Management of Hot Flashes in Men With Prostate Cancer

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Prostate cancer is the most common cancer in men in North America. One of the treatment options is medical castration using LHRH agonists to reduce the production of testosterone by the Leydig cells in the testes. One of the side effects of this class of agents is hot flashes, which can be very disabling and can affect a man's quality of life. This article will discuss the pathophysiology of hot flashes and the treatment of this common side effect with natural and synthetic female hormones, as well as non-hormonal therapies.

Key words: prostate cancer, hot flashes, LHRH agonists, hormone therapy.

Introduction

Prostate cancer is the most common malignancy in men and the second most common cause of cancer death in older men. There are more than 250,000 new cases of prostate cancer each year in the United States and it causes 40,000 deaths annually. Among Canadian men, prostate cancer is the leading form of cancer incidence, accounting for an estimated 17,800 newly diagnosed cases and 4,300 deaths in 2001.[1] The most common treatment options for localized disease are radical prostatectomy or radiation therapy. For patients who have metastatic disease or recurrence after surgery or radiation therapy, the treatment of choice is hormone deprivation, as prostate cancer growth is promoted by endogenous testosterone. Hormone deprivation was achieved in the past by either orchiectomy or using oral estrogens such as diethylstilbestrol. Oral estrogens were as efficacious as orchiectomy and lessened the psychological impact created by removal of the testes. However, estrogens were associated with significant side effects, including increased risk of cardiovascular disease and gynecomastia. Currently, hormonal ablation can be accomplished using luteinizing hormone releasing hormone (LHRH) agonists, such as leuprolide acetate (Lupron) or goserelin acetate (Zoladex). All forms of hormonal ablation have an incidence of hot flashes ranging from 50–66%.[2] This can be an incapacitating symptom that significantly affects a man's quality of life. This article will review the pathophysiology of hot flashes and the available treatment for this common side effect of androgen ablation.

Incidence and Pathophysiology of Hot Flashes Following Prostate Cancer Treatment

Hot flashes, flushing or hot flushes are synonymous words for episodes of sensation of increased warmth, usually in the upper body and face. Technically, hot flushes is the correct term, but hot flashes is more commonly used. Hot flashes are relatively common in men who undergo androgen suppression therapy for prostate cancer, and may persist for years. Hot flashes occur in two-thirds of the men who receive drugs that inhibit the production of male hormone, and at least 50% of the men who have undergone removal of the testicles. In many patients the incidence of hot flashes decreases over time, whereas in other patients the flushing continues unabated for years.[3] For example, in a study of 63 men treated with orchiectomy or LHRH agonists, 68% reported hot flashes and 48% still had hot flashes five years after treatment.[4]

The pathophysiology of hot flashes in men undergoing androgen deprivation therapy is not fully understood, but may be similar to the mechanisms of hot flashes in menopausal women. In men, a sudden decrease in androgens as a result of surgical or medical castration for prostate cancer is the triggering event for hot flashes. Medical castration, which involves the chronic occupancy of the gonadotropin-releasing hormone (GnRH) receptors in the pituitary by LHRH receptor agonists, prevents the production of testosterone in the testes. The loss of androgen and perhaps the resultant altered levels of LH play a role in the vasomotor instability that characterizes hot flashes. The same situation occurs with surgical castration, i.e., the sudden cessation of androgen production by the testes.

Androgens (and estrogens) maintain vasomotor tone. Men with reduced androgen levels have increased skin temperature and blood flow, resulting in uncomfortable flushing and sweating. The reason for the loss of vasomotor tone in response to decreased androgen levels is still uncertain. In women, decreased beta-endorphin during menopausal hot flashes has been observed, and it is thought that this may also occur in men with androgen deprivation. In a recent study of men with hot flashes after androgen ablation for prostate cancer, the potent vasodilator, calcitonin gene-related peptide, was noted in the serum of men during hot flashes. This may provide an explanation for hot flashes since estrogens and androgens are known to regulate beta-endorphins which, in turn, regulate calcitonin gene-related peptide.[5]

