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An Update on the Screening Information and the Use of LEuprolide in Prostate Cancer

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Introduction

Prostate cancer (PCA) is a major public health problem in this country. It is second to lung cancer as the leading cause of death in men. Approximately 189,000 new cases of PCA are expected in 2002 and about 30,200 men will die this year from PCA.

Some of the major risk factors for developing PCA include: a positive family history (first degree relative), race (African Americans are twice as likely as Caucasians to have the disease) and age (patients older than 65 years of age account for 70% of patients with PCA). Also, at a higher risk of developing PCA are people who smoke, have a high fat diet, have high circulating androgens and those who have high insulin-like growth factors. PCA is less prevalent in Asia, Africa, and South America but more prevalent in North America and northwestern Europe. The American Cancer Society suggests vitamin E 50 mg per day, foods high in lycopene (tomato, grapefruit, watermelon) and regular physical activity as means to help decrease the risk of developing PCA.[1]

The main objective of this article is to educate clinicians on the new screening tools used for PCA. It also discusses the role of leuprolide as a treatment option for patients with moderate to severe PCA.

Screening Tests

The initial screening test is usually the digital rectal exam (DRE). It is recommended annually starting at age 50. However, if risk factors are present, it is recommended to start at age 45.[1]

Another screening tool is the Prostate Specific Antigen (PSA). Like the DRE, it should be offered annually beginning at age 50 (45 if a risk factor is present). The normal range is < 4 ng/ml; between 4 and 10 ng/ml is the intermediate range and PSAs > 10 ng/ml are considered high. Unfortunately, there are some limitations to the utility of PSA. It is not specific for PCA and some benign conditions can cause it to be elevated. Also, PCA can exist even when a patients' PSA is within the normal range. Nevertheless, the PSA may help detect PCA at an earlier and potentially more treatable stage and thus improve the chances for survival.[8]

There are two distinct forms of PSA: free PSA and a complexed form that is attached to the serum protease inhibitor alpha 1-antichymotrypsin (ACT). The complexed PSA does not appear to be correlated with cancer at least at the tissue level. Antibodies have been identified so the assay can specifically measure the free form and the total PSA (complexed plus free).[13] A higher ratio of free to total PSA correlates with a lower risk of PCA. The free type of PSA has three different forms of inactive PSA. The free/total PSA increases the specificity of PSA for PCA without compromising its sensitivity. A threshold of 0.20 free/total detected 91% of cancers and relieved 48% of men with BPH from progressing to biopsy.[3]

The first type of free PSA is a proenzyme, or precursor, called pPSA and is associated with PCA. It is difficult to know if pPSA is present in PSA levels less than 10 ng/ml. The pPSA is only found in the blood.

A second type of free PSA, BPSA, is a degraded form of PSA that is more correlated with benign prostatic hypertrophy (BPH). BPSA seems to be elevated in the serum of biopsy negative men with elevated PSA levels. It appears to be correlated with higher prostate volume, regardless of whether cancer is present. BPSA can be detected in the seminal plasma. The BPSA level also can change if the patient is using 5-alpha-reductase inhibitors like finasteride (Proscar).

The third type is similar to active PSA, however there is some conformational changes that renders it enzymatically inactive. There is a positive correlation between benign disease and increased percentage of free PSA. Measuring the pPSA may be helpful to increase the specificity for cancer diagnosis.[13]

Another advance in testing is the measurement of serum total sialic acid (TSA) to distinguish patients with Benign Prostatic Hypertrophy (BPH) from patients with PCA. TSA has been found to be elevated in patients with prostate cancer. Furthermore, the TSA is elevated during the final four months of terminal care for those patients with PCA compared to patients earlier in the disease process. The TSA alone is not helpful, but when combined with the DRE, PSA, free/total PSA ratio, it can be helpful in distinguishing patients with cancer form those with BPH, even if their PSA is in the intermediate zone between 4-10 ng/ml.[16]

A retrospective analysis was done to distinguish BPH from PCA when the PSA was less than 10 ng/ml. MRI-based PSA density (PSAD) and prostatic transitional zone (PSAT) were measured. The optimal cutoff point for PSAD was 0.07 ng/ml/cc and 0.15 ng/ml/cc for the PSAT. The authors concluded that the use of PSA with PSAD and PSAT can help avoid unnecessary biopsies in patients with PSA less than 10 ng/ml. It requires a single, axial, T2 weighted prostate scan and takes about 2-6 minutes.[14]

