Module in the Area of

Medical Oncology

UNDERSTANDING THE USAGE PATTERN OF LEUPROLIDE IN MANAGEMENT OF PROSTATE CANCER

Module II

TABLE OF CONTENT

INTRODUCTION TO PROSTATE CANCER

Prostate cancer stands as the most prevalent non-skin malignancy affecting men in the United States. Predominantly diagnosed in older men, the incidence of prostate cancer is expected to rise as the population continues to age. With the advent and ensuing debates surrounding prostate specific antigen (PSA) testing, an increasing number of men are consulting their healthcare providers to make informed decisions about prostate cancer screening. The considerable patient volume seeking care for prostate cancer across various medical settings necessitates that oncology nurses possess a robust foundational knowledge of the disease. This encompasses understanding the risk factors, diagnostic processes, treatment options, and the latest advancements in therapies.[1]

Epidemiology of Prostate Cancer

In 2010, approximately 217,730 new cases of prostate cancer were diagnosed in the United States, resulting in nearly 32,050 prostate cancer-related deaths. Approximately one in six men will be diagnosed with prostate cancer during their lifetime, and about one in 36 will die from the disease. Between 2000 and 2006, the incidence of prostate cancer among all men in the United States decreased by 2.4% per year, while deaths from prostate cancer decreased by 4.1% annually from 1994 to 2006. These trends suggest improvements in early detection and treatment options over the years.[1]

The incidence of prostate cancer varies significantly among different racial groups. From 1999 to 2007, the highest incidence rates were observed among African-American men, with rates exceeding 250 per 100,000 individuals. In comparison, the incidence was about 160 per 100,000 for Caucasian men, approximately 130 per 100,000 for Hispanic-American men, and less than 100

per 100,000 for Asian/Pacific Islanders and American Indian/Native Alaskan men. The lifetime probability of developing prostate cancer is 18.25% for African-Americans and 15.25% for Caucasians.[1]

Risk Factors for Prostate Cancer

Advanced age is the leading risk factor for prostate cancer. Approximately 75% of prostate cancer cases are diagnosed in men over the age of 65, while the disease is rarely seen in men younger than 40. Autopsy data suggests an age-specific prevalence rate of prostate cancer as high as 90% in men aged 70 to 90. This high prevalence in older men indicates that more individuals may die with prostate cancer rather than from it, highlighting the importance of distinguishing between aggressive and indolent forms of the disease. With the aging population and increased life expectancy, prostate cancer will continue to be a major health concern.[1]

Race is another significant risk factor for developing prostate cancer. African-American men are at the greatest risk, with a 60% higher incidence rate than Caucasian men between 2001 and 2005. In 2009, approximately 27,130 cases were diagnosed in African-American men, accounting for 34% of all cancer diagnoses in this population. The role of race and ethnicity in the development of prostate cancer may be influenced by socioeconomic factors such as income, health insurance, education, barriers to medical care, as well as environmental and dietary factors.[1]

Family history also plays a crucial role in the risk of developing prostate cancer. The risk is doubled for men who have a first-degree relative with prostate cancer. The risk is further elevated if the relative was diagnosed at an age younger than 60 and if more than one first-degree relative has been diagnosed. These familial patterns suggest a genetic component to prostate cancer risk, emphasizing the need for targeted screening and preventive measures for individuals with a family history of the disease.[1]

PATHOPHYSIOLOGY OF PROSTATE CANCER

The prostate gland, a crucial part of the male reproductive system, is responsible for making and storing seminal fluid. Typically, an adult male prostate is about 3 centimeters long and weighs approximately 20 grams. Due to its anatomical location, diseases affecting the prostate can impact urination, ejaculation, and occasionally defecation. The prostate contains numerous small glands that produce about 20% of the fluid that constitutes semen.[2]

