at the time of docetaxel discontinuation (due to reversible side effects). Patients with symptomatic bone metastases and no visceral metastases should be offered radium-223.

Index patient 6 is symptomatic, with metastases, a poor performance status

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and prior docetaxel treatment. The goal of palliation is to prevent and relieve suffering, and to support the best possible quality of life for the patient and family. Palliative radiotherapy can be an option to control bone pain in some patients and should be offered. Alternatively, in select cases clinicians may offer treatment with abiraterone + prednisone, enzalutamide, ketoconazole + steroid or radionuclide therapy. Clinicians should not offer systemic chemotherapy or immunotherapy to these patients.

The guidelines also address bone health and indicate that all patients with CRPC should be offered preventive treatment (eg supplemental calcium, vitamin D) to reduce the risk of fractures and skeletal related events.[13] Denosumab or zoledronic acid may be selected as preventive treatment for skeletal related events in patients with mCRPC and bony metastases.[14, 15]

The treatment of CRPC is undergoing an evolution with multiple new agents on the horizon, from immune modulators to vaccines to novel antiandrogens. In addition, use of approved agents is being clinically trialed in earlier stages of the disease. The potential benefits beyond delaying the development of metastases in the M0 CRPC disease state, as well as the impact on subsequent therapies and quality of life, are just a few of the anticipated areas to be investigated. In addition, the use of genetic testing for germline and somatic mutations appears to be increasingly more important in men with advanced and CRPC, particularly in areas where there is an actionable therapeutic associated with the mutation. It is highly anticipated that new AUA guidelines will be available within the year, and these guidelines will cover metastatic and castration resistant prostate cancer. The goal of the AUA remains to keep clinicians abreast of this rapidly changing field for hormone sensitive and castration resistant prostate cancer.

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COURSE #037IC

Using Shared Decision Making to Help Patients Decide on Prostate Cancer Screening and Treatment

Danil Makarov, MD, Course Director; Michael Barry, MD and Angela Fagerlin, PhD, Faculty

The goal of this course was to teach the essentials of shared decision making (SDM) to practicing urologists who would then, in turn, help their patients make complex decisions about prostate cancer screening and treatment. The latest research was summarized documenting the benefits and drawbacks of treatment approaches for incident localized prostate cancer as well as prostate specific antigen (PSA) screening. The course also engaged participants in group role play, instructing and allowing them to practice SDM based counseling. At the end of the session, participants understood how to apply SDM to counseling patients in their practice and how to comply with the USPSTF (U.S. Preventive Services Task Force) Grade C recommendation for PSA screening.

Dr. Fagerlin began the session by describing what SDM is, when it is useful and how to improve its use in clinical practice. SDM is a collaborative decision making process between patients and their health care providers relevant to medical decisions when multiple options are considered clinically acceptable. Numerous studies have documented the benefits of SDM counseling for patient engagement. However, a number of barriers prevent it from being used as widely in clinical practice as it should. Patients are often unaware of what SDM is, may have limited literacy or numeracy skills, may lack awareness of their own values or preferences or be unable to communicate them, may base their decisions on extraneous factors or may be unable to communicate effectively with their physician. Physicians may lack the time to devote to SDM, question its value or simply lack the skills necessary to execute SDM when counseling patients.

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SDM is most relevant when there is clinical equipoise about what to do next. These areas are also known as preference sensitive decisions and are characterized by having more than 1 reasonable option (including the option of doing nothing) and having those different options entail varying combinations of potential benefits and risks. In this context, a high quality decision entails the patient having a high level of decision specific knowledge and that the course of action reflects the patient's values for the various outcomes associated with the options. For example, a man diagnosed with early stage prostate cancer who has a strong preference for decreasing the likelihood of erectile dysfunction should be more likely to choose active surveillance over other management strategies. Another example is the patient who does not want to live with the idea of having cancer potentially growing inside him should be more likely to choose radical prostatectomy. Traditionally, physicians have made such decisions on behalf of the patients. However, significant research suggests that physicians are not good at discerning what is considered important to a particular patient. This practice often leads to low quality decisions because patient preferences are not adequately considered and incorporated into the decision making process.

A number of techniques can be used to facilitate communication between patients and physicians, the most important of which are decision aids. Decision aids explain what the problem is in language patients can understand. They provide detailed information about the options, and the risks and benefits. Decision aids can serve as a written or digital record of complex medical information. They can also help patients articulate their values and goals of care and, ultimately, help them better communicate with their providers. Decision aids can be used before the visit, during the visit or even after the visit. They can increase patient knowledge, involvement and accurate reception of risk as well as consistency between patient decisions and their values. Finally, decision aids have also been shown to decrease patients feeling uninformed or unclear about personal values, the proportion of patients who remain undecided and the number of patients who choose to undergo major elective surgery.

Next, Dr. Barry reviewed the literature relevant to a case scenario of an asymptomatic patient coming to see a urologist for an unrelated issue who is considering undergoing PSA screening. Three of 4 major medical societies instruct physicians to have a discussion with patients about the screening decision. The American Cancer Society says to offer prostate cancer screening to men with more than a 10-year life expectancy at ages 50, 45 and 40 years for those at average risk, with risk factors and at very high risk of prostate cancer, respectively. The American College of Physicians recommends discussing the benefits and harms of PSA screening with men 50 to 69 years old. The AUA recommends shared decision making for men 55 to 69 years old who are considering PSA screening. And finally, the USPSTF has determined that PSA screening is a grade C (shared decision making) recommendation for men 55 to 69 years old and a grade D recommendation (against routine PSA) for men age 70 years old or older.

The performance of PSA screening is highly variable in clinical practice, ranging from single digit percentages to almost 60% of Medicare beneficiaries depending on the particular hospital referral region. Such unwanted practice variation can be driven by patients making decisions in the face of avoidable ignorance and physicians not doing a good job of discerning patient preferences. Decision aids, such as those listed on the comprehensive Ottawa Inventory of Patient Decision Aids (https://decisionaid.ohri.ca/azinvent.php), can help rectify this situation.

The proper elements of a patient PSA discussion were reviewed, including information gleaned from the 3 most important trials of PSA screening in the literature, which are the Prostate, Lung, Colon and Ovarian Cancer Screening trial, European Randomized Screening for Prostate Cancer trial and CAP Randomized Clinical trial. The summary recommendation that the likelihood of benefit from PSA screening is small but significant for some men and the likelihood of harm is also significant creates a true preference sensitive decision, depending on how men value these various health states. With that as an introduction, course participants broke into small groups to engage in exercises with hands-on use of decision aids for PSA screening and subsequent debrief including critiquing the pros and cons of the various aids.

