Updates in Managing Advanced Prostate Cancer

BACKGROUND

According to the estimated data for 2020, the incidence of prostate cancer is 191 930 in the United States, making it the most common cancer among men.[1,2] Although the 5-year survival rate is 97.8%, prostate cancer is responsible for 5.5% of all cancer deaths in 2020.[2] About 6% of prostate cancer cases are metastatic at diagnosis, which have a 5-year survival rate of 30.2%.[2] The substantial difference in the 5-year survival rates for all versus metastatic prostate cancers highlights a continued need for further advancements in treatment.

Typical risk factors for developing prostate cancer consist of age, race/ethnicity, family history, and diet.[3] As age passes the 40-years-old mark, the risk for developing prostate cancer starts to increase, with over 70% of cases occurring in men older than 65 years old.[3] African American men have twice the rate of prostate cancer compared with White men in the United States.[3] About 5% to 10% of prostate cancers have genetic risk factors, with the risk doubling if a man has a brother or father diagnosed with prostate cancer.[3] The consumption of red meat, milk, and dietary fat increases the risk for prostate cancer.[4]

Prostate cancer screenings may identify the disease before patients develop any symptoms.[3] According to the 2018 prostate cancer screening recommendations from the United States Preventative Services Task Force (USPSTF), clinicians should apply individual decision-making to screen prostate-specific antigen (PSA) levels in men aged 55 to 69 years and avoid the screening in men 70 years and older.[5] The risk of false-positive results is the main reason for the cautious approach to PSA-based screenings, because false-positive results may lead to additional testing, biopsy, overtreatment, and treatment complications.[5] Clinicians should consider family history, race/ethnicity, and other conditions when deciding about the PSA-based screening; patients should be involved in the final decision-making.[5] If elevated PSA levels are detected, the next steps within the diagnostic workup typically include a digital rectal exam (DRE) and eventually a biopsy.[6] Some patients, who have opted out of PSA-based screenings, may present with symptoms of urinary hesitancy, urinary retention, painful urination, hematuria, and erectile dysfunction, which may indicate the presence of prostate cancer, necessitating a prostate cancer workup.[3]

The typical approach to early-stage prostate cancer includes surgery, radiation, or watchful waiting, while the treatment for advanced prostate cancer focuses on androgen deprivation therapy (ADT).[3] The goal of ADT is to decrease serum testosterone to castrate levels of <50 ng/dL or <1.7 nmol/L, which may improve cause-specific survival.[6,7] Bilateral orchiectomy or a luteinizing hormone-releasing hormone (LHRH) agonist or antagonist represent the primary options for ADT.[6]

On December 18, 2020, the US Food and Drug Administration (FDA) approved relugolix (Orgovyx), an LHRH antagonist, that binds to gonadotropin-releasing hormone receptors and decreases the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH).[6,8,9] As a result, testosterone levels decrease.[10] Relugolix is the first oral LHRH antagonist allowing patients to self-administer.[9] Richard Pazdur, MD, the director of the FDA's Oncology Center for Excellence, acknowledged "Today's approval marks the first oral drug in this class and it may eliminate some patients' need to visit the clinic for treatments that require administration by a health care provider. This potential to reduce clinic visits can be especially beneficial in helping patients with cancer stay home and avoid exposure during the coronavirus pandemic."[9]

EDUCATIONAL ANALYSIS

Gap #1: Clinicians may be unaware of the most recent surveillance recommendations for a PSA-based screening and genetic testing in patients at risk for or diagnosed with prostate cancer.

Learning Objective #1: Recommend an appropriate screening and genetic testing plan to a patient based on the medical history and risk factors.

