Healthy lifestyle for men living with hormone therapy for prostate cancer

HEATHER A. PAYNE, ROBERT LAING, ROBERT THOMAS, BERTRAND TOMBAL AND JANIS TROUP

This report is based on discussions held at the 7th Annual Meeting of the British Uro-oncology Group in Birmingham last September. One topic of equal value to all healthcare professionals spanning primary and secondary care was a review of developments in hormone therapy for prostate cancer and the ways to reduce the associated toxicities of testosterone depletion.

Many men benefit from treatment with androgen deprivation therapy (ADT), both in terms of symptomatic relief and increased survival when ADT is given in combination with radical therapy. It is vital that healthcare professionals and men are aware of the toxicities of this therapy and that they are fully informed as to the best ways to reduce side-effects and monitor and treat any complications early in order to maintain a healthy life while they live with hormone therapy.

DEVELOPMENTS IN HORMONE THERAPY FOR PROSTATE CANCER

Hormone therapy in the form of ADT has an important role in the management of prostate cancer. ADT was initially achieved by surgical castration, which results in a rapid reduction in the circulating testosterone to <2nmol/l within 12 hours. Surgical orchidectomy was found not only to reduce the painful symptoms of the disease, but also to slow the overall progression of prostate cancer.

ADT with castration-based therapy remains the first line and mainstay of management for men with advanced or metastatic disease. Although an effective therapy, the surgical approach had a psychological impact on many men and this led to the development of medical castration in the form of luteinising hormone-releasing hormone (LHRH) agonists, over 20 years ago.

LHRH agonists are administered as subcutaneous or intramuscular long-acting depot implants every one to three months. They are associated with an initial flare of testosterone, but chronic administration results in pituitary depletion of LH and therefore testosterone to castrate levels. The initial testosterone surge following the first exposure to LHRH agonists may theoretically result in a tumour flare, which can be dampened by treatment with an oral anti-androgen before the first LHRH agonist injection and continuing to cover the period of testosterone surge for one to two weeks.

A recent development in castration-based therapy has been the introduction of gonadotrophin-releasing hormone (GnRH) antagonist therapy; Professor Bertrand Tombal presented data on one such agent.1 GnRH antagonists produce a direct and rapid decline of LH, follicle-stimulating...
hormone and testosterone. Because there is no stimulation of GnRH receptors, there is no testosterone surge or clinical flare and there is a rapid suppression of testosterone and prostate-specific antigen (PSA).

The GnRH antagonist therapy degarelix (Firmagon) was approved on the basis of a pivotal phase 3 study, in which it was shown to be as effective as standard leuprolide on the regulator-specific endpoint of lowering testosterone <0.5ng/ml between days 28 and 364. Degarelix also had a faster onset of action and a more rapid decline in PSA than leuprolide given at a dose of 7.5mg per month. Suppression of PSA and testosterone was maintained throughout the study.

Professor Tombal also reported the results of a preplanned subanalysis of the study, which demonstrated that in metastatic disease, degarelix patients did not display the rises in serum alkaline phosphatase (S-ALP) seen in patients receiving leuprolide after one year of treatment ($p=0.014$ at day 364). S-ALP has been associated with progression of bone metastases and reduced overall survival. The exact significance of this is currently unclear as there was no bone scan monitoring in this trial.

In addition, a further subanalysis of the one-year study demonstrated a 10 per cent difference in PSA progression, with the greatest benefits for degarelix seen in men with metastatic disease and the highest baseline level of PSA. Results of the impact of degarelix on robust endpoints such as time to objective progression and survival are pending. There remains a need for further ongoing studies to confirm the findings and to understand these suggested advantages for degarelix as therapy for prostate cancer.

Degarelix is licensed for treatment of advanced hormone-dependent prostate cancer in the UK and has the clinical advantage of a rapid and sustained testosterone reduction without the need for co-administration of an anti-androgen to prevent testosterone and potential tumour flare, which can be of particular concern for those men presenting with incipient nerve root or spinal cord compression or urological obstruction.