Finally, Dr. Makarov presented a case of newly diagnosed, favorable, intermediate risk prostate cancer. Based on AUA localized prostate cancer treatment guidelines, such a patient may consider choosing nearly any therapeutic modality including active surveillance. The same guidelines also suggest that a SDM counseling approach be used to help the patient arrive at the best choice for him.

Data on patient outcomes were reviewed and studies were presented to demonstrate that prostate cancer specific mortality is low irrespective of treatment modality. Patient reported outcomes from these treatment modalities suggest that surgery and radiation therapy (and active surveillance) each has specific side effect profiles that are likely to be valued differently by individual patients. However, treatment decisions have been shown to be based more on recommendations by the urologist than on the patient's personal views. Also, urologists tend to make decision recommendation during counseling visits based on clinical factors and rarely, for example, on patient preferences for and interest in sex. The specialist (urologist vs radiation oncologist) seen by the patient was strongly associated with the treatment modality the patient ultimately received, with specialists overwhelmingly recommending the therapy they delivered. Patient decision aids were again presented as an option to improve patient counseling and increase SDM use.

COURSE #048IC

Novel Agents and Concepts in the Management of Hormone Naïve and Castrate Resistant Prostate Cancer

Judd W. Moul, MD, FACS, Course Director; Lawrence I. Karsh, MD, FACS and Christopher Sweeney, MBBS, Faculty

As the course director, I have been fortunate to host a course on advanced prostate cancer at the annual AUA meeting since 2012 and the changes in these 8 years have been nothing less than breathtaking! In the early years it was all about metastatic (M1) castrate resistant prostate cancer (CRPC) with multiple new therapeutic advances starting in 2010 (sipuleucel-T) followed by abiraterone and enzalutamide, and a focus on bone targeted agents. In 2015 we expanded to cover hormone sensitive (HS) advanced disease due to the new data on docetaxel and abiraterone extending survival in new M1 cases.[1-3] In 2017 we added the topic of non-metastatic (M0) CRPC due to emerging data on the use of apalutamide and enzalutamide for this disease.[4,5] Now in 2019 we doubled down on HS new M1 disease with emerging data that 4 agents (docetaxel, abiraterone, apalutamide and enzalutamide) all improve survival for men with new metastatic prostate cancer.[6-9] Some may have argued that the value of the course for urologists was a stretch back in 2012 because of the mistaken and incorrect belief by some that metastatic CRPC should be managed only by medical oncologists. (We never felt this way.) However, in the last few years the course is even more relevant to practicing urologists as most M0 CRPC and virtually all new M1 HS cases are initially managed by urologists.

Newly Diagnosed Hormone Sensitive M1 Prostate Cancer

Four years ago hormone naïve/hormone sensitive newly diagnosed metastatic prostate cancer became hot news with the release of the CHAARTED trial data in 2015 and the STAMPEDE trial results in 2016 showing a benefit of up-front docetaxel chemotherapy for new M1 disease.[1,2] Primary androgen deprivation therapy (ADT) had been the only treatment for new M1 disease for more than three-quarters of a century. In the last few years CHAARTED and STAMPEDE taught us that adding 6 cycles of docetaxel within 4 months of starting hormone therapy/ADT resulted in a major survival benefit. For high volume disease (4 or more bone metastases and/or visceral metastases), the addition of chemotherapy resulted in a 17-month survival advantage compared to ADT alone. However, the initial publication hazard ratio generally supported a benefit of docetaxel for low volume M1 disease as well. The STAMPEDE trial confirmed the benefit of docetaxel and generally supported the use of chemotherapy for all men with new M1 disease. Median overall survival (OS) was 65 months for men randomized to receive docetaxel vs 43 months for men randomized to standard of care ADT alone. In 2018 Kyriakopoulos et al reported longer followup from CHAARTED, confirming the benefit of docetaxel for high volume disease but not supporting up-front chemotherapy for low volume disease.[9]

In 2017 the LATITUDE trial showed that abiraterone added to ADT for men with new M1 disease resulted in a survival benefit similar to that of docetaxel.[3] In 2019, less than 1 month after the AUA annual meeting, we learned that apalutamide and enzalutamide also significantly extend survival compared to traditional ADT alone.[7,8] Although we did not have final access to these data at our course, we prepared the attendees for the likely possibility of these agents being proven effective. Then at the 2019 meeting of the American Society of Clinical Oncology, less than 1 month later, results of the TITAN (apalutamide) and ENZAMET (enzalutamide) trials were released and published.[7,8]

In TITAN 1,052 men were randomized to traditional ADT alone vs ADT plus apalutamide (240 mg orally daily).[7] Of the participants 10% had received prior docetaxel, 80% had M1 disease at initial diagnosis and 63% had high volume disease. At a median followup of 22.6 months 66% of the men remained on apalutamide and 46% assigned to traditional ADT alone remained on initial therapy. Apalutamide conferred a 52% reduction in risk of death or radiographic progression (HR 0.48) regardless of disease volume or prior docetaxel. At 2 years overall survival was 82% in the apalutamide arm and 74% in the ADT plus placebo group.

The ENZAMET trial documented a similar benefit for enzalutamide for new M1 HS disease.[8] The 1,125 patients with new M1 disease receiving testosterone suppression with or without docetaxel and stratified by high or low volume disease were randomized to receive enzalutamide versus standard oral antiandrogen. Overall survival at 3 years was significantly improved with enzalutamide for high and low volume disease as well as for men not receiving early docetaxel but not for those who received early docetaxel.

In our opinion, these are the first trials to truly prove the benefit of combined or maximal androgen blockade as first proposed by Labrie et al in the mid 1980s. Finally, the third generation nonsteroidal antiandrogens (apalutamide and enzalutamide) prove beyond a reasonable doubt this long postulated concept.

However, it is unclear if patients should receive docetaxel plus an oral agent or only a new therapy plus traditional ADT. The ENZAMET trial did not confirm a survival benefit (at 3 years) to adding enzalutamide for

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men who received early docetaxel. Furthermore, no head-to-head comparisons allow us to determine which oral agent among the three is better. However, the key message for urologists is that traditional ADT alone for newly diagnosed M1 HS prostate cancer is not the current standard of care for the majority of men.