Prostate cancer occurs when the cells within these prostate glands undergo mutations, transforming into cancerous cells. The proper functioning of prostate glands relies on male hormones known as androgens, which include testosterone (produced in the testes), dehydroepiandrosterone (produced in the adrenal glands), and dihydrotestosterone (converted from testosterone within the prostate). These androgens are also responsible for male secondary sexual characteristics such as facial hair and increased muscle mass.[2]

Prostate cancer is classified as an adenocarcinoma, which is a type of glandular cancer. This malignancy begins when normal prostate gland cells mutate into cancer cells, most commonly in the peripheral zone of the prostate gland. Initially, small clusters of cancer cells are confined within the normal prostate glands, a condition known as carcinoma in situ or prostate intraepithelial neoplasia (PIN). Although there is no definitive evidence that PIN is a direct precursor to cancer, it is closely associated with it.[2]

Over time, these cancer cells begin to multiply and invade the surrounding prostate tissue, forming a tumor. As the tumor grows, it may invade nearby organs such as the seminal vesicles or the rectum. Tumor cells can also enter

the bloodstream and lymphatic system, leading to metastasis. Prostate cancer typically metastasizes to the bones and lymph nodes and can invade the rectum, bladder, and lower ureters as it progresses locally. The venous route, particularly through the prostatic venous plexus connecting to the vertebral veins, is thought to be the primary pathway for bone metastasis.[2]

The prostate is notable for its ability to accumulate zinc and produce citrate, an essential component of semen. The protein ZIP1 facilitates the active transport of zinc into prostate cells, which alters their metabolism to produce citrate. This process is energy-intensive, causing prostate cells to expend significant energy (ATP). Prostate cancer cells, however, generally lack zinc, which allows them to conserve energy by not producing citrate, thus facilitating their growth and spread. The reduction of zinc in these cells is believed to result from the epigenetic silencing of the gene responsible for producing ZIP1, a tumor suppressor gene product of SLC39A1.[2]

Research has shown that strategies to transport zinc into cancerous prostate cells can effectively eliminate them in animal models. Zinc inhibits NF-kB pathways, is anti-proliferative, and induces apoptosis in abnormal cells. However, oral ingestion of zinc is ineffective because high concentrations of zinc cannot be achieved in prostate cells without the active transporter ZIP1.[2]

Additionally, the transcription factor RUNX2 contributes to the development of prostate cancer by preventing cancer cells from undergoing apoptosis. The androgen receptor is another critical component that helps prostate cancer cells survive and is a target for many anticancer research studies. Prostate-specific membrane antigen (PSMA) also plays a role in prostate cancer by increasing folate levels, which cancer cells use for growth and survival. PSMA increases available folates by hydrolyzing glutamate folate.[2]

Clinical Manifestations

Early prostate cancer often presents without clear symptoms, making it difficult to detect in its initial stages. When symptoms do occur, they are frequently similar to those of benign prostatic hyperplasia, including frequent urination, nocturia (increased urination at night), difficulty starting and maintaining a steady stream of urine, hematuria (blood in the urine), and dysuria (painful urination). According to a study based on the 1998 Patient Care Evaluation in the US, approximately one-third of patients diagnosed with prostate cancer exhibited one or more of these symptoms, while two-thirds were asymptomatic.[2]

As prostate cancer progresses, it can significantly impact urinary and sexual function. Given that the prostate gland surrounds the prostatic urethra, any changes within the gland can directly affect urinary function, leading to issues such as urinary retention or incontinence. Furthermore, because the prostate contributes to seminal fluid, prostate cancer can interfere with sexual function, causing difficulties in achieving an erection or resulting in painful ejaculation. In advanced stages, prostate cancer may metastasize to other parts of the body, commonly causing bone pain in areas such as the vertebrae, pelvis, or ribs. Metastasis to bones like the femur typically affects the proximal part of the bone. Additionally, cancer in the spine can compress the spinal cord, leading to symptoms such as tingling, leg weakness, and urinary or fecal incontinence. Other late-stage symptoms may include fatigue due to anemia.[2]