PSA velocity (PSAV) was evaluated in patients with a PSA of 2-4 ng/ml. The sensitivity and specificity of a PSAV of 0.1 ng/ml/year was 81% and 50% respectively. The 10 year cumulative freedom from PCA was 97.1% and 35.2% when the PSAV was less than 0.1 ng/ml/yr respectively ($p<0.05$). The PSAV may be helpful in the risk assessment of patients with low PSA values.[5]

A separate study demonstrated that African American men tended to have higher PSA levels and more variable carcinomas compared with white American men. In this study, Gleason and PSA scores were better at detecting the disease in African Americans versus Caucasians. Therefore, it raised the question that African Americans less than 70 years of age may need to have a lower cutoff PSA value than the usual <4.0 ng/ml due to their high PSA level; and concluded that having a uniform range may lead to an under diagnosis of early stage prostate carcinomas in African Americans.[6]

On the other hand, Britain has chosen not to screen using the PSA test. Observational studies have demonstrated that PSA levels >4 ng/ml have a sensitivity and positive predictive value (PPV) of 79-82% and 32-40% respectively. The Finnish community-based trial demonstrated similar results with 92% sensitivity and a 29% PPV. Therefore, they concluded that due to the inaccuracy of the test and the morbidity from the biopsy and treatment, that population-based screening would not be introduced.[15]

Finally, core needle biopsy is an option for evaluation of the patient suspected of having PCA. A needle is guided by Transrectal Ultrasound (TRUS) and a 1/2" to 3/4" core is removed.[1] Samples from two different areas in the prostate can be used to develop the Gleason score. Each sample is graded 1-5 and the sum is used to develop the Gleason score. This is a grading system on a scale of 1-10. A score of 2-4 is considered low, 5-6 intermediate and 7-10 is considered high.[1] The prognostic value of the Gleason Score was evaluated in 305 patients documenting their disease-specific mean survival (DSMS). Patients with scores of 4-5, 6, 7 and 8-10 had DSMS of 20, 16, 10 and 5 years respectively ($p<.001$). This Gleason score breakdown was also predictive of those who died from prostate cancer. A total of 4.5%, 23.6%, 41.8% and 70.2 % died based on their Gleason scores of 4-5, 6, 7, 8-10 respectively. The DSMS did not significantly differ between 4-5 and 8-10. The authors concluded that Gleason scores are good indicators of long-term prognosis and suggest four categories (4-5, 6, 7, 8-10).[4]

All of the previous testing information is combined to determine the stage of the disease.

Table 1. Decrease in serum PSA from baseline in response to leuprolide implantation [7]

Months Post Implantation	Group 1 (27 patients) (% mean +/- SD, median)		Group 2 (24 patients) (% mean +/- SD, median)	
Month 1	65.5 +/-18.8	67.0	68.5 +/- 17.9	66.0
Month 3	86.1 +/- 15.2	91.0	87.8 +/- 11.7	92.0
Month 6	88.3 +/- 14.0	94.0	89.7 +/- 10.1	92.5
Month 12	84.2 +/- 26.5	95.0	90.7 +/- 10.2	95.5
Month 14	79.3 +/- 44.5	95.0	91.2 +/- 10.6	96.0

Staging is from I-IV with stage IV being the most severe form of the disease. Stage I is low grade and localized. It can not be felt during DRE. Stage II is an intermediate grade, localized and present in more than 5% of the prostate tissue. Stage III has spread outside the prostate to the seminal vesicle, but not to any other organs and can be any grade or score. Stage IV has spread to organs or lymph nodes and can be any grade or score.[1]