Hormone Sensitive Biochemically Recurrent M0 Prostate Cancer

In the area of hormone naïve advanced prostate cancer we also briefly covered the use of ADT for biochemically recurrent/prostate specific antigen (PSA) prostate cancer.[10] While the timing (early vs later), method (intermittent vs continuous) and agent (luteinizing hormone-releasing hormone [LHRH] agonist, antagonist etc) remain debated, we also addressed a number of interesting ongoing clinical trials that may shed some light. In particular, the EMBARK trial is now closed to enrollment for patients with high risk PSA recurrent disease. These men were randomized to receive LHRH alone, enzalutamide alone or LHRH plus enzalutamide. We anticipate that the eventual results will help put to rest some of the controversies. In particular, is there a role for enzalutamide alone in earlier advanced prostate cancer and is this modern era combined androgen blockade (ie enzalutamide or apalutamide plus LHRH) more effective than monotherapy?

Castration Resistant Prostate Cancer

Since 2010, 6 new agents have been approved by the FDA (U.S. Food and Drug Administration) for M1 CRPC, including sipuleucel-T, cabazitaxel, abiraterone acetate, denosumab, enzalutamide and radium-223.[11,12] Except for cabazitaxel, all of these agents are commonly available to urologists and oncologists to prescribe. Some of the new concepts related to the agents that urologists may use for CRPC are discussed.

Denosumab. Denosumab is prescribed at a dose of 120 mg (tradename XGEVA®) subcutaneously monthly to prevent skeletal related events in men with M1 CRPC and bone metastases. The FDA also approved a 60 mg dose (tradename Prolia®) subcutaneously twice a year to prevent bone loss (osteopenia and osteoporosis) in men without bone metastases who are on gonadotropin-releasing hormone analogue therapy for prostate cancer. Urologists are reminded to use supportive agents including vitamin D and calcium supplements, and monitor for osteopenia and osteoporosis with annual dual energy x-ray absorptiometry scanning.[13]

Sipuleucel-T. Sipuleucel-T is a novel immunotherapy approved by the FDA in 2010 for asymptomatic or minimally symptomatic M1 CRPC.[14-16] The ideal patient for sipuleucel-T should have documented clinical metastases and a rising PSA while on continuous hormonal therapy, and not have bone or cancer pain requiring narcotic pain medications. In men with PSA levels in the lowest quartile of the IMPACT trial (PSA less than 22 ng/ml) there was a more robust overall survival advantage to sipuleucel-T.[16] Specifically, the estimated 3-year survival in this group of treated patients was 62.6% compared to 41.6% of men randomized to the control arm of the study. This agent should be used early in the course of M1 CRPC. Since sipuleucel-T was studied and approved before the other novel agents, it is unclear if the survival benefit would be seen in men pretreated with novel oral agents abiraterone, enzalutamide and apalutamide, particularly with regard to the role of sipuleucel therapy after these oral agents were used for M0 CRPC.

Abiraterone. Abiraterone is a 17-lyase and 17-hydrolase inhibitor that blocks key pathways in the steroidal synthesis pathways leading to androgen production. Low dose prednisone (5 to 10 mg daily is a physiological dose) administered with abiraterone is recommended to help limit overproduction of aldosterone and the side effects of hypertension, hypokalemia and fluid retention. The FDA approved the indication for abiraterone as before or after docetaxel chemotherapy in men with M1 CRPC based on evidence from the Cougar-AA-301 and 302 clinical trials. The dose for abiraterone is 1,000 mg orally once daily in the fasted state along with low dose steroid (5 mg prednisone orally twice daily). The final analyses of both trials were reviewed, showing clinically meaningful end points of overall survival and radiographic progression-free survival (Cougar 302) benefits. Abiraterone is also available in a 500 mg oral dose which allows for 2 rather than 4 pills a day and may help with compliance for some patients.[17]

Abiraterone was FDA approved for use in men with newly diagnosed hormone sensitive M1 prostate cancer in February 2018. Approval was based on LATITUDE (NCT01715285), a placebo controlled international clinical trial that randomized 1,199 patients with metastatic high risk disease.[6] Patients received 1,000 mg abiraterone acetate orally once daily with 5 mg prednisone once daily (597) or matching placebos orally once daily (602). Patients in both arms received a gonadotrophin-releasing hormone analogue or underwent bilateral orchiectomy. The major efficacy end point was overall survival. Median OS was not estimable and was 34.7 months in the abiraterone acetate and placebos arms (HR 0.621; 95% CI 0.509, 0.756; $p < 0.0001$). Median duration of abiraterone use was 24 months.

Enzalutamide. Enzalutamide, a next generation androgen receptor antagonist, was FDA approved in 2012 to treat men with disease that progressed after docetaxel based chemotherapy based on level 1 evidence from the AFFIRM trial. It received expanded approval in 2014 for use before chemotherapy in the PREVAIL trial. Enzalutamide is taken orally at a dose of 160 mg daily with or without food and unlike abiraterone, it does not require prednisone. However, enzalutamide does have an approximate 1% risk of seizures associated with its

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use and crosses the blood-brain barrier, implicating it with some risk of falls and fatigue.[18]

PROSPER is a phase 3, randomized, double-blind, placebo controlled study of enzalutamide in men with M0 CRPC.[5] The results demonstrated an approximate 2-year metastasis-free survival (MFS) benefit over placebo, indicating MFS as a meaningful end point. As of July 13, 2018 enzalutamide was the second FDA approved drug for M0 CRPC. As noted previously, enzalutamide has now been shown to extend survival for men with newly diagnosed HS M1 prostate cancer and is pending FDA approval in this setting as of July 2019.[8]

Apalutamide. Apalutamide, with a mechanism of action similar to enzalutamide, was the first drug for M0 CRPC approved by the FDA. The data from the SPARTAN trial were presented at ASCO GU 2018 back-to-back with the similarly designed PROSPER trial showing that apalutamide delayed MFS by about 2 years.[4] Overall the drug was well tolerated. Unique side effects included maculopapular rash in 24% of patients which was grade 3 to 4 in only 5%. The rash usually resolved with topical lotions, drug holiday and temporary dose reduction. Approximately 4% of patients required systemic corticosteroids. In addition, 8% of patients had decreases in thyroid hormone (considered chemical hypothyroidism) and there were no grade 3 to 4 adverse events. The FDA did not mandate thyroid testing on the approval label. Seizure was reported in 2 cases (0.2%). Apalutamide was also proven to extend survival in patients with newly diagnosed HS M1 prostate cancer but as of July 2019 is awaiting FDA approval.[7]

