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REVIEW ARTICLE

Strategy towards Diagnosis and Treatment for Prostate Cancer

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ABSTRACT

Prostate Cancer (PCa) is one of the major causes of death in men worldwide. Prostate-Specific Antigen (PSA) test and Digital Rectal Examination (DRE) improves the detection rate of prostate cancer. There are several types of hormone and chemotherapy drugs that are used for the treatment of prostate cancer. Enzalutamide is a non-steroidal, orally bioavailable, synthetic molecule that targets AR and inhibit PCa growth. But, due to over-expression in PCa, It will become resistance to PCa. Still, the efficacy and treatment strategies with null side effects are needed more attention. In this review, we broadly focused the symptoms, diagnosis techniques and treatment options for prostate cancer and future prospective.

Introduction

Prostate Cancer (PCa) is one of the widely diagnosed malignancies in men in the United States. The prostate is a small, walnut-shaped gland that makes up part of a man's reproductive system and urinary systems located in the pelvis, between the penis and bladder and in front of the rectum. The function of the prostate is to release the fluid portion of semen by a protein called PSA as well as other substances to maintain and nourish sperm. The prostate inclines to enlarge with age and raise prostate problems including inflammation (prostatitis), enlarged prostate (BPH, or benign prostatic hyperplasia), and PCa [1]. The human prostate gland lies below the urinary bladder and in front of the rectum. The mature gland consists of branched alveolar-ductal structures embedded in a fibromuscular stroma. Although its define function remains unclear, the prostate produces a clear, slightly alkaline fluid that constitutes 10-30% of the seminal fluid volume. The prostate functional unit comprises of the epithelium and stroma components [2]. The epithelium consists mainly of secretory columnar epithelial cells, which arranges into a single cell layer, lining the epithelium. They synthesize proteins such as PSA and prostate-specific phosphatase and secrete them into the ductal lumen mucin. The majority of cancer in prostate arises from abnormally functioning secretory epithelial cells. The prostate tissue is also composed of basal epithelial cells, neuroendocrine cells, non-epithelial fixed macrophages and intra-acinar lymphocytes. The secretory epithelial cells express AR and they required continuous direct androgenic stimulation to maintain structural and functional viability [2]. PCa occurs due to the formation of malignant cells within the

prostate gland, referred to as localized PCa. If it spreads to the tissues closely encircling the prostate gland called extracapsular PCa. When cancer spreads to other parts and organs, is called as metastatic PCa. National cancer institute has estimated that there would be 161,360 new cases of PCa and 26, 730 people will die of this disease in the year 2017 [3] and increases every year due to the growth and aging of the global population. The statistic and epidemiological modulations in developing countries have depicted a rising curve in the burden of various cancer cases including PCa [4]. In most cases, PCa symptoms are not apparent in the early stages of the disease. Even etiology of PCa is still obliterated; the incidence and progression of PCa are linked with several risk factors [5] including the increasing age, race/ethnicity, family history, diet, lifestyle and behavioural factors (Figure 1). There are several types of PCa depending on the states of cancer. Several types of therapeutic options for the treatment of PCa are available such as surgery, endocrine therapy, hormone therapy, radiation therapy, chemotherapy, radical prostatectomy, vaccine treatment, bone directed treatment, etc [6]. These treatments are used alone or in combination that depends on the stage of the PCa, age of the patients, and so on. PCa magnification is mainly prompted by androgen and Androgen Receptor (AR), initially respond to standard androgen deprivation therapies usually relapse into a more truculent, Castration-Resistant Prostate Cancer (CRPC).

Signs and Symptoms of Prostate Cancer

Symptoms of PCa are quite similar with benign (non-cancerous) prostate conditions. Common symptoms include weak urine stream, painful and burnable during urination, blood in the urine (hematuria), lack of ability to pass urine, and frequent urination (especially at night). However, there are several chances for developing cancerous condition due to increasing age, history of PCa in their family, or other factors such as smoking and dietary, hormonal and environmental influences [7,8].

Prevention and Diagnosis of Prostate Cancer

There is no particular precaution to prevent PCa, but healthy diet and exercise may reduce the risk factors. The principal report of a diagnosis of prostate malignancy goes back to 1853. The goal is to prevent men from developing PCa. The symptoms and results indicate for PCa that can be initially diagnosed using prostate biopsy test guided by Transrectal Ultrasound (TRUS). Also, robotic methods have been developed to target cancer guided by Magnetic Resonance Imaging (MRI) and indirect MRI, also to depict Cancer Suspicious Region (CSR) within the prostate. The Gleason grading system is used to help evaluate the prognosis of men with prostate cancer using samples from a prostate biopsy. The cells are scored on a scale of 1 to 5. Those cells closest to 1 are considered to be "Low-Grade" tumour cells and tend to look similar to normal cells. Cells closest to 5 are considered "High-grade" and have mutated so much that they barely resemble normal cells. The combination of both Prostate-Specific Antigen (PSA) test and a Digital Rectal Examination (DRE) improves the overall rate of PCa detection. The U.S. Food and Drug Administration (FDA) has sanctioned the approval of the PSA test in men of age 50 and older for annual screening of PCa [9].

