Management of fatigue and anaemia in men treated with androgen deprivation therapy

ALEJO RODRIGUEZ-VIDA, SUBHRA CHOWDHURY AND SIMON CHOWDHURY

In this series, the authors present cases of men being treated with androgen deprivation therapy, and highlight their management to prevent and treat associated toxicities. This sixth and final article will consider the management of fatigue and anaemia.

In spite of the recent approval of new, effective anti-cancer drugs such as docetaxel, abiraterone and enzalutamide, ADT remains the initial cornerstone treatment of patients with metastatic prostate cancer. Because these patients can have a life expectancy of eight years or more and will receive ADT as a lifelong medication, the appropriate screening and management of its adverse events are highly relevant.

Among common side-effects of hormone therapy, patients usually perceive fatigue to be more distressing than hot flushes, osteoporosis or erectile dysfunction because, unlike the latter, fatigue cannot generally be managed successfully by medications. However, due to its subjective nature, fatigue is usually an underdiagnosed and undertreated symptom.

Importantly, fatigue in prostate cancer patients is multifactorial and contributed to by anti-cancer treatment, chronic disease anaemia, undertreatment and underlying cancer-related fatigue. As anaemia is at the same time a known adverse event of ADT, fatigue and anaemia are therefore two interconnected entities in which appropriate management is essential for minimising hormone therapy-related morbidity.

FATIGUE

Fatigue can be defined as the subjective sensation of lacking energy or being exhausted related to cancer or cancer treatment that is not proportional to recent activity and interferes with daily activities. ADT-induced fatigue is a complex multidimensional entity that shares many overlapping features with other ADT-related toxicities such as depression, low

THE CASE

A 75-year-old man presented to his GP with decreased energy levels, low appetite and pelvic pain. A blood test demonstrated a haemoglobin level of 9.0g/dl and a prostate-specific antigen (PSA) of 350ng/ml. Prostatic biopsy revealed an adenocarcinoma of the prostate with a Gleason score of 9 (5+4). Staging scans showed the presence of widespread bone metastases and pelvic and retroperitoneal metastatic lymphadenopathy. He was commenced on androgen deprivation therapy (ADT) with a luteinising hormone-releasing hormone (LHRH) agonist achieving a PSA nadir of 10.5ng/ml. Four months after starting hormone treatment, he complained about worsening fatigue and mild shortness of breath on exertion. A routine blood test evidenced a haemoglobin of 7.9g/dl with a mean corpuscular volume of 92fl.

Alejo Rodriguez-Vida, MD, Clinical Fellow Medical Oncologist, Guy’s and St Thomas’ NHS Foundation Trust; Subhra Chowdhury, MB BS, BSc, MRCP, FRCR, Locum Consultant in Clinical Oncology, Royal Free London NHS Foundation Trust; Simon Chowdhury, MB BS, MA, MRCP, Consultant Medical Oncologist, Guy’s and St Thomas’ NHS Foundation Trust, London

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mood and reduced libido. Depression and low mood can cause fatigue and fatigue may lead to depression and low mood. Moreover, fatigue interferes with usual functioning, contributing to functional dependence, sleep disturbances, frailty and decreased quality of life.

The pathophysiology of ADT-induced fatigue is multifactorial and complex. Loss of muscle mass (sarcopenia), increase in fat mass and depression, along with genetic predisposition, are the most probable underlying mechanisms. Physiological sarcopenia with advancing age is known to be related with normal gradual decline in testosterone levels. Because androgens promote lean body mass over fat mass, hormone therapy iatrogenically accelerates the loss of muscle bulk by inducing castrate levels of testosterone. On average, men lose almost 2kg of lean muscle mass during the first 12 months of ADT. Sarcopenia then leads to decreased functional mobility and muscle weakness, which are the most relevant components of fatigue and frailty.

Ultimately, genetic variation factors might modulate the development of ADT-induced fatigue. One study looking at the relationship between changes in fatigue following initiation of ADT in prostate cancer patients and single nucleotide polymorphisms evidenced that patients who carry specific variants in genes regulating pro-inflammatory cytokines are susceptible to increased ADT-induced fatigue.

The extent of the problem
Fatigue is one of the most frequent adverse events described by prostate cancer patients on hormone therapy. The prevalence of fatigue in published trials varies from 66% to 77% per cent and it is more common in patients treated with an LHRH agonist than with bicalutamide. Similarly, greater tumour burden, older age and prolonged treatment duration are usually associated with higher levels of fatigue.

Stone and colleagues prospectively analysed a group of 62 men on LHRH agonist and cyproterone acetate treatment for prostate cancer and assessed fatigue and muscle strength at baseline and after three months of therapy. The study revealed a significant increase in median fatigue prevalence and a small but significant increase in hand-grip fatigability after three months of therapy. There was also a significant decline in the mid-arm muscle circumference with no alteration in the body mass index, suggesting a change in body composition, ie a loss of muscle bulk with no overall weight gain, probably due to increased fat mass. Interestingly, on multivariate analysis, psychological distress and depression explained only 28 per cent of the variance in fatigue scores. Another larger cross-sectional study, assessing 198 men on long-term ADT, showed that depression and bone pain were the only independent factors associated with increased ADT-induced fatigue.