In the last decade, the USPSTF recommendations regarding screening for prostate cancer changed twice. In 2012, the task force recommended against PSA-based screening.[11] The guideline argued that PSA-based screenings led to a minimal reduction in mortality but increased the risk for adverse events associated with screenings and led to overtreatment.[11] Starting in 2018, the task force advised clinicians to discuss PSA-based screening with men aged 55 to 69 years old, especially African American men and/or men with a family history of prostate cancer.[5] Although screening may detect prostate cancer earlier, the risk for overdiagnosis and overtreatment remains.[5] Treatment complications, including incontinence and erectile dysfunction, are the drawbacks of early PSA-based screening.[5] Currently, PSA-based screening is not recommended for men 70 years and older.[5] The National Comprehensive Cancer Network (NCCN) guideline on prostate cancer fully supports the updated recommendations from the USPSTF on PSA-based screenings to "allow for a more balanced approach to prostate cancer early detection."[6]

Certain patients at risk for or diagnosed with prostate cancer may benefit from genetic testing. The NCCN recommends germline testing (which can detect mutations in genes such as *MLH1*, *MSH2*, *MSH6*, *PMS2*, *BRCA2*, *BRCA1*, *ATM*, *PALB2*, *CHEK2*) for patients who have a family history of certain cancers, regional or metastatic prostate cancer, Ashkenazi Jewish ancestry, and/or intraductal/cribriform histology.[6] For example, up to 16.2% of men with metastatic prostate cancer have germline mutations in DNA repair genes such as *BRCA2*, *ATM*, *CHEK2*, and *BRCA1*.[12,13] *BRCA2* mutations also increase the risk for prostate cancer, contribute to the early onset of prostate cancer, and reduce survival.[6] Patients with regional or metastatic prostate cancers are candidates for somatic tumor testing (eg, *BRCA1*, *BRCA2*, *ATM*, *PALB2*, *FANCA*, *RAD51D*, *CHEK2*, *CDK12*) and testing for microsatellite instability (MSI) or deficient mismatch repair (dMMR).[6] The results of MSI and dMMR testing inform the prescribing of pembrolizumab, which is indicated for unresectable or metastatic solid tumors positive for MSI-high or dMMR and progressing while on other treatments.[6] A newly published implementation framework from the Philadelphia Prostate Cancer Consensus Conference 2019 recommends germline panels and somatic testing focusing on *BRCA2*, *BRCA1*, dMMR, and *ATM* in patients with metastatic prostate cancer.[14]

Because the recommendations from the USPSTF, NCCN, and Philadelphia Prostate Cancer Consensus Conference 2019 have been released recently, clinicians may lack the awareness of recent guidelines and recommendations relating to biomarkers and genetic screenings in prostate cancer. A study by Birmingham and colleagues revealed that only 21% of primary care physicians and urologists would recommend genetic testing to the first-degree relatives of patients with prostate cancer, while 52% of the relatives expressed interest in receiving such testing.[15] But genetic testing may help with selecting the appropriate candidates for PSA-based surveillance, deciding on the best treatment, and referring patients to the right clinical trials.[16] Todd Morgan, a urologic oncologist at the University of Michigan, believes that genetic testing "increases the number of patients who go on active surveillance ... safely saving some men unnecessary treatment."[16]

Gap #2: Clinicians may be unaware of the comparative efficacy and safety of the newly approved ADT agents

Learning Objective #2: Summarize the comparative efficacy and safety of available agents, including newly approved agents, that are used as part of ADT in prostate cancer

According to the NCCN guideline on prostate cancer, ADT is a first-line systemic therapy in patients with regional or advanced disease.[6] Potential candidates for ADT therapy are men with node-positive prostate cancer and a life expectancy of 5 years and longer; men with high-risk, very-high-risk, regional or metastatic prostate cancer and a life expectancy of less than 5 years; and men with metastatic disease at presentation.[6] Bilateral orchiectomy, an LHRH agonist or antagonist, an LHRH agonist with a first-generation androgen, and an LHRH antagonist with abiraterone are the recommended options for ADT.[6] The goal of ADT is to reach castrate levels of serum testosterone (<50 ng/dL or <1.7 nmol/L).[6] The NCCN guideline lists goserelin, histrelin, leuprolide, or triptorelin as options for an LHRH agonist and degarelix