In recent years, hormone therapy has evolved to play an increasingly important role in the management of the other stages of prostate cancer, both alone and in combination with radiotherapy and/or surgery. Locally advanced or high-risk localised (Gleason grade ≥8, PSA ≥20) prostate cancer is associated with a significant risk of undetectable microscopic metastases. The optimal treatment for this group is with a multimodality approach and external beam radiotherapy in combination with ADT for two to three years. This is now considered standard of care. There is a wealth of robust evidence to support combination therapy from a number of multicentre randomised clinical studies. These have all demonstrated highly significant improvements in disease-specific and overall survival outcomes for this group of patients. ADT is also commonly used in the neoadjuvant setting prior to radical radiotherapy for men with low- and intermediate-risk prostate cancer.

MANAGING THE EFFECTS OF ADT

The side-effects of ADT are well documented and include erectile dysfunction, loss of libido, hot flushes, osteopaenia/osteoporosis, reduced lean muscle mass and strength, breast swelling, mastalgia, weight gain, tiredness, anaemia, mood swings, depression and metabolic complications. These toxicities should not prevent the use of hormone therapy for those men who will benefit, but the potential risks should be discussed so that early detection of toxicities and intervention can be achieved.

DIET AND THE METABOLIC SYNDROME

The metabolic syndrome (Box 1) can potentially be a cause for significant morbidity for men treated with ADT. Dr Robert Laing stated that the metabolic syndrome is present in 50 per cent of ADT-treated men compared to 20 per cent of disease- and age-matched controls. The hypogonadal state is associated with adverse changes, which include decreased insulin sensitivity, arterial stiffness, QT-interval prolongation, increased body mass index, reduced lean body mass, osteoporosis and dyslipidaemia. Unlike men with the classic syndrome, those treated with hormone therapy have a higher high-density lipoprotein cholesterol and increased subcutaneous, rather than intra-abdominal, fat mass. There are several reports of increased cardiovascular morbidity and mortality for men treated with ADT compared to age-matched controls.

Individual dietary components that have been shown to effect the development of metabolic syndrome include consumption of saturated fats, monosaturated fats and n-3 fatty acids. A variety of diets have been proposed that may prevent or reduce the incidence of metabolic syndrome in the general population. These include the Mediterranean diet (high fruit and vegetables, low glycaemic index [GI], high mono-unsaturated fats), Ornish diet (very low total fat, high vegetable, low GI, no meat) and the South Beach diet (low GI/carbohydrate, high fat, regular snacks).

**BOX 1. Classic metabolic syndrome in men**

Three out of the following five risk factors:

- Abdominal girth >102cm
- Fasting glucose ≥6.1mmol/l
- Blood pressure ≥130/85mmHg
- Triglycerides ≥1.7mmol/l
- High-density lipoprotein cholesterol <1.0mmol/l

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There are very few data on dietary manipulation to prevent ADT-associated metabolic syndrome, but studies show that it is possible to reduce risk of progression to diabetes in people with impaired glucose tolerance in the general population.

In MADAMS, a pilot study conducted by Dr Laing, 40 men treated with hormone therapy at his centre were randomised between ADT alone or ADT with lifestyle intervention (GI diet and exercise) in addition to metformin therapy (850mg once daily for two weeks, then 850mg twice daily as tolerated). Results at six months demonstrated a reduction in metabolic syndrome in the intervention arm. There was a decrease in abdominal girth, weight and body mass index as well as a reduction in physical effects in this group. However, biochemical markers of insulin resistance did not significantly differ between each group.

The pilot study has demonstrated the potential of a preventative role of metformin and lifestyle changes in reducing metabolic syndrome in men treated with ADT. This will now be evaluated in a larger randomised multicentre study, which will also aim to ascertain the relative importance of the separate interventions and whether overall survival can ultimately be improved by this approach, because of a reduction in cardiovascular toxicity. It is important that all men treated with ADT have regular monitoring for metabolic syndrome during their therapy and early intervention for complications such as hypertension and dyslipidaemia.