Comparing and sequencing oral agent options. While all 3 novel oral hormonal agents, abiraterone, enzalutamide and apalutamide, are active in advanced prostate cancer, their benefit is not necessarily synergistic or cumulative. In other words, patients will likely have an initial robust response to any of the 3 agents. However, switching men to one of the other agents will likely not result in a sustained response and the response to the second/third agent may be more short-lived. Furthermore, now that apalutamide and enzalutamide are FDA approved for M0 CRPC, how will urologists decide between them? Finally, while delaying metastases and the transition from M0 to M1 CRPC for an average of 2 years with apalutamide or enzalutamide is important, is use before documented metastases truly helping our patients to live longer and better? PROSPER (enzalutamide) and SPARTAN (apalutamide) showed trends toward an overall survival benefit when used for M0 CRPC. However, the OS data are not yet mature or proven for either drug. Some clinicians may still choose to hold novel therapy until M1 disease develops or use abiraterone (as it is now generic and less expensive), despite the fact that it is not FDA approved for M0 CRPC.

Another topic of interest related to use of abiraterone and enzalutamide/apalutamide is molecular profiling. The discovery of the AR-V7 splice variant of the androgen receptor offers an intriguing glimpse of the future of personalized medicine.[19] Specifically, the response to abiraterone or enzalutamide was less robust in men who harbored this variant in circulating tumor cells. In February 2018 Genomic Health, Inc., Redwood City, California, received FDA approval for Oncotype DX® AR-V7 Nucleus Detect™ test, a commercially available assay for AR-V7.

Radium-223. Radium-223 is a parenteral radiopharmaceutical that can be ordered by urologists and is usually given in a nuclear medicine or radiation oncology department setting, although many large group practices have incorporated it into their centers. It is an alpha-emitting liquid radiation product that received FDA approval in May 2013 based on results from the ALSYMPCA trial.[20] Radium-223 is indicated for the treatment of symptomatic M1 CRPC with bone metastases and no known visceral metastatic disease. The dose regimen is 50 kBq (1.35 microcurie) per kg body weight given at 4-week intervals in 6 injections.[21]

Urologists may be familiar with earlier generation beta radiopharmaceuticals such as samarium and strontium. However, radium-223 is different. It is a large molecule alpha particle and does not penetrate the bone marrow to the degree of older agents. In other words, radium-223 is much less likely to cause serious bone marrow toxicity. In addition, the use of radium-223 was associated with an overall survival benefit whereas the older beta-emitting radiopharmaceuticals were never proven to extend survival. For radium-223 to be associated with improved survival at least 4 monthly cycles must be administered.

Radium-223 should not be used in patients currently being treated with abiraterone/prednisone. The phase III ERA223 trial compared abiraterone/prednisone plus radium-223 vs abiraterone/prednisone plus placebo in patients with asymptomatic or mildly symptomatic chemotherapy naïve metastatic CRPC. The study was unblinded in late 2017. Bayer, the manufacturer of radium-223, reported that the unblinding followed the recommendation of an independent data monitoring committee that observed an imbalance with more fractures in and deaths of patients receiving radium-223 and abiraterone/prednisone vs abiraterone alone. The big question is what about prior treatment with abiraterone and subsequent use of radium-223? Opinions vary among experts in the field.[21]

Darolutamide. On July 31, 2019 darolutamide was FDA approved for M0 CRPC making this the 3rd approved agent (apalutamide, enzalutamide and daralutamide) for this disease state. This 3rd generation nonsteroidal oral antiandrogen prolonged metastases-free survival also by approximately 2 years

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compared to placebo in patients with M0 CRPC. The drug has twice daily oral dosing which may be a slight disadvantage compared to enzalutamide and apalutamide. However, darolutamide does not appear to cross the blood brain barrier to the extent of the other 2 agents, is reportedly less apt to cause falls and seizures, and might even result in less fatigue and fractures, although this remains to be proven.

Summary

The management of advanced prostate cancer continues to evolve in exciting and sometimes unexpected ways. This year has brought further options to our patients, including abiraterone, enzalutamide and apalutamide for newly diagnosed, hormone sensitive M1 prostate cancer as well as apalutamide, enzalutamide and darolutamide for M0 CRPC.

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COURSE #065IC

Prostate Cancer Update

William J. Catalona, MD, Course Director; Douglas M. Dahl, MD, FACS, Stanley L. Liauw, MD, Stacy Loeb, MD, MSc, Robert B. Nadler, MD and Russell Szmulewitz, MD, Faculty

This course highlights the important findings on prostate cancer (PCa) published during the last year.

Epidemiology, Etiology and Genetics

In the interval from 2012 to 2016, in the aftermath of the USPSTF (U.S. Preventive Services Task Force) 2012 Grade D recommendation against prostate cancer screening, PCa incidence rates in the U.S. plummeted to the pre-prostate specific antigen (PSA) era levels. Although there remains a 53% decrease in the PCa mortality rate during the PSA screening era, for the first time in 2 decades there was also a slight uptick in the U.S. PCa mortality rate curve, and PCa again displaced colorectal cancer as the second-leading cause of death from cancer (after lung cancer) in U.S. men. In 2018 the USPSTF upgraded its recommendation to Grade C (ie informed discussion of risks and harms of screening for men 55 to 69 years old) but it still recommends against screening in men 70 years old or older. For the last several decades the 5-year survival rate for men diagnosed with distant metastases has remained approximately 30%. For a man whose brother has nonlow risk PCa, his risk of being diagnosed with a similar PCa is 3.8-fold higher in identical twins and 20% higher in nonidentical full siblings. Men with inflammatory bowel disease are at higher risk for PCa. A meta-analysis found that omega-3 fatty acids are not associated with cardiovascular events. However, there is conflicting evidence on their relationship with prostate cancer risk and aggressiveness. A study reported that finasteride use was not associated with higher PCa mortality. However, another study suggested that the failure to adjust for finasteride induced reductions in PSA levels led to delayed diagnosis, more advanced disease and worse outcomes.