as an option for an LHRH antagonist.[6] Patients with castration-naive disease, marked by not receiving ADT or having recovered testicular function at the time of disease progression, may also receive abiraterone or docetaxel in combination with orchiectomy, LHRH agonist, or LHRH antagonist.[6] Men with advanced prostate cancer whose disease progresses on ADT are diagnosed with castration-resistant prostate cancer.[6] These men continue ADT, but additional agents such as secondary hormone therapies, chemotherapies, immunotherapies, radiopharmaceuticals, or target therapies are initiated.[6] Overall, the NCCN guideline concludes that options for ADT – an LHRH agonist, an LHRH antagonist, or bilateral orchiectomy – are equally effective.[6]

Historically, clinicians started using LHRH agonists first, followed by a more recent approval of LHRH antagonists. The first LHRH agonist, leuprolide, was approved in 1985, with more approvals following in the next decades.[8] Unfortunately, the LHRH agonists lead to a testosterone surge resulting in a tumor flare, causing pain and debilitation for patients.[8] On the other hand, the LHRH antagonists have not been associated with tumor flare by signaling to the pituitary to limit the secretion of LH and FSH, and this leads to an immediate decrease in testosterone levels.[8] Degarelix (Firmagon), available as a subcutaneous injection, was the first approved LHRH antagonist starting in 2008.[8,17] On December 18, 2020, the US FDA approved the second LHRH agonist, relugolix, which is available as an oral formulation.[10] A phase 3 trial, the HERO trial, revealed that 96.7% of men in the relugolix group and 88.8% in the leuprolide group ($P < .001$) maintained testosterone at castrate levels (<50 ng/dL) at week 48 among 930 men with advanced prostate cancer.[18]

According to recent evidence, LHRH agonists increase the risk for coronary artery disease, acute myocardial infarction, sudden cardiac disease, peripheral artery disease, and venous thromboembolism.[19-21] On the other hand, LHRH antagonists display a more favorable side effect profile related to cardiovascular disease.[22] A meta-analysis of 6 randomized controlled trials revealed a significantly lower risk for cardiovascular events or mortality with LHRH antagonists compared with LHRH agonists (HR, 0.60; 95% CI, 0.41–0.87; $P = .008$).[23] In the HERO trial, the incidence of major adverse cardiovascular events was 2.9% in the relugolix group and 6.2% in the leuprolide group after 48 weeks of treatment (HR, 0.46; 95% CI, 0.24-0.88).[18]

Some providers may lack the knowledge of the newly approved agents in prostate cancer. A survey of 100 urologists and 100 medical oncologists revealed that close to 30% of the urologists had not prescribed one of the newly approved agents to patients with castration-resistant prostate cancer, which signals a knowledge gap in the awareness of newly approved agents as well as their role in treatment.[24] Thus, various providers may benefit from an educational program describing the efficacy and safety of various agents used as part of ADT, including the newly approved agents.

Gap #3: Clinicians may be unaware of current guidelines and recent literature on nutritional interventions and physical exercise for patients with prostate cancer receiving ADT.

Learning Objective #3: Evaluate current guidelines and recent literature on nutritional interventions and physical exercise for patients with prostate cancer receiving ADT.

Nutritional interventions may play a role in managing the side effects of ADT, but data remain conflicting. Initiating ADT with an LHRH agonist or antagonist can contribute to several side effects, including insulin resistance, obesity, an increase in intra-abdominal fat mass, dyslipidemia, hypertriglyceridemia, an increase in bone loss – all attributed to low testosterone levels.[22] The American Cancer Society (ACS) prostate cancer survivorship care guideline, also endorsed by the American Society of Clinical Oncology, promotes optimal healthy lifestyle options, including nutrition.[25,26] Prostate cancer survivors should consume vegetables and fruits, low amounts of saturated fat, at least 600 IU of vitamin D per day, and daily calcium not exceeding 1200 mg/day.[25] The guideline panel points out that especially survivors receiving ADT should follow the recommendations because of the increased risk for osteoporosis and fractures.[25] However, a recent review analyzed studies that implemented nutritional interventions to manage the side effects of ADT.[27] Besides counseling and physical activity, other interventions specific to nutrition consisted of introducing a Mediterranean diet, supplementing a diet with whey or soy protein, and recommending Vitamin D and calcium.[27] Overall, the review concluded that the evidence remains