The events that trigger hot flashes in men who receive endocrine treatment for prostate cancer are not completely understood. Although the sudden perceived increase in body temperature, reddening of the skin and profuse sweating characteristic of these episodes usually occur spontaneously, hot flashes may be

triggered in some instances by changes in body position, ingestion of hot liquids or alterations in the environmental temperature. It is likely that the symptoms are attributable to changes in catecholamine levels in the hypothalamus, which appears to be the neurotransmitter responsible for LHRH production. Due to the profound decrease in serum testosterone, a loss of regulatory feedback in the hypothalamus occurs, leading to increased catecholamine levels. Since the thermoregulatory centre has a close anatomic relationship to the LHRH-secreting neurons, the increase in catecholamine concentration is likely to stimulate the LHRH-secreting neurons, as well as the neurons involved in body temperature control. This stimulation of the thermoregulatory system leads to heat loss, which is manifested clinically as a hot flash.[6]

Signs and Symptoms

Hot flashes occur with a reddening of the skin and often with sweating. The episodes may last anywhere from a few seconds to several minutes; however, most episodes usually last two to three minutes. Symptoms associated with hot flashes can be graded from mild to severe, as shown in Table 1. A study of 138 medically or surgically castrated men presented at the 2001 American Society of Clinical Oncology Annual Meeting showed that hot flashes occurred an average of four times per day.[7] Younger men were more likely to report hot flashes than older men. In addition to flushing and sweating, the majority of men reported warmth, dry mouth and clammy skin. Fatigue and weakness were experienced in 45% of men, whereas emotional symptoms such as distress, anxiety and irritability were reported by less than 40%. However, secondary symptoms, such as sleep disturbance, interference with the ability to enjoy life and interference with daily activities, were experienced by the majority of men in this study.[7]

Treatment

A range of treatments for hot flashes has been studied (Table 2). One option is to limit intervention to alternative support and education, since some survey results have suggested that less than half of the patients who experience hot flashes would consider pharmacological intervention.[7] In patients with more severe symptoms, prescription drugs have been considered.

Natural Female Hormones

Historically, one of the earliest treatments for hot flashes is the use of a female hormone, usually diethylstilbestrol (Stilbestrol). Given in low doses (as low as 0.25mg / day), diethylstilbestrol treatment is at least 70% effective in treating hot flashes.[8] Unfortunately, the female hormone causes breast swelling or tenderness in almost all patients.[9] More importantly, the use of diethylstilbestrol may increase the risk of heart attack or stroke.[10] Many reports suggest these significant side effects do not occur at low doses (1mg / day) and may possibly be prevented with the concomitant use of Aspirin or other anticoagulants. In one study, estrogens were found to lead to significant improvement and were well-tolerated with no patient discontinuation of therapy due to side effects.[6] In patients who are at high risk for heart attack or stroke, the use of diethylstilbestrol is probably contraindicated, but it is likely the most simple and least expensive treatment available.

Table 1
Hot Flash Scoring Scale

Severity	Score	Duration	Observations
Mild	1	<1 minute	– warm, slightly uncomfortable – no sweating
Moderate	2	<5 minutes	– warmer, perspiration – removal of some clothing
Severe	3	>5 minutes	– burning, warmth – disruption of normal life – difficulty sleeping – excessive perspiration

Table 2
Treatments for Hot Flashes in Men

Treatment	Examples
Natural female hormones	– diethylstilbestrol
Synthetic female hormones	– megestrol acetate – medroxyprogesterone acetate
Non-hormonal therapies	– clonidine – gabapentin – venlafaxine

Synthetic Female Hormones

Megestrol acetate (Megace)—a synthetic derivative of the hormone progesterone—is almost as effective as estrogen in the management of hot flashes. The usual dose of megestrol is one 20mg tablet twice a day. One study of 66 men showed an 85% reduction of hot flashes in the treatment group compared with 21% in the placebo group.[11] A follow-up study to determine the long-term effectiveness of megestrol in the management of hot flashes found 45% of those contacted had continued to take megestrol for three years or longer with continued control of hot flashes.[12] Megestrol acetate has a very similar response rate to diethylstilbestrol, but is associated with substantially fewer side effects than diethylstilbesterol. In some women using large doses of megestrol acetate (e.g., 160mg / day for weight loss due to HIV or breast cancer), retention of water is seen with edema of the legs. Howev-

er, this is seen infrequently with the doses used in men for treatment of hot flashes. There have been some reported cases of PSA increases in patients with prostate cancer using even the low megestrol acetate doses for control of hot flashes.[13]

Medroxyprogesterone acetate (Depo-Provera) is a drug with similar properties to megestrol but it is administered by injection. The suggested dose is 300–400mg as an intramuscular injection once a month, although some physicians give it on an "as needed basis" for the management of symptoms of hot flashes. Weight gain and fluid retention can be a problem in some patients. Complete or partial responses have been reported in 70–90% of men. In one study, the response lasted four to 12 months in over 60% of participants, and over a year in 25% of participants.[14]