Treatment

Treatment options for PCA include orchiectomy (surgical castration), androgen ablation through the use of leutinizing hormone releasing hormone (LHRH) agonists or antagonists, gonadotropin-releasing hormone antagonists (Gn-RH), non-steroidal anti-androgens, combined androgen blockade with a leutinizing hormone releasing hormone agonist or orchiectomy and non-steroidal anti-androgen, radiation, prostatectomy or watchful waiting. If a patient has undergone surgery or radiation and their PSA starts to rise, this is often indicative of recurrent cancer. Studies have evaluated watchful waiting as well as short term and long term androgen ablation on survival. A recent study, showed no difference between radical prostatectomy and watchful waiting in terms of overall survival after 6 years of follow-up.[17] Additional studies evaluated survival when combined androgen blockade was compared to single androgen ablation. However, there are no clear-cut guidelines in place to help practitioners decide whether or not to treat these patients. Nevertheless, it is generally recommended to treat patients with recurrent prostate cancer with androgen deprivation while the PSA is rising and before symptoms develop. This is especially true for patients with aggressive disease (Gleason scores >8).[10]

Androgen Ablation with Leuprolide

Pharmacology/Pharmacokinetics

Leuprolide (Leupron® or Viadur®) is a newly modified Gn-RH antagonist that directly antagonizes LHRH. Leutinizing hormone releasing hormone is normally released from the hypothalamus in a pulse-like manor. This causes a release of LH and follicle-stimulating hormone (FSH). Leutenizing hormone attaches to the leydig cells in the testes and is responsible for promoting testosterone production. Constant exposure to a leutinizing hormone releasing hormone agonist can cause down-regulation of the receptors in the pituitary gland and thus can decrease the release of LH and FSH. This in turn causes a decline in the testosterone level.[10]

Leuprolide is given either intramuscularly or subcutaneously. It has a bioavailability of 94% and peak levels are achieved within 4 hours of the intramuscular injection. Approximately 20-25% of the drug is absorbed into the circulation each week. Once the drug is absorbed, high concentrations can be found in liver, pineal, pituitary and kidney tissues. The plasma half-life is 3 hours.

Viadur® is a subcutaneous formulation that provides continuous, osmotically driven delivery of the medication for up to one year. The patient requires an implant placed in their upper arm. Water from the tissue enters one end of the cylinder through a semi-permeable membrane. This causes the osmotic engine to swell, which then pushes the piston toward the drug compartment, causing a drug-release rate equal to the influx of water. The drug is delivered from an exit port opposite the semi-permeable membrane. The intramuscular formulations that are available include: 1, 3 and 4-month formulations.[2]

Dosing

Leuprolide dosing is dependent on the formulation used. The SC injection can be dosed daily as a 1mg injection and monthly (Eligard®) as a 7.5 mg depot injection. Viadur® contains 72 mg of leuprolide acetate which delivers 120 mcg of leuprolide a day for 12 months. The intramuscular injection can be given as a 7.5 mg dose once monthly, 22.5 mg every 3 months or 30 mg every 4 months.[2]

Clinical Trials

The safety and efficacy of the Viadur® delivery system for patients with advanced PCA was evaluated. The primary endpoint was testosterone suppression at 12 months, but PSA and LH were also evaluated. Fifty-one patients entered the study and 27 received one (group 1) and 24 received two (group 2) implants. Forty-nine patients completed the trial. After initial exposure to leuprolide, an initial LH and testosterone surge occurred during the first week, subsequently castration levels (below 50 ng/dl) were maintained through week 60 of the study. There was no transient increase in testosterone after the implants were removed and a new one was inserted. Testosterone suppression was 100% in both groups. The authors concluded that leuprolide was effective at causing androgen ablation and offered the patient convenience of yearly dosing as opposed to the intramuscular injections.[7]

A separate study evaluated the benefit of 3 to 8 months of neo-adjuvant hormonal therapy with leuprolide 7.5 mg IM monthly and 250 mg of flutamide PO tid before radical prostatectomy. Initially, PSA was less than 10 ng/ml in 63%, 10-20 ng/ml in 27% and greater than 20 ng/ml in 10% of patients in the study. After treatment, PSA values were less than 0.1 ng/ml in 43.3% versus 75% ($p<0.0001$) of patients and 0.3 ng/ml or larger in 21% versus 9.2% ($p<0.0006$) of patients after 3 versus 8 months of treatment respectively. Prostatic volume decreased by 37% after the third month ($p=0.0001$) and an additional 13% in the 8-month group ($p=0.03$). This study suggested that optimal duration of neoadjuvant hormonal therapy may be longer than 3 months. However, the authors concluded that more data was needed to determine whether this longer treatment altered the PSA recurrence rate.[9]