**EXERCISE AND PROSTATE CANCER**

The importance of exercise to reduce side-effects and risks of hormone therapy was further discussed by Professor Robert Thomas (Box 2). The loss of bone density is a recognised complication of ADT and is not usually apparent until it causes serious complications. On average, a 2.2–5.4 per cent loss of bone density is seen in the spine and 0.5–6.5 per cent in the hip over the course of a year.

Retrospective information from the records of over 50,000 men diagnosed with prostate cancer in the Surveillance Epidemiology and End Results (SEER) database has been evaluated to determine the fracture risk for men treated with ADT. The results demonstrated the occurrence of any fracture in 19.4 per cent of men treated with ADT compared with 12.6 per cent of men with prostate cancer who were not androgen-deprived. The relative risk of fractures increased with the duration of therapy.

The overall risk of osteoporosis can be reduced by ensuring sufficient vitamin D and calcium in the diet, with advice to eat more foods such as soya products, spring greens, beans and fish with soft bones (sardines and pilchards) and, if necessary, adding a calcium/vitamin D supplement. It is also important to maintain a healthy weight, as men with a body mass index greater than 19 are also at additional risk of osteoporosis.

In men receiving ADT, progressive resistance training improves muscle strength, functional performance and balance, while gentle regular exercise reduces cancer-related fatigue, especially when delivered in supervised programmes. Regular exercises are also important to maintain and build healthy bones. These should include weight-bearing exercises (regular walking), flexibility exercises (gentle yoga) and resistance exercises that build muscle (weight training or water exercise).

A randomised controlled trial of resistance and aerobic exercise in 121 men receiving radical radiotherapy plus ADT for prostate cancer demonstrated a significant improvement in muscle strength, abdominal fat, triglyceride levels and quality of life.

As well as improving wellbeing and reducing the risks of ADT, exercise appears to have a direct anticancer effect. A trial in the USA, involving men who were managed by active surveillance, showed that men randomised to a healthy eating and exercise programme had a significantly slower rate of cancer progression. A larger UK trial showed that nearly 40 per cent of men with progressive PSA on either active surveillance or a relapse after treatment managed to slow the rate of progression by healthy eating and exercise, delaying the need for ADT.

A recent study showed that men who exercised for more than two hours a week had a better overall survival and lower risk of prostate cancer relapse. Those who exercised for more than five hours a week had a lower risk of dying specifically of prostate cancer.

Professor Thomas is author of the book *Lifestyle and cancer: the facts* (www.cancernet.co.uk) and chair of the Macmillan exercise.
lifestyle and cancer expert advisory committee, which aims to persuade doctors and specialist nurses to encourage and motivate their patients to exercise after prostate cancer.

This initiative also aims to provide practical facilities for men to exercise in a safe and supervised environment. This group has ensured that cancer rehabilitation is now included in the National Activity Health Referral Scheme. Training companies are now designing courses for UK exercise professionals to be qualified in cancer rehabilitation (www.wrightfoundation.com). This will enable doctors to prescribe a 12-week exercise programme for their men at municipal gyms. For further information about this initiative, see http://www.cancernet.co.uk/newsletter.pdf

FURTHER RESOURCES
In 2009, the British Uro-oncology Group, together with Prostate UK (now Prostate Action) acted as lead advisors to Ferring Pharmaceuticals Ltd in the development of a DVD for men being treated with ADT, providing practical advice for men to maintain a healthy lifestyle during therapy. The DVD gives an overview of the disease, including a patient perspective of being diagnosed with prostate cancer and treatment options and their complications for different stages of the disease.

There is a chapter on the importance of a healthy diet, including involvement of a dietician and celebrity chef, and advice on recommended food types with ‘prostate-healthy’ recipe suggestions. The importance of exercise for healthy living and the relevance to men on hormone therapy is demonstrated with a live workout exercise programme with an exercise professional and patients. The DVD also covers advice on lipid and blood pressure numbers, prostate-related test results, sexual dysfunction, osteoporosis, hot flashes, mood and cognitive changes. The DVD is available from Prostate Action and Ferring Pharmaceuticals Ltd.

Declaration of interests
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