TREATMENT AND MANAGEMENT OF PROSTATE CANCER

The management of prostate cancer involves considering a range of prognostic factors, including initial PSA level, clinical TNM stage, Gleason's score, baseline urinary function, comorbidities, and patient age. Advances in diagnostic and treatment modalities have enabled clinicians to better classify patients by risk and tailor therapy based on cancer prognosis and patient preferences.[3]

Standard Treatments for Prostate Cancer

For patients with stage I–III prostate cancer, the standard treatment options include active surveillance, radical prostatectomy, and radiotherapy. For stage IV and high-risk stage III patients, androgen ablation through surgical or pharmacological castration is often employed, sometimes supplemented with first-generation antiandrogens such as flutamide and bicalutamide.[3]

Active Surveillance

Active surveillance is a structured program of monitoring and delayed intervention, suitable for patients with low-risk cancers or those with a short life expectancy. The advantages include preservation of erectile function, reduced treatment costs, and maintaining quality of life. Disadvantages include the risk of cancer metastasis, missed opportunities for cure, and the need for frequent medical checks.[3]

Radical Prostatectomy

Radical prostatectomy involves the surgical removal of the prostate gland. This procedure is generally recommended for younger patients with organ-confined prostate cancer and a life expectancy greater than ten years.

Complications can include urinary incontinence and erectile dysfunction due to potential surgical damage to the urinary sphincter and erectile nerves.[3]

Cryotherapy

Cryotherapy involves freezing the prostate gland using cryoprobes. While effective, it carries risks of complications such as urinary incontinence, erectile dysfunction, fistulas, and rectal pain.[3]

Radiation Therapy

Radiation therapy, which includes techniques such as brachytherapy and external beam radiation therapy (EBRT), targets prostate cancer cells with high-energy rays. Brachytherapy involves placing radioactive sources directly into the prostate, while EBRT projects energy through the skin. Radiation therapy is especially useful for patients unsuitable for surgery and can effectively treat both early-stage and advanced prostate cancer. Side effects may include urinary urgency, frequency, erectile dysfunction, dysuria, diarrhea, and proctitis.[3]

Radium-223 Therapy

Radium-223 dichloride (Xofigo) is used for patients with metastatic prostate cancer resistant to hormone therapy. It mimics calcium, targeting cancer cells in bone tissue, and has shown to improve survival and delay the onset of bone fractures and pain.[3]

Hormonal Therapy

Hormonal therapy, or androgen deprivation therapy (ADT), blocks testosterone production and other androgens, thus inhibiting prostate cancer cell growth. Common luteinizing hormone-releasing hormone (LHRH) agonists include leuprolide, goserelin, triptorelin, and histrelin. While effective, ADT is associated with side effects such as hyperlipidemia, fatigue, hot flashes, osteoporosis, cardiovascular disease, and sexual dysfunction.[3]

Second-Generation Hormonal Agents

Abiraterone: Inhibits CYP17A, crucial for androgen production, and is used for metastatic prostate cancer. Side effects include edema, hypertension, fatigue, and hypokalemia.[3]

Enzalutamide: A second-generation AR inhibitor that blocks androgen receptor signaling, used for castration-resistant prostate cancer (CRPC). Side effects include fatigue, diarrhea, and vomiting.[3]

Chemotherapy

Chemotherapy employs drugs to kill or inhibit cancer cell growth. The most common drug is docetaxel, an antimicrotubule agent used as first-line therapy for CRPC. Cabazitaxel, a second-generation agent, is used for docetaxel-resistant cases.[3]

Immunotherapy

Immunotherapy, or biological therapy, stimulates the immune system to fight cancer. Sipuleucel-T (Provenge) is an autologous dendritic cell-based vaccine for advanced and metastatic prostate cancer. It has fewer side effects than traditional chemotherapy, primarily causing fever, nausea, chills, and muscle aches.[3]