Non-hormonal Therapies

Clonidine (Catapres) is an alpha-adrenergic agonist used primarily for the treatment of hypertension. Although its effectiveness has generally been studied in women, the role of clonidine in reducing hot flashes in men also has been investigated. Clonidine is generally used as a patch but can be taken orally. A 1982 study found that oral clonidine at a dose of 0.2–0.4mg twice daily reduced hot flashes in women by 46%.[15] Side effects included nausea, dizziness and fatigue. A recent University of Rochester Cancer Centre study found clonidine to have a "small beneficial effect" in reducing hot flash frequency, duration and severity.[16] This double blind, placebo-controlled clinical trial reported that 0.1mg / day oral clonidine was effective in reducing tamoxifen-induced hot flashes in postmenopausal women. The clonidine patch is applied once per week and has fewer side effects than the oral preparation. In one randomized, prospective, double blind study, 80% of women who received the clonidine patch reported fewer hot flashes compared to 36% of those given the placebo.[17] Parra and Gregory studied transdermal clonidine in seven men experiencing hot flashes after bilateral orchiectemy for prostate cancer, and found that a patch containing a dose of 0.1mg / week and changed every seven days decreased or abolished hot flashes.[18] However, hypotension and allergic skin reactions to the transdermal preparation have limited the use of this medication for the management of hot flashes.[19] Further, since a subsequent randomized, double blind crossover clinical trial of 70 men with prostate cancer found that transdermal clonidine did not significantly decrease hot flash frequency or severity post-orchiectomy,[20] the role of clonidine as a treatment for hot flashes in men remains uncertain.

Ergotamine, belladonna and phenobarbitol (EBP) is a drug combination that has been used for the treatment of hot flashes in menopausal women. EBP, which contains 40mg phenobarbital, 0.6mg ergotamine tartrate and 0.2mg belladonna, is most commonly prescribed for patients with migraine headaches but has been approved by the FDA for the treatment of menopausal hot flashes. There has been minimal exploration of EBP in men; however, in a study of 21 prostate cancer patients receiving the combination of phenobarbital plus ergotamine for hot flashes, a 5% complete response and 45% partial response was observed.[8] The dose of EBP is one tablet in the morning and one in the evening with a weekly maximum of 16 tablets. It has the potential of interacting with CNS depressants, anticholinergics and monoamine oxidase inhibitors and is not recommended in patients with peripheral or coronary vascular disease and hypertension. It also should be avoided in patients with glaucoma, bronchial asthma and obstructive uropathy. In addition, due to the addictive potential of phenobarbital, EBP should not be prescribed for long-term use.[21]

Gabapentin (Neurontin), an anticonvulsant structurally related to the neurotransmitter GABA, may reduce the frequency of hot flashes, according to a recent report. In this case report of six patients, including one prostate cancer patient, an average 87% reduction in frequency of hot flashes was reported.[22] A recent case report demonstrated that gabapentin almost completely resolved the symptoms of hot flashes in a 70-year-old man with advancing prostate cancer who had failed to respond to clonidine, megestrol acetate, diethylstilbestrol and venlafaxine.[23] More research is needed to determine the potential efficacy of gabapentin for the reduction of hot flashes in men.

Venlafaxine (Effexor) is an antidepressant that has been explored as another non-hormonal strategy to reduce the incidence of hot flashes. Both extended release and immediate release formulations have been used in exploratory trials. In one small study of 16 men receiving 12.5mg venlafaxine orally twice daily, 10 reported a greater than 50% reduction in hot flashes after four weeks of drug treatment.[24]

Summary

As long as the reduction of testosterone remains the primary treatment for advanced prostate cancer, hot flashes will continue to be a problem. There are several treatment options, but it is recommended to begin with 20mg megestrol acetate twice a day and, if effective, gradually increase or decrease the dose to the lowest effective level. Medroxyprogesterone acetate is another acceptable first-line treatment, and if not effective, diethylstilbestrol can be started at 1.0mg per day and slowly increased or decreased to find the lowest but most effective medication level. However, diethylstilbestrol should only be used with the understanding that breast tenderness and a possible increased rate of stroke or heart attack might result.

Although hot flashes remain an incapacitating side effect as a consequence of prostate cancer treatment, most men with this condition can be helped and the symptoms controlled with medical management. ◆

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