Treatment options
Lifestyle changes
Physical exercise and dietary counselling are considered the best first-line treatment interventions in order to mitigate ADT-induced fatigue. Various studies have shown the efficacy of regular exercise programmes in combating weakness and muscle wasting and reducing the frequency and severity of fatigue. Galvão and colleagues randomised 57 patients with non-metastatic prostate cancer on ADT to a programme of resistance and aerobic exercise or usual care. Patients in the exercise arm experienced significantly less fatigue, a higher quality of life and showed an increase in lean muscle mass and better muscle strength compared with usual care.

Moreover, physical exercise contributes to alleviate depression and anxiety and reduces other ADT-related adverse events such as insulin resistance and decreased bone density. Therefore, prostate cancer patients should be repeatedly counselled regarding regular physical exercise prior to and during ADT. Recommended exercise programmes should be tailored for every patient and should ideally include 15–20 minutes of cycling or jogging twice a week with general flexibility exercises performed prior to and after the exercise programme.

Similarly, dietary counselling is recommended to counteract the increased fat mass related to ADT and contributes to ameliorate fatigue and quality of life. Practical and realistic dietary advice, such as replacing saturated acids with unsaturated fat, consuming fruits and vegetables on a regular basis and increasing dietary fibre consumption, should be given prior to and during ADT to promote general health and wellness.

Intermittent ADT
Intermittent hormone therapy with LHRH agonist or antiandrogen has classically been a common strategy aiming to minimise ADT-related toxicities. Several randomised phase 3 trials have compared the intermittent and continuous ADT approaches in prostate cancer. While improvement in hot flushes, low libido and erectile dysfunction with intermittent ADT has been described in various studies, changes in fatigue have less frequently been assessed and available data remain controversial. In a recent randomised study, intermittent ADT was associated with a non-statistically significant trend toward improvement in the level of fatigue as compared with continuous ADT in patients with biochemical recurrence after radical radiotherapy to the prostate (p=0.07). In another randomised study, intermittent ADT evidenced a significant amelioration in quality of life but failed to show any benefit in fatigue management.

ANAEMIA
The extent of the problem
Anaemia is the most common haematological change encountered in men receiving ADT. It has been demonstrated that testosterone
Haemoglobin levels tend to rise slowly to the duration of androgen blockade.10 Similarly, a greater incidence of anaemia tends to be worse when an LHRH agonist alone than with a LHRH agonist or antiandrogen.11 Anaemia tends to be worse in men with newly diagnosed metastatic prostate cancer.12 A systematic review by Caro and colleagues13 showed that although haemoglobin levels decreased in anaemic prostate cancer patients compared to non-anaemic patients. Moreover, a study by Beer and colleagues14 demonstrated that the decline in haemoglobin levels after three months of ADT in metastatic prostate cancer patients was associated with shorter overall survival and progression-free survival. Therefore, the fact that both pre-treatment anaemia and ADT-related anaemia lead to significantly reduced survival highlights the clinical relevance of anaemia in prostate cancer.

**Management and treatment options**

Newly diagnosed prostate cancer patients should be tested with a blood count prior to starting ADT to exclude the presence of pre-treatment anaemia and address possible underlying causes such as deficiencies in vitamin B12, folate or iron. Haemoglobin levels should be monitored throughout hormone therapy. Awareness that ADT can cause anaemia should prevent practitioners from undertaking unnecessary exhaustive and invasive evaluation in men with mild normochromic and normocytic anaemia. While the majority of patients with ADT-induced anaemia need no treatment, severe anaemia cases, especially in metastatic patients with limited bone marrow reserve, may require further diagnostic evaluation and treatment. Current guidelines recommend red blood cell transfusions for haemoglobin values less than 10g/dl in symptomatic patients and in asymptomatic patients with comorbidities such as congestive heart failure or cerebral vascular disease.15

Several studies16,17 have demonstrated that recombinant human erythropoietin therapy increases haemoglobin levels, decreases red blood cell transfusion requirements and improves fatigue and quality of life in patients with prostate cancer and ADT-related anaemia. However, its use in cancer patients remains controversial, as many studies have reported possible increased mortality risk caused by stimulation of cancer cells as well an increased risk of thrombotic events. As avoidance of transfusion is the main benefit with erythropoietin therapy, its use should be individualised and patients should be informed of the associated risks and benefits.

**CONCLUSION**

The patient from our case was studied with a full blood count, which showed a normochromic and normocytic anaemia with normal levels of iron, vitamin B12 and folate. He was administered a 2-unit red blood cell transfusion, achieving a haemoglobin level of 10.1g/dl. In order to mitigate his ADT-induced fatigue, a programme of regular moderate physical activity was recommended and dietary advice was given. He reported a substantial improvement in his energy levels and in his quality of life.

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**REFERENCES**