1. Prostate-specific antigen

Prostate-Specific Antigen (PSA) is also known as gamma-seminoprotein or kallikrein-3 (KLK3), which belongs to the protease family of kallikrein, and is secreted by the epithelial cells of the prostate gland. PSA is a glycoprotein enzyme encoded in humans by the KLK3 gene but is often increased in the presence of PCa or other prostate disorders. PSA is measured by a blood test or monoclonal antibody technique. The "normal" PSA serum concentration ranges between 1.0 and 4.0 ng/ml. Unfortunately, the PSA test can result in false positives. When a PSA threshold of 4 ng/mL or above is regarded as an indicator for prostate biopsy, it misses between 20% and 40% of cancers. Lowering the PSA threshold has been suggested as an alternative to satisfy the current problems of the PSA test. However, when the PSA threshold is decreased, there is an increased risk of

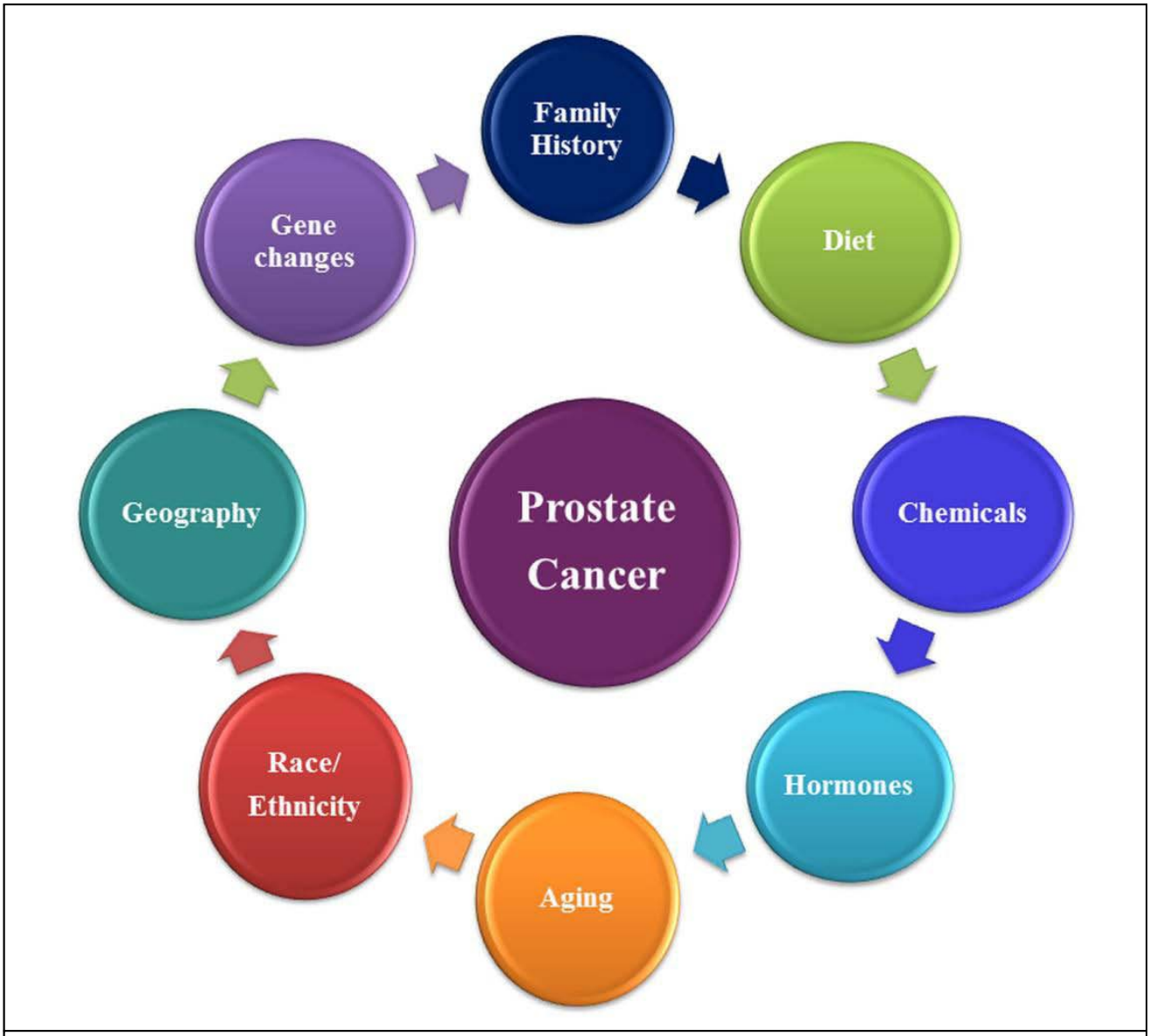

Figure 1: Risk factors for prostate cancer.

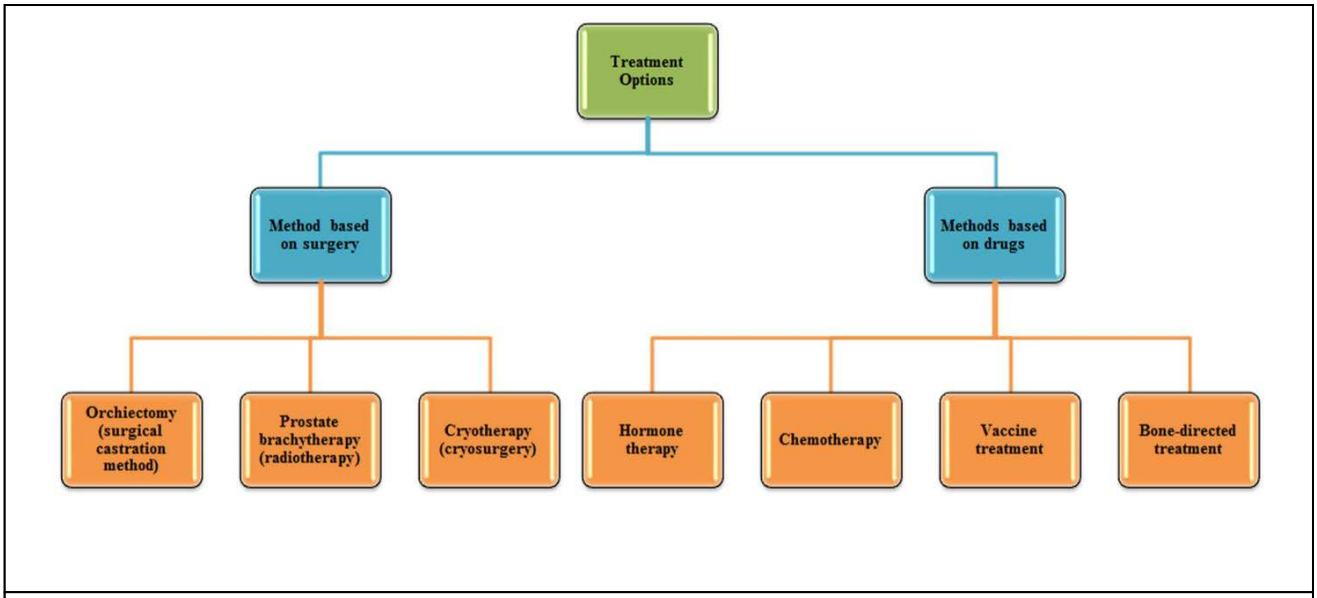

Figure 2: Treatment options for prostate cancer

identifying and unnecessarily treating indolent disease. However, since the prostate gland increases in size and produces more PSA with increasing age, it is normal to have lower levels of young men and higher levels in older men. The PSA level also depends on ethnicity and family history of PCa. The typical increase less than 0.75 ng/ml is used to determine levels of disease and to counsel men in management. Clinically localized PCa does not usually cause any clinical symptoms [10]. Further support of the activity of the drug was shown by the improvement in overall soft-tissue response rate (58.8% vs 4.9%; P < .0001) and the rate of a post-therapy PSA decline of 50% or greater (78% vs 3.5%; P < .0001). There is no fixed PSA serum levels cut off point that could distinguish the indolent from the aggressive prostate cancer. Currently, some authors accepted the cutoff of 2 ng/ml because, as Thompson et al. stated, 15% men with a PSA <4 ng/ml were diagnosed with intermediate to high-risk PCa [11].

2. Digital Rectal Examination

Digital Rectal Examination (DRE) is a simple procedure to examine the rectum and other internal organs for checking the signs of enlargement or irregularity which leads to a biopsy [12].