Screening and Biopsy

The Prostate Health Index (PHI) helps to identify individuals at higher risk for PCa among Asian and European men. However, lower reference ranges

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should be used for Asian men. A mathematical model suggested using SelectMDx® before a biopsy is cost-effective. Men with a PSA density less than 0.08 ng/ml/cm^3 are unlikely to harbor Gleason Grade Group 2 or greater PCa. Black men with Gleason Grade Group 1 disease were more likely to have intermediate or high genomic risk scores that are associated with an increased risk of metastasis. Using multiple genetic variants together with PSA levels better predicts the risk of PCa.

Predictive Markers and Imaging

Multiparametric magnetic resonance imaging (MRI) findings are associated with biological features of aggressive PCa, including genomic mutation density, a higher prevalence of intraductal/cribriform architecture and altered abundance of genetic transcripts. In men who have not previously undergone biopsy MRI targeted biopsies are superior to transrectal ultrasound guided biopsies, and targeted biopsies detect more clinically significant PCa. MRI enables some patients to avoid biopsy. ^{68}Ga-prostate specific membrane antigen (PSMA) positron emission tomography (PET)/computerized tomography is superior to a bone scan but has poor sensitivity if used to defer pelvic lymphadenectomy. ^{11}C acetate PET has moderate accuracy to detect lymph node recurrences.

Active Surveillance

Active surveillance (AS) continues to gain increasing acceptance (approximately 50%) in the U.S. for favorable risk PCa. However, substantial variation in rates is observed among practices and providers. In the Veterans Affairs system AS uptake was nearly 80%. Anxiety levels decrease with time during AS. Approximately 10% of patients on AS are lost to followup within 2 years. Surveillance biopsies are necessary for AS. A negative confirmatory fusion biopsy confers a favorable prognosis for lack of progression on AS. Higher genetic risk scores or a PI-RADS (Prostate Imaging Reporting and Data System) score 4-5 on MRI are associated with increased risk of biopsy upgrading, but they are not yet a substitute for surveillance biopsies. Among patients who convert from AS to delayed treatment, a large proportion has unfavorable pathology findings. AS is more likely to fail in men with intermediate risk disease. Therefore, caution is recommended using AS in this population.

Focal Therapy

Focal therapy with partial gland high intensity focused ultrasound or photodynamic therapy using intravenous photosensitizer, then transperineal light fibers to activate, is being studied in patients with low and intermediate risk disease. Although generally well tolerated, these modalities remain experimental according to guidelines.

Prostatectomy

The long-term results of a Swedish trial of radical prostatectomy (RP) vs watchful waiting for men with clinically detected PCa revealed markedly fewer metastatic cases and PCa deaths, and longer overall survival with RP. A 2-surgeon trial comparing robotic and open RP reported similar functional outcomes and possibly better oncologic outcomes with robotic RP. Salvage RP has a significant risk of complications but may benefit selected patients.

Radiation Therapy

For newly diagnosed PCa hypofractionated radiation therapy (RT) (2.4 to 3.4 Gy per fraction) is now considered a standard of care option that should be offered, according to an ASTRO/ASCO/AUA guideline, given that multiple randomized studies (still early data) show no difference with disease control or late toxicity. Less supportive data exist for stereotactic body RT (SBRT, up to 36.25 Gy in 5 fractions) that may be offered for low or intermediate risk disease. In separate randomized trials 18 months of androgen deprivation therapy (ADT) with primary RT was superior to 6 months in reducing PCa mortality. Concurrent weekly 20 mg/m^2 docetaxel with RT and ADT did not improve biochemical control. However, 6 cycles of 75 mg/m^2 adjuvant docetaxel improved survival in patients with high risk disease. Hypofractionated RT to the prostate improved survival in men with low volume metastatic disease with minimal severe toxicity.

There were several AUA/ASTRO guideline amendments on postoperative RT. 1) Adjuvant RT for margin positive pT3 disease decreases PSA and clinical progression rates but has a less clear impact on metastasis and survival. 2) ADT should be offered with salvage RT if PSA is 0.2 ng/ml or greater. Salvage low dose rate brachytherapy after external beam RT is associated with reasonably low toxicity. Using ^{68}Ga-PSMA PET scans after the failure of primary therapy and delivering RT without additional ADT to up to 5 oligometastatic sites yielded a PSA response in 97% of patients and about half remained free from biochemical failure for 18 months. ^{177}Lu-PSMA-617 has promising antitumor activity and low toxicity for castration resistant PCa (CRPC).

Advanced Disease

Oligometastatic disease is defined as 3 or fewer to 5 metastases in 1 or fewer to 2 sites. Some studies exclude lymph node or intracranial metastases. There are 21 ongoing prospective studies, with reported results including 1) with SBRT to metastases–31% distant progression-free and 95% overall survival at 3 years followup; 2) with RP–delayed progression by 1 year, a 21% postoperative complication rate and 89% overall survival at 2 years; 3) with prostate RT–improved failure-free and overall survival at 3 years; 4) for patients with limited sites of recurrence after primary treatment, recurrence surgery plus SBRT–delay in the need for ADT if the PSA doubling time is less than 3 months.

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ADT prolongs the QTc interval to a small degree. Longer increases may increase the risk of tachyarrhythmias and sudden death. There is conflicting evidence on whether ADT increases the risk of Alzheimer's disease. Diabetic patients on ADT seem to benefit from metformin. Among veterans on ADT overall survival was better in men exposed to the "Agent Orange" herbicide compared to those who were not exposed. Four vs 10 months of degarelix for intermittent ADT revealed no difference in time to the need for the next induction and yielded a better quality of life. The FDA (U.S. Food and Drug Administration) approved apalutamide and enzalutamide for nonmetastatic CRPC (nmCRPC). Darolutamide is a nonsteroidal androgen receptor antagonist with fewer risks for seizures that is also a new option for nmCRPC. Abiraterone is active in nmCRPC, reasonably well tolerated, and could be considered if enzalutamide, apalutamide or darolutamide are not available or affordable. However, there is no level 1 evidence for abiraterone in this population. Abiraterone has limited efficacy in patients with progression on enzalutamide and there is no benefit to combining the 2 agents. In addition, abiraterone should not be combined with ^{223}radium because of an increased risk of pathological fractures. A validated assay for the AR-V7 androgen receptor status can predict the benefit of taxane vs ADT.