limited regarding the benefits of nutritional interventions for managing the side effects of ADT.[27] The studies assessing diet-only interventions found minimal benefits for reducing the side effects, while exercise appears to improve quality of life and body composition.[27]

Physical exercise is the key intervention for preventing osteoporosis due to ADT treatment.[28] The ACS guideline recommends 150 minutes per week of moderate-intensity or 75 minutes per week of vigorous-intensity exercises in prostate cancer survivors.[25] This recommendation is not specific to survivors receiving ADT.[25] Other exercises consist of weight-bearing training, progressive resistance training, and balance training in patients receiving ADT.[28] Interestingly, progressive resistance training did not improve bone mineral density (BMD) in the majority of studies.[28] One randomized study revealed that recreational football, in fact, decreased the BMD by 1.7% at the total hip ($P = .015$) in patients with prostate cancer receiving ADT.[29] Other evidence suggests that exercise improved reduced muscle mass and strength, fatigue, and worsening physical function in patients on ADT.[30]

To date, patients with prostate cancer continue to request more information on diet and exercise and view their health professionals as the primary source for such information. In a survey, over 60% of health professionals reported that men with prostate cancer are interested in receiving nutrition information, but only 27% of organizations offered nutritional services to men with prostate cancer.[31] As part of the survey, a literature review of 33 articles determined that nutritional studies in prostate cancer primarily focused on men receiving ADT (55% of the studies) and that the majority of interventions (52% of studies) involved both diet and exercise.[31] Another scoping review of 16 studies revealed that prostate cancer survivors view health professionals as facilitators for a lifestyle change.[32] In another study, 82% of patients receiving ADT marked “glad” or “very glad” for receiving written educational materials involving diet and exercise.[33] At the second visit, 84% of the patients started implementing the recommendations from the educational materials.[33] At the same time, 62% of the health professionals reported improved dialogue with patients who received the educational materials.[33] Thus, clinicians working directly with patients receiving ADT may benefit from additional education on the guideline recommendations regarding diet and exercise as well as the most recent evidence for these lifestyle interventions.

SUGGESTED FACULTY LIST

CONCLUSION

Prostate cancer remains the most common cancer among men, with an incidence of 191 930 in the United States and a 5-year survival of 30.2% for metastatic cancer. In the past decade, recommendations from the USPSTF regarding PSA-based screening changed twice, and the Philadelphia Prostate Cancer Consensus Conference 2019 lead to a publication of the implementation framework that addresses germline and somatic testing in patients with metastatic prostate cancer. Genetic testing may also guide the selection of the most appropriate candidates for PSA-based screenings. Early-stage prostate cancer is treated with surgery, radiation, and watchful waiting, while ADT is the mainstay for advanced stages. Bilateral orchiectomy, an LHRH agonist, or an LHRH antagonist comprise the primary options for ADT. Goserelin, histrelin, leuprolide, and triptorelin are LHRH agonists. Degarelix and relugolix represent LHRH antagonists and entered the market more recently. Patients with prostate cancer continue to demand more information on lifestyle interventions, and recent literature has explored nutritional interventions and physical exercise for managing the side effects of ADT. Healthcare providers would benefit from additional education on the updates in the recommendations for PSA-based screenings and genetic testing, novel agents to use as part of ADT, and literature updates on lifestyle interventions for patients experiencing side effects from ADT.

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