Combination Therapy

Combination therapy is an effective strategy for treating prostate cancer, especially CRPC. It involves using multiple treatment modalities, such as combining ADT with radiation therapy, chemotherapy, or immunotherapy. These combinations can increase patient survival and suppress tumor growth. Ongoing clinical trials are exploring various combinations to optimize outcomes and extend patient lifespans.[3]

In summary, the treatment and management of prostate cancer are multifaceted, with options tailored to disease stage, patient health, and personal preferences. Advances in diagnostic and therapeutic strategies continue to improve the prognosis and quality of life for patients with prostate cancer.[3]

ANDROGEN DEPRIVATION THERAPY (ADT)

Mechanism of Action

ADT is a cornerstone in the treatment of prostate cancer, particularly in cases of metastatic prostate cancer. ADT works by reducing the levels of androgens, such as testosterone and dihydrotestosterone (DHT), which are essential for the growth, function, and proliferation of prostate cells. The majority of testosterone is produced in the Leydig cells of the testes, with a small amount produced in the adrenal glands. The hypothalamic-pituitary axis regulates the production and release of testosterone: the gonadotropin-releasing hormone (GnRH or LHRH) stimulates the pituitary gland to release luteinizing hormone (LH), which in turn stimulates the testes to produce testosterone.[4]

In the prostate, testosterone is converted by the enzyme 5-a-reductase to DHT, a potent androgenic metabolite that binds to and activates the androgen receptor (AR). The androgen-bound AR enters the nucleus, where it forms dimers that regulate the expression of androgen-dependent genes, driving the growth and survival of prostate cancer cells. By reducing androgen levels, ADT causes cancer regression by decreasing cell proliferation and increasing apoptosis.[4]

Benefits of ADT

Advanced Prostate Cancer[5]

- The VACURG I study showed no survival advantage of early vs. late ADT in metastatic prostate cancer.
- The Medical Research Council's trial found that early ADT improved survival and reduced metastases, fractures, spinal cord compression, and ureteral obstruction compared to deferred ADT.

- Meta-analyses have shown that GnRH agonists and orchiectomy provide equivalent outcomes.
- ADT typically remains effective for 14-20 months in metastatic settings before the cancer becomes androgen-independent.
- ADT improves quality of life by reducing bone pain, pathological fractures, spinal cord compression, and ureteral obstruction.

ADT as an Adjuvant to Radiation Therapy or Prostatectomy[5]

- ADT combined with radiation therapy has shown improved survival in locally advanced prostate cancer.
- The European Organisation for Research and Treatment of Cancer reported 5-year survival rates of 78% with combined treatment vs. 62% with radiation alone.
- The Radiation Therapy Oncology Group Trial 85-31 found a 10-year survival improvement (53% vs. 38%) with ADT plus radiation.
- D'Amico's trial showed better 5-year survival and reduced need for salvage ADT with combined therapy.
- Messing et al. found that early ADT improved survival and disease-free rates in men with pelvic lymph node involvement post-prostatectomy.

Biochemical Failure[5]

- Rising PSA levels after prostatectomy predict a median 8-year time to metastasis.
- High-grade tumors have a higher risk of metastasis, suggesting potential benefits of early ADT in this subset.
- No definitive data supports a survival benefit of early ADT for biochemical failure, but it may benefit high-risk patients. Prospective studies are needed.

Adverse Effects of ADT

Hot Flashes[5]

- Hot flashes affect up to 80% of men on ADT, with 27% finding them most troublesome.
- Megestrol acetate significantly reduces hot flashes but may increase PSA levels.
- Antidepressants are sometimes used but lack large-scale efficacy trials.

Skeletal Complications[5]

- ADT significantly decreases bone mineral density (BMD), increasing fracture risk.
- Zoledronic acid and pamidronate can prevent BMD loss in men on ADT.
- Men on ADT should be assessed for osteoporosis risk and take calcium and vitamin D supplements.