Inactivation of the CDK12 gene delineates a distinct immunogenic class of advanced PCa. CDK12 regulates genes involved in DNA damage repair that give rise to features favoring responsiveness to immunotherapy. PCa with DNA mismatch repair gene mutations are aggressive but very sensitive to ADT and also demonstrate anecdotal sensitivity to PD-1 inhibitors. Pembrolizumab is one such inhibitor that is FDA approved for microsatellite instablity high or mismatch repair deficient cancer, regardless of the primary tumor type, and some patients with PCa have demonstrated responses. The PARP inhibitor olaparib, combined with abiraterone in patients with metastatic CRPC, also yielded some encouraging results. ^{177}Lu-PSMA-617 radionuclide therapy yields a high response rate in PSMA+ refractory CRPC, with phase III trials underway. In the current era of modern androgen receptor targeted therapy, neuroendocrine or small cell differentiated tumor clones emerge, forming a distinct subset of refractory metastatic CRPC with poorer survival, unique genomic/transcriptional findings and no obvious therapeutic target at present.

Conclusions

Advances are being made in the understanding of PCa and PCa care. Hopefully, new guidelines incorporating shared decision making about PSA based screening and improved uptake and implementation of AS for favorable risk disease will enhance benefits and decrease harms going forward. New biomarkers and imaging techniques offer promise for new and better treatment selection and for the development of new targeted systemic therapies.

UROLOGIC CARE FOR THE ADVANCED PRACTICE PROVIDER

Building a Prostate Cancer Survivorship Program

Ashley Brown, PA-C

I spend a significant part of my clinical practice taking care of veterans who are prostate cancer survivors. While my attending and resident physician colleagues focus on prostate cancer diagnosis and treatment, I have the opportunity to focus on quality of life concerns, including incontinence, erectile dysfunction, anxiety and depression. My patients are often surprised to learn about the quality of life therapies and resources available to them. I was struck by the common refrain, "No one's ever told me that."

Recognizing this opportunity for improving the prostate cancer survivorship experience in my clinical practice was the genesis of our Prostate Cancer Survivorship Program. Our program builds on survivorship paradigms that are well-established in oncology, while leveraging the unique assets of the Veterans Administration (VA) health system and my role in our VA practice. Specifically, as a clinic provider and robotic first assistant, I am present throughout our veterans' entire prostate cancer experience. The result is a level of continuity and patient familiarity which are unique in an academic VA clinical setting.

The program's vision is to maximize the quality of life for patients following radical prostatectomy. Our mission is to integrate the delivery of comprehensive post-prostatectomy services, including surveillance for cancer recurrence, monitoring quality of life indicators, coordination of additional care needs, and educating patients and their family members. Services provided include a personalized survivorship care plan that outlines prostate specific antigen (PSA), treatments, pathology and plan of care; continued assessment for cancer recurrence; evaluation and treatment of complications; and quality of life complaints, referrals to other health professionals and communication with the primary care physician and treatment team.

In terms of quality of life measures, we focus on incontinence, erectile dysfunction and depression. I performed a literature search to create an inventory

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of measures that were concise, actionable for clinicians and meaningful to patients. It was critical that patients view these indices as helpful tools to capture and monitor their quality of life, and not as cumbersome and tedious paperwork. Towards that end, we chose the Prostate Cancer Survivorship Plan, the Expanded Prostate Cancer Index Composite for Clinical Practice (EPIC-CP) and the Patient Health Questionnaire (PHQ-9).

The survivorship protocol outlines our program and our commitment to our patients. After initial diagnosis, if a patient decides to pursue prostatectomy as treatment, I meet with him to discuss the overall survivorship program. Patients are given printed literature and a list of trusted web-based resources. Details of the prostatectomy and expected outcomes, including quality of life measures, are discussed. At this time, baseline depression, erectile dysfunction and incontinence are assessed. On the day of surgery I will once again check-in with the patient before he leaves for the operating room.

Postoperatively I meet with the patient at the 6-week followup visit. In addition to the standard postoperative PSA check, he is given a completed Survivorship Care Plan which includes information such as Gleason score, pathology and treatment plan. The patient is then assessed at the 3, 6, 12, 18 and 24-month postoperative clinic visits. At each visit he completes the EPIC-CP and PHQ-9. Based on the score of these assessments, needs are addressed including erectile dysfunction treatments and incontinence supplies. A PSA is also drawn at each of these visits.

In addition, we deploy a Behavioral Health Protocol to provide a plan for behavioral health intervention should the screening assessments indicate a moderate (or greater) level of depression. That is, if a patient scores a 10 or above on the PHQ-9 he is identified as moderately depressed. With the patient's consent a referral is then made for him to see a behavioral health counselor. It is important to note that the PHQ-9 is not a diagnostic instrument, but rather serves as a signal to consider intervention. If a patient exhibits signs of suicidal ideation, there is a detailed plan in place for alerting emergency personnel and, if necessary, escorting the patient to the emergency department.

By building the Prostate Cancer Survivorship Program, patients are given comprehensive, consistent and high-quality care. My hope is that as a result of this work, I will never hear our veterans say, "no one's ever told me that."

Patients Receiving Androgen Deprivation Treatment for Prostate Cancer: Managing Side Effects

Anne E. Lizardi-Calvaresi, DNP, CRNP, RNFA, Edouard J. Trabulsi, MD, FACS, Mark Hurwitz, MD and Hong Truong, MD

Prostate cancer is the most commonly diagnosed solid tumor among American men. A standard of care in the treatment of some intermediate and high risk prostate cancer is the use of androgen deprivation treatment (ADT). Nearly all men with advanced stages of prostate cancer will receive some form of ADT,[1] and those who do experience a range of adverse symptoms due to medically induced castration.[2]

Men on ADT typically experience life altering effects including hot flashes, weight gain, fatigue, erectile dysfunction, and decreased muscle strength and stamina, bone density and cardiovascular function.[3] Anecdotally, patients are not typically given instruction on how to minimize the symptoms. In a study conducted at the University of Michigan, Moyad et al suggested that men receiving ADT would experience less severe side effects (body mass index) with a diet rich in fruits and vegetables high in vitamins, including vitamin B6, and an exercise plan during treatment.[4] There is also anecdotal evidence in this patient population which indicates an improvement in hot flashes when taking 200 mg vitamin B6 (M. Hurwitz, personal communication, March 23, 2017).