3. Transrectal ultrasound

Transrectal Ultrasound (TRUS) is used to scan the prostate and surrounding tissues by inserting an ultrasound probe. Similarly, a biopsy can be done by placing a needle into the correct location of the prostate gland through the rectum by the help of the ultrasound. The biopsies can be examined under a microscope whether cancerous cells are present. X-ray, MRI, scintigraphy and CT Scans are required to assess whether cancer has spread to other areas of the body, such as bones and internal organs, etc. If PCa has confirmed [13].

Treatment of Prostate Cancer

The treatment of prostate cancer will differ for each individual due to age, health factors, stage of cancer, etc. Several types of therapeutic options are available such as surgery, cryosurgery, radiation therapy, chemotherapy, radical prostatectomy, endocrine therapy, hormone therapy, brachytherapy, vaccine treatment, bone directed treatment, etc. (Figure 2) [6]. These treatments are used alone or in combination that depends on the stage of the PCa, the age of the patients, and so on. PCa magnification is mainly prompted by androgen and Androgen Receptor (AR), initially respond to standard androgen deprivation therapies usually relapse into a more truculent, Castration-Resistant Prostate Cancer (CRPC). If PCa is causing low urine flow or blockage, surgery may be required before other treatments. Transurethral Resection of the Prostate (TURP) is a surgical technique that allows blockages within the prostate gland to be removed by inserting a resectoscope into the penis and up the urethra to remove excess prostate tissue or section of the prostate gland [13]. Radiotherapy is used to control or stop the growth of cancer cells by radiation. There are two main types of radiotherapy for PCa such as external beam and brachytherapy. The implantation of radioactive seeds directly into the prostate gland, which reduces the risk of damage to surrounding healthy tissues, is called Prostate brachytherapy [14]. If cancer has spread beyond the prostate gland, hormone treatment may be encouraged. Orchiectomy is used for the surgical removal of the testicles if there is no alternative.

Chemotherapy is used to treat advanced metastatic PCa. Sipuleucel-T is used for immunotherapy to boost the body's natural defences to fight against cancer. It was approved for the treatment of asymptomatic or minimally symptomatic metastatic CRPC. It is the first therapeutic cancer vaccine to receive FDA approval. Blocking the release of Luteinizing Hormone-Releasing Hormone (LHRH) through the use of LHRH agonists or LHRH analogues is common hormone therapies used in men with PCa. Drugs in this class, including leuprorelin, goserelin, triptorelin and Histrelin are used as LHRH agonists. Leuprorelin is in the Gonadotropin-Releasing Hormone (GnRH) analogue family of medication. It decreases the level of gonadotropin, testosterone and estradiol. Goserelin or goserelin acetate is a synthetic hormone used to suppress the production of the sex hormones (testosterone and estrogen), particularly in the

treatment of PCa. Triptorelin is a GnRH agonist that is a potent inhibitor of the synthesis of sex hormones and is used to treat advanced PCa. Histrelin acetate is a nonapeptide analogue of GnRH with added potency. It stimulates these cells to release luteinizing hormone and follicle-stimulating hormone. Buserelin and Deslorelin are the synthetic analogues of LHRH agonists that also used for the treatment of PCa [15]. Cetrorelix, Ganirelix and Abarelix are injectable Gonadotropin-Releasing Hormone (GnRH) antagonists that are used to inhibit premature luteinizing hormone surges. Degarelix and Relugolix are used as LHRH antagonists and are also used for the treatment of advanced PCa [16]. At present, newly-developed non-steroidal AR antagonists, such as RD162, BMS-779333, ONC1-13B, MDV3100, and BMS-641988 show more potent activity and are currently being tested in clinical trials. RD162 is an orally active and very potent second-generation AR antagonist for the treatment of advanced PCa. BMS-641988 is a novel non-steroidal AR antagonist that has high affinity to bind with AR and designed for PCa treatment. Antiandrogens, such as abiraterone acetate, cyproterone acetate, flutamide, nilutamide, and bicalutamide, have been used to block the androgen signal [6]. Also, there are several on-going types of research work from our group on the design and development of new novel molecules for the treatment of PCa [17-20].

Conclusion

The occurrence of PCa is expanding with time, and it is currently diagnosed at a disturbing rate everywhere throughout the world. There is a need to produce for early impeccable identification devices or systems for PCa. Surgery is one of the treatment choices, which offers alleviation to PCa patients some extent. Numerous treatments are available, yet their use has been constrained in light of the poor oral bioavailability, absence of selectivity and high dangers of literal side effects. This survey may enable scientists to be better helpful for finding new dynamic medications for prostate growth.

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