Sexual Function[5]

- ADT negatively impacts sexual function, reducing sexual interest, erections, and activity.
- Options for managing erectile dysfunction include phosphodiesterase type 5 inhibitors, penile implants, vacuum devices, and intracavernosal injections.

Metabolic Changes[5]

- ADT increases body fat, BMI, cholesterol, triglycerides, and glucose intolerance.
- These changes are consistent with metabolic syndrome and can increase cardiovascular risks.

Cognitive and Mood Changes[5]

- Conflicting studies on cognitive effects of ADT, with some showing declines in attention and memory, while others do not.
- ADT may worsen fatigue and psychological distress, and men on ADT have higher depression rates.

Other Changes[5]

- ADT can cause normocytic, normochromic anemia, contributing to fatigue.
- Gynecomastia occurs in 1% to 16% of men on ADT, with treatment options including breast irradiation, surgery, and tamoxifen.
- Other side effects include dry eyes, body hair loss, and vertigo.

LEUPROLIDE AND ITS ROLE IN ADT

LHRH/GnRH Agonists

The discovery of GnRH, also known as LHRH in 1971 paved the way for the development of several GnRH/LHRH agonists. These agonists are particularly significant in the ADT of prostate cancer. GnRH/LHRH is a small decapeptide, specifically pyroGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-amide, synthesized and stored in the hypothalamus. It is released in a pulsatile manner to act on anterior pituitary gonadotrophs, which express GnRH receptors (GnRHRs). This action stimulates both the synthesis and secretion of the gonadotropins-luteinizing hormone (LH) and follicle-stimulating hormone (FSH) — into the bloodstream.[4]

The continuous administration of synthetic LHRH agonists results in the down-regulation of GnRH receptors in the pituitary gland. This process leads to a significant decrease in bioactive LH and FSH, effectively causing a selective medical hypophysectomy. Consequently, the production of testosterone by the testes is inhibited, a condition often referred to as chemical castration. These compounds are typically administered subcutaneously or intramuscularly in the form of depot injections. Some of the currently available synthetic LHRH agonists include Buserelin, Goserelin, Histrelin, Triptorelin, and the most widely used, Leuprolide.[4]

Role of Leuprolide Acetate in ADT

Leuprolide acetate (LA) is the most commonly prescribed depot LHRH agonist, with a history of over 20 years in the treatment of prostate cancer. LA, chemically known as 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate, is a synthetic peptide analog of LHRH. It has a longer half-life (>3 hours) compared to the natural LHRH (3-4 minutes) and a higher affinity for the GnRH/LHRH receptor.[4]

Upon initial administration, LA causes a temporary increase in testosterone levels due to the hyperstimulation of GnRHRs in the pituitary, a phenomenon known as the "testosterone flare." This flare typically occurs within three days of the initial treatment. To mitigate the effects of this testosterone surge, concurrent use of an antiandrogen such as Bicalutamide or Flutamide is recommended, a strategy referred to as anti-androgen flare protection.[4]

Prolonged administration of LA leads to the inhibition of the hypophyseal–gonadal axis through various feedback mechanisms. This inhibition results in the down-regulation of GnRHR, desensitization of pituitary gonadotrophs, and suppression of LH and FSH, ultimately reducing testosterone production in the testes. Under LA treatment, testosterone serum levels typically drop to castrate levels (<20 ng/dL) within 2 to 4 weeks. LA offers a less cardiotoxic, easier, and more patient-friendly method of ADT compared to estrogens, and its effects are reversible, providing a therapeutic outcome equivalent to surgical castration.[4]

PHARMACOKINETICS OF LEUPROLIDE IN PROSTATE CANCER

Initially, leuprolide acetate (LA) was administered through daily subcutaneous injections, necessitating frequent visits to healthcare providers and increasing the likelihood of adverse effects such as injection site reactions. However, over the past few decades, extended-release formulations have been developed, significantly improving patient adherence to LA therapy. These formulations are available in short- and long-acting versions, providing sustained release of the drug over periods ranging from 1 to 6 months after a single administration.[4]

