Contemporary hormone therapy with LHRH agonists for prostate cancer: avoiding osteoporosis and fracture

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Introduction Prostate cancer is a large clinical burden across Europe. It is, in fact, the most common cancer in males, accounting for more than 92,300 deaths annually throughout the continent. Prostate cancer is androgen-sensitive; thus an androgen deprivation therapy (ADT) is often used for treatment by reducing androgen to castrate levels. Several ADT agents have achieved benefits with effective palliation, but, unfortunately, severe adverse events are frequent. Contemporary ADT (Luteinising Hormone Releasing Hormone agonist- LHRHa injections) can result in side effects that include osteoporosis and fractures, compromising quality of life and survival.

Methods In this review we analysed the associated bone toxicity consequent upon contemporary ADT and based on the literature and our own experience we present future perspectives that seek to