Women experiencing menopausal symptoms often suffer similar effects as men on ADT. Data showed that supplementation with vitamin B helps to reduce the vasomotor flushes (hot flashes) that occur in close to 70% of perimenopausal women.[5] The Institute for Quality and Efficiency in Healthcare reported that patients taking vitamin B supplementation experienced clinically significant improvement in hot flashes when the supplement was taken daily.[6]

Search of the relevant literature concerns the effects of diet and exercise plans on hot flashes and side effects of ADT for prostate cancer. Few studies have been dedicated specifically to the use of vitamin B and the treatment of side effects of ADT. In this study we assess the effects of vitamin B6 supplementation and its ability to decrease the severity of hot flashes of ADT in men undergoing treatment for prostate cancer.

Methods

This retrospective chart review from the radiation oncology and urology departments, which was approved by the Sidney Kimmel Cancer Center Protocol Review Committee and the Thomas Jefferson University Institutional Review Board, was performed to evaluate the effects of vitamin B6 on hot flash side effects of ADT in patients with prostate cancer. Patient charts were queried for ICD 10 code C61 (prostate cancer) and 96402 procedure code for hormonal

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injection. A total of 524 charts were identified and reviewed for inclusion/exclusion criteria. Visits occurred between November 2016 and June 2018.

Inclusion criteria were subjects who received ADT for prostate cancer, reported bothersome hot flashes of 1 or greater on the 10-point hot flash scale and were not receiving treatment for hot flashes. Exclusion criteria were subjects who were not receiving androgen deprivation for prostate cancer, were without bothersome hot flashes and who received other treatment for hot flashes.

Data collection and documentation. Data collection included patient reported hot flash scores (numerical and categorical) before and after vitamin B6 consumption. Numerical and subjective verbal response was documented in patient progress notes according to a standard validated tool in the form of subjective based questionnaires evaluating the severity of hot flashes. Patient reported categorical data (mild, moderate and severe) documented in charts were extracted for those patients who did not have numerical reports documented. The numerical values for mild, moderate and severe were 1 to 3, 4 to 6 and 7 to 10, respectively. The written version of the numerical scale is the 10-point scale which asks the patient, on a scale of 0 to 10, how severe their hot flashes have been in the last 4 weeks.

Analysis. For the primary objective, the null hypothesis was tested that the mean response to the 10-point hot flash scale did not change after 12 weeks of vitamin B6. The pretreatment and posttreatment scores for those on vitamin B6 were compared using a 2-sided Wilcoxon signed-rank test with alpha=0.05. The intended sample size (80 cases) provided 86% to 91% power to detect the change in response on the 10-point hot flash scale from pretreatment median 5 to posttreatment median 3, using a 2-sided Wilcoxon Signed-Rank test with alpha=0.05.

Results

A total of 71 cases were included in this analysis. The age of the patient population was a median of 70 years. Of the 28 patients who received vitamin B6, symptoms of baseline hot flashes were reported as mild (1 to 3) by 13 (18.31%) and as severe (7 to 10) by 25 (35.21%), with some improvement noted by 57.1% vs 16.3% of those not taking vitamin B6.

The pretreatment median hot flash score was 2 in both groups with an IQR of 1 to 3 in the control group and an IQR of 2 to 3 in the vitamin group. Posttreatment median hot flash score was 2 and IQR was 1 to 3 in both groups. In patients who did not receive vitamin B6 the IQR of symptoms score remained consistent but was lower in the vitamin group. Overall, the vitamin group experienced significant improvement in hot flashes, as symptom categories changed from moderate to mild in 32.1% of patients and from severe to moderate in 21.4% (OR 6.86, 95% CI 2.28-20.65, p=0.001). No change in symptom category occurred in 83.7% of those in the control group (see table).

Table.

Category (numerical) Score	% Before Treatment	% After-Treatment
Vitamin group:		
Mild (1-3)	3.6	39.3
Moderate (4-6)	50	35.7
Severe (7-10)	46.4	25
Control group:		
Mild (1-3)	28	35
Moderate (4-6)	46.5	48.8
Severe (7-10)	25.5	16.2

Strengths and Limitations

The initial goal of this study based on a power analysis was to identify 80 men on ADT for prostate cancer to include 40 in the control group and 40 in the vitamin group. We were not able to identify 40 patients who had taken vitamin B6 within the specified visit interval, which resulted in a smaller sample size of 28 patients. Additionally, some patients reported categorical responses rather than numerical responses and, therefore, all patients reporting symptoms of 1 or greater on the numerical scale were included.

Because this was a retrospective analysis, proper supplementation with vitamin B6 at 200 mg daily could not be verified. Other limitations included inconsistent reporting of numerical/categorical data on hot flashes as well as random placement of the information in patient charts, which may have led to underreporting or smaller than actual sample size.

Implications

From the available literature on vitamin supplementation for men with hot flashes on ADT for prostate cancer, our study represents a novel evaluation of the need for further and larger studies to evaluate the true effect of vitamin B6 prospectively. This study introduces promising evidence for providers of patients with prostate cancer. Limited options are currently available to treat the side effects of hot flashes in men on ADT for prostate cancer. Typically, providers have prescribed progestin supplementation, antidepressants and acupuncture for hot flashes. However, vitamin B6 is a nonprescriptive alternative which is free of side effects in doses as low as recommended in our study.

Conclusions

As mentioned, our study was limited due to a smaller than expected sample size. However, supplementation with vitamin B6 produced statistically significant improvement in men who reported bothersome hot flashes. Providers who treat patients with prostate cancer are now equipped to recommend a nonprescription treatment alternative which should be added to the followup armamentarium. Additional larger and prospective studies on vitamin and supplemental therapy are warranted.

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PANEL DISCUSSION

BIOMARKERS IN PROSTATE CANCER

Ganesh Raj, MD, PhD, Moderator; Leonard G. Gomella, MD, FACS, Eliezer Van Allen, MD and Thomas Polascik, MD, FACS, Panelists

Precision medicine through the identification of specific patient characteristics is having a major impact in all areas of medicine. For precision management of prostate cancer, increasing numbers of biomarkers and the identification of genetic alterations are being used clinically to direct care. In the area of cancer detection the goal of precision medicine is to identify high risk men in need of definitive biopsy and reduce unnecessary biopsies. Once a diagnosis is established these precision medicine approaches relying on biomarkers allow further risk stratification to discriminate clinically significant from insignificant disease. Predicting outcomes and assisting in decision making from early through late stages of prostate cancer are also goals of this precision medicine approach. Capitalizing on unique biomarkers and genetic alterations in metastatic castrate resistant prostate cancer has allowed the investigation of entirely new classes of drugs. Understanding the inherited genetic risk for prostate and other familiar cancers is also a rapidly evolving area.