Two main technologies are employed for drug delivery: microsphere delivery systems and biodegradable solid depot application systems. Microsphere delivery systems involve the encapsulation of LA, which is then slowly released into the bloodstream after intramuscular injection. The release rate depends on the composition of the microspheres, with polylactic-co-glycolic acid microspheres being a common formulation. On the other hand, biodegradable solid depot systems consist of biodegradable polymers dissolved in a carrier containing the active drug. After injection, the suspension transitions into a solid implant, continuously releasing LA over time as the polymer matrix degrades.[4]

While long-acting formulations of LA have been shown to improve patient satisfaction and adherence, ongoing research aims to develop even longer-lasting formulations. For instance, a non-biodegradable titanium implant capable of delivering LA continuously over 12 months has been approved for use in metastatic prostate cancer. This implant maintains steady serum leuprolide concentrations and effectively reduces testosterone levels, although it requires a surgical procedure for implantation and removal.[4]

CLINICAL TRIALS OF LEUPROLIDE IN PROSTATE CANCER

In a comparative study, leuprolide (1 mg subcutaneously daily) was evaluated against diethylstilbestrol (DES, 3 mg by mouth daily) in patients with metastatic prostate cancer (Stage D2) who had not received systemic treatment previously. The study involved 98 patients assigned to leuprolide and 101 to DES. Results showed that leuprolide offered therapeutic equivalence to DES with fewer side effects. Both treatments effectively suppressed testosterone and dihydrotestosterone levels, with comparable decreases in acid phosphatase. However, patients receiving DES experienced more frequent adverse effects, including painful gynecomastia ($P < 0.00001$), nausea, vomiting ($P = 0.02$), edema ($P = 0.008$), and thromboembolism ($P = 0.065$), compared to those receiving leuprolide. Despite more "hot flashes" reported in the leuprolide group, the overall objective response rate was similar between the two groups (86% for leuprolide vs. 85% for DES). Additionally, actual survival rates at one year were higher in the leuprolide group (87%) compared to the DES group (78%).[6]

In another phase III study, the safety and efficacy of the depot formulation of leuprolide (7.5 mg injected intramuscularly every 4 weeks) were assessed in patients with stage D2 prostate cancer who had not previously received systemic treatment. The study included 56 patients, with 53 evaluable for treatment response. Results showed that 81% of evaluable patients achieved an objective response to treatment. Pharmacokinetic analysis revealed that median interval to onset of castrate testosterone levels was 21 days, with mean testosterone levels decreasing to within the castrate range by week 3 of treatment. There were no escapes of testosterone levels above 50 ng/dL during the 24-week study period. The response rate and incidence of adverse

events with the depot formulation did not significantly differ from those observed with the daily subcutaneous formulation.[7]

Additionally, a study investigated the safety, efficacy, and pharmacokinetics of a unique 3-month subcutaneous depot of leuprolide acetate (LA-2550, 22.5 mg depot) in 117 patients with prostate cancer. Results showed that 98% of patients completed the 6-month study, with 98% achieving serum testosterone levels of 50 ng/dL or less by day 28. By day 35, all patients had testosterone levels below 50 ng/dL. At study completion, all patients-maintained testosterone suppression below 50 ng/dL, with 94% achieving levels of 20 ng/dL or less. Mean luteinizing hormone (9.2 ± 1.1 to 0.08 ± 0.01 mIU/mL) and prostate-specific antigen levels decreased significantly, and no flare reactions were observed. The most common treatment-related adverse event was hot flashes, with most cases being mild. The study concluded that LA-2550 effectively suppressed serum testosterone to well below the medical castrate level, with a favorable safety profile.[8]

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Notes

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