Managing hot flushes in men receiving androgen deprivation therapy for prostate cancer

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In this series, the authors present cases of men being treated with androgen deprivation therapy, and highlight management strategies to prevent and treat associated toxicities. In this fourth article, the authors consider the management of hot flushes.

Hot flushes are characterised by the subjective sensation of a rise in temperature in the face and trunk and are accompanied by cutaneous vasodilatation predominantly in the face, throat and extremities, usually followed by profuse sweating. Following the administration of LHRR agonists, the steep decline in serum luteinising hormone and follicle-stimulating hormone results in the release of hypothalamic catecholamines, in particular norepinephrine. These flood the thermoregulation centre in the upper hypothalamus, resulting in abnormal and poorly regulated peripheral vasodilatation and the occurrence of hot flushes and perspiration.

It is estimated that up to 80 per cent of patients on androgen deprivation therapy (ADT) will experience hot flushes and up to 27 per cent of patients report them as their most troublesome side-effect. They can improve spontaneously, but most patients will continue to experience these symptoms for as long as they are receiving ADT. Hot flushes can significantly impact on a patient’s quality of life. Given that exposure to ADT may be lifelong in the palliative setting and may be two to three years in the adjuvant setting, there is a need to address all associated side-effects and deal with them effectively in order to improve compliance with treatment and quality of life.

METHODS OF REDUCING HOT FLUSHES

A variety of treatments have been assessed for reducing hot flushes, including hormonal therapies, complementary treatments and non-hormonal drug treatments such as clonidine, gabapentin and selective serotonin reuptake inhibitors (SSRIs). Most of these treatments have been evaluated predominantly in postmenopausal women and those receiving therapy for breast cancer. There have been far fewer trials in men undergoing ADT for prostate cancer. Those trials that have taken place have been based on small numbers and only a few have compared the efficacy of one treatment against another.
Oestrogens and progesterones

Sex hormone treatments with oestrogens and progesterones were some of the earliest therapies explored in the treatment of hot flushes and are often successful.

Cyproterone acetate is a synthetic antiandrogen with pro-oestrogenic effects and can be administered both orally and intramuscularly. A study of intramuscular depot injections of cyproterone acetate 300mg every two weeks found it reduced hot flushes by 80 per cent.6 However, the medication can be hepatotoxic and it is important to monitor liver function tests carefully. Cyproterone acetate can also have an unfavourable effect on lipid profile and increases cardiovascular risk. At lower doses, the side-effects include fatigue and gynaecomastia.

In a double-blind placebo-controlled trial, 20mg megestrol acetate twice a day was found to be well tolerated and efficacious in decreasing the frequency of hot flushes in men receiving ADT.7 In another study, 70 per cent of men receiving either diethylstilbestrol or megestrol acetate had a complete resolution of symptoms and 20 per cent had up to 50 per cent decrease in the severity of hot flushes.8 The main disadvantage of using oestrogens is the associated risk of cardiovascular and thromboembolic complications, which can occur even at low doses. The other potential drawback is the risk of developing tender gynaecomastia. Furthermore, while lower doses improve the side-effect profile of these drugs, their efficacy also decreases.4 The side-effect profile of progesterones is more favourable, with the main side-effect being weight gain.

Neuroendocrine agents

Clonidine is an alpha-2 receptor antagonist that reduces the release of noradrenaline in the hypothalamus. In addition, it stabilises the peripheral vasculature and reduces the vasodilatation seen with hot flushes.7 Given these characteristics, it should be ideal in reducing hot flushes. However, clonidine is inferior to sex hormonal replacement therapy and carries a higher risk of side-effects.9 These include dry mouth, constipation, drowsiness and orthostatic hypotension. Gabapentin has also been reported to reduce the incidence of hot flushes in some case studies and pilot studies.9

Selective serotonin-reuptake inhibitors

This class of drugs is used to treat depression and pilot trials have shown that they can reduce the incidence of hot flushes in more than 50 per cent of men.10 Randomised clinical trials have also confirmed these findings in women undergoing treatment for breast cancer.11 It is estimated that 10–20 per cent of patients suffer side-effects from SSRIs, which commonly affect the central nervous or gastrointestinal systems. The gastrointestinal symptoms include nausea, anorexia and weight loss. Central nervous system symptoms include headaches, agitation and tremor. Abrupt withdrawal can result in sweating, dizziness and confusion.

A prospective double-blind randomised controlled trial compared the efficacy of venlafaxine 75mg per day, medroxyprogesterone acetate 20mg per day and cyproterone acetate 100mg per day in preventing hot flushes in 311 men receiving LHRH analogues for prostate cancer.12 It concluded that all three therapies were effective in reducing hot flushes after six months of treatment, but both the hormonal treatments were significantly more effective than the SSRI venlafaxine. There was little difference in tolerance between the three treatments. The number of patients that presented with adverse events leading to discontinuation of the drug was comparable in all three treatment groups and overall compliance was greater than 96 per cent; however, the follow-up period was only six months from randomisation.12

Complementary therapies

A wide variety of complementary and alternative therapies have been used to treat hot flushes. The majority of the data investigating the use of these agents comes from work into their use in menopausal women and patients being treated for breast cancer. There are only a few that have specifically investigated their use in men with prostate cancer receiving ADT.

Vitamin E is a commonly used remedy for women with breast cancer suffering from hot flushes, but in a trial it decreased the symptoms by only 25 per cent compared to placebo, which decreased symptoms by 22 per cent.13 Furthermore, a trial to determine the long-term effect of vitamin E and selenium on risk of prostate cancer in healthy men actually found an increased risk of prostate cancer with vitamin E supplementation.14

Soya products contain phytoestrogens, which may relieve symptoms associated with menopause such as hot flushes. However, results from several randomised controlled trials have not found soya products to be any better than placebo in reducing hot flushes.5

Acupuncture was evaluated in a study where 60 men receiving LHRH agonists for prostate cancer had auricular acupuncture weekly for 10 weeks. All the patients completed the treatment and 95 per cent reported a decrease in the severity of their symptoms.15

Herbal remedies such as red clover, black cohosh and evening primrose oil have also been used in men and women for the treatment of hot flushes. Red clover is a source of phytoestrogens and as yet there is no strong evidence that it is effective in reducing hot flushes. Black cohosh has been studied in women with menopausal symptoms, but again there is no evidence that it is superior to placebo in alleviating hot flushes. Neither treatment has been studied in men with hot flushes from ADT. Furthermore, some herbal remedies can have anticoagulant activity and adverse interactions with other medications.5
CONCLUSION
In conclusion, we have presented the case of a man experiencing hot flushes secondary to ADT. These symptoms can be difficult to improve and can often continue throughout treatment. It is important to acknowledge the effect that hot flushes can have on a patient’s quality of life and to suggest lifestyle adjustments to help alleviate the discomfort they cause.

There are several hormonal treatments available that are efficacious but all can have detrimental side-effects. Progestins such as megestrol acetate appear to have the best side-effect profile. Other newer agents such as SSRIs are likely to be less effective but more tolerable. There have been very few head-to-head comparisons between treatments and little is known about the long-term efficacy and side-effects.

At present there are very few data available to support the use of complementary therapies and further work is needed to determine their safety and efficacy before any of them can be recommended.

Declaration of interests
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REFERENCES