This panel discussion of illustrative case presentations focused on the current application of biomarkers in prostate cancer care. The session provided a practical overview of how biomarkers and genetics are being used for prostate cancer in the 3 main areas of diagnosis, genetic testing for inherited risk and treatment of advanced disease.

Dr. Polascik provided information on how biomarkers can be used in the early detection of prostate cancer and improve decision making for disease detection and treatment choices. He also noted that other modalities such as magnetic resonance imaging (MRI) serve as precision markers in early prostate cancer detection. Multiparametric MRI is increasingly used for the early detection of prostate cancer but variables, such as the characteristics of the specific MRI machine, sequencing protocol used, and skill and experience of the radiologist and urologist, must be considered.

Blood testing for prostate specific antigen (PSA), our most studied prostate cancer biomarker, and a variety of PSA related tests (free and total PSA, phi index, 4K score) are used clinically in the decision making process whether or not to perform prostate biopsy. Another area of ongoing clinical use includes prostate cancer biomarkers that can be detected in the urine (eg Progensa® PCA3, MiPS assay, ExoDx™, Select MDx®). Other serum circulating factors such as cell-free DNA and exosome encapsulated nucleic acids are in the earliest stages of biomarker discovery in prostate cancer and have the potential to further enhance precision medicine in prostate cancer. Dr. Polasick concluded his presentation on how these various biomarkers are incorporated in his clinic using a Duke Cancer Institute algorithm that integrates biomarkers with multiparametric MRI.

The use of germline genetic testing for inherited mutations is beginning to impact the spectrum of prostate cancer care from diagnosis through treatment. Many studies have identified prostate cancer related inherited mutations. While these mutations do not cause prostate cancer, their presence can significantly increase the risk of aggressive disease. Genetic testing for inherited prostate cancer risk was presented by Dr. Gomella.

Critical mutations in multiple genes, including BRCA1, BRCA2, HOXB13, ATM and DNA mismatch repair genes, have all been reported in prostate cancer. While these are just a few of the many altered genes that have been identified, those most significant for increased risk of aggressive prostate cancer involve mutations in BRCA1 and BRCA2, similar to those alterations seen in breast and ovarian cancers. Mutations in the BRCA2 gene in particular have been associated with poor prostate cancer outcomes. Many of these mutated genes, if inherited, also increase risk in the patient and other blood relatives of cancer of the breast (male and female), ovaries and pancreas, Lynch syndrome and other related gastrointestinal tumors.

Current prostate cancer genetic testing guidelines from the National Comprehensive Cancer Network® (NCCN®) were reviewed. Genetic testing and counseling are recommended for 1) metastatic prostate cancer regardless of family history; 2) high risk disease regardless of family history; 3) low to unfavorable intermediate risk disease and brother, father or multiple male

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Panel Discussion

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relatives diagnosed with prostate cancer before age 60 years, family history of one or more blood relatives with ovarian, pancreatic, metastatic prostate or breast cancer before age 50 years, family history of 2 or more blood relatives with cancers suggestive of hereditary breast and ovarian cancer, or Lynch syndrome; 4) Ashkenazi Jewish ancestry and Gleason score 7 or greater; and 5) if BRCA mutations are identified in somatic tumor profiling. Beyond the individual patient with prostate cancer, urologists should be mindful of the maternal, paternal and sibling family cancer history beyond prostate cancer. This family history review may identify other cancers that may be associated with familial cancer risk syndromes.

Of importance is the need to discuss the Genetic Information Nondiscrimination Act (GINA) of 2008 in the pretest counseling session regarding its implications for men with prostate cancer and their families. GINA generally provides protections for mutation carriers in health insurance and employment discrimination, except in small businesses with fewer than 15 employees. Importantly, GINA does not protect against genetic discrimination in life insurance, long-term care, disability and other government clinical care settings. These GINA issues may not be relevant for men with metastatic castrate resistant prostate cancer. However, many younger men or those with earlier stage disease may enter long periods of survivorship. These issues need to be discussed with patients to understand the potential impact of the genetic testing results.

From a translational bench to bedside research approach, some of the most significant advances in our understanding the behavior of castrate resistant prostate cancer has come from the study of the molecular and genomic alterations in this disease state. The area of castrate resistant prostate cancer genomic alterations was addressed by Dr. Van Allen. He provided a concise overview on how integrated genomic studies have identified many new therapeutic targets for mutated genes as well as important oncogenes in the development of androgen resistance.

As an example of this translational research approach based on genomic biomarkers, poly (ADP-ribose) polymerase inhibitors such as olaparib and rucaparib received FDA (U.S. Food and Drug Administration) breakthrough therapy designation. These designations are based on clinical trial data demonstrating that patients with specific germline mutations such as BRCA1 or BRCA2 had improved responses particularly in the subset with DNA repair mutations. Another example is pembolizumab which was granted FDA accelerated X in microsatellite instability-high or mismatch repair deficient solid tumors refractory to other treatments. This approval was not specific to prostate cancer, but has become an important salvage option for patients after other therapies have failed and is based on genomic profiling determined on tumor biopsy. These genetically informed clinical trials are continuing to expand in prostate cancer.

Several groups in the United States are reaching out directly nationwide to collect genetic samples (buccal swabs) from men with advanced metastatic castrate resistant prostate cancer to help further define mechanisms of resistance and actionable targets in this incurable disease. An area of Dr. Van Allen's research involves this direct to patient approach through the Metastatic Prostate Cancer Project (MPCProject.org) coordinated by The Broad Institute and the Dana Farber Cancer Center. This accumulating repository has the potential to identify additional biomarkers, define additional genomic alterations, identify mechanisms of progression and define actionable drug therapy targets.

This AUA2019 panel discussion on "Biomarkers in Prostate Cancer" provided an overview of the rapidly evolving field of markers and genetics in the management of this common cancer. Case presentations illustrated how molecular markers and genetic information can be used clinically today as useful tools in the management of prostate cancer.


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