A separate study evaluated the benefit of androgen ablation in reducing the prostate volume so brachytherapy could be initiated. The goal was a prostate volume less than 50 ml. Other reasons for reducing the prostate include a prostate length exceeding 5.5 cm or having some pubic arch bone interference. This retrospective study included 107 patients who were on one of the following protocols for androgen ablation: leuprolide alone (37.4%), leuprolide and bicalutamide (46.8%), leuprolide plus nilutamide (7.5%) or some other combination of LHRH agonist and a non-steroidal anti-androgen combination. The mean percentage in reduction of prostate volume was 33% after 3.7 months of treatment. Among those who had a volume greater than 50 ml at the beginning of the study, 82% had a volume of less than 50 ml after the androgen ablation treatment was completed.[11]

Lee, et al. evaluated the benefit of hormonal therapy in intermediate to high risk PCA patients with radioactive seed implantation. Two hundred and one patients with stage T1b-3b PCA, Gleason scores >7 or PSA >10 ng/ml were treated with permanent seed implantation either with or without hormonal therapy. Sixty-six percent of patients were treated with hormonal therapy (leuprolide or goserelin) and anti-androgen (flutamide or bicalutamide) for 3 months before brachytherapy and 2-3 months afterward. Patients on hormonal treatment had lower PSA values as evidenced by the 66% (hormone) versus 87% (non-hormone) of patients having PSAs >10 ng/ml ($p=0.02$). However, Gleason scores were higher for the hormone treatment group. Forty-nine percent of patients in the hormone group had a Gleason score higher than 7 compared to only 30% in the non-hormone group. The five-year freedom from biochemical failure (FFBF) was evaluated and those with the hormonal therapy faired better (79%) versus the non-hormone group (54%) ($p=0.0001$). This retrospective study showed some beneficial effects of hormonal therapy for patients with intermediate PCA.[12]

Adverse effects

The most common side effects (occur in greater than 2% patients) are listed in Table 2. They are usually a result of testosterone suppression.[7]

Table 2. Adverse events documented during clinical trials [7]

Adverse Event	No. Pts (%)
Asthenia	4 (7.8)
Headache	3 (5.9)
Extremity pain	2 (4.9)
Vasodilatation (hot flashes)	38 (74.5)
Diarrhea	2 (3.9)
Anemia	2 (3.9)
Peripheral edema	4 (7.8)
Bone pain	2 (3.9)
Depression	5 (9.8)
Impotence	3 (5.9)
Testicular atrophy/pain	3 (5.9)
Gynecomastia	2 (3.9)

It is recommended to monitor FSH, LH and testosterone levels during treatment. Bone pain, weakness, urinary tract obstructions and paresthesias can also occur during the first few weeks of treatment. Contraindications include spinal cord compression and hypersensitivity to benzyl alcohol.

There are no reported drug-drug interactions with leuprolide. However, androgens and estrogens can counteract the effects of leuprolide and would therefore not be recommended. Dehydroepiandosterone is a weak androgen and thus may antagonize leuprolide's effect and is not recommended. Agents that can cause hyperprolactinemia (anti-psychotics, metoclopramide, reserpine, and methyldopa) can cause a down regulation of Gn-RH receptors and should not be used concomitantly.

Cost of therapy

See retail costs of treatment in Table 3.

Summary

Leuprolide is a Gn-RH antagonist that is used in advanced PCA to decrease circulating testosterone. It is useful to halt the tumor size and metastases. The main marker for PCA is the PSA. Multiple trials have demonstrated leuprolide to be helpful in decreasing the PSA. It can be used alone or in combination with an anti-androgen or orchiectomy. It usually will increase testosterone for 2-4 weeks after initiating therapy, then decrease testosterone levels to castration levels. Clinical trials for up to 18 months have demonstrated no rebound increases in PSA. It has multiple dosage forms and can be given in a once a year implant in the arm.

Table 3. Retail price for a month supply of leuprolide

Dose	Price
1mg SC QD	$300 - $600
3.75mg IM every month	$300 - $400 (3.75mg) $600 - $800 (7.5mg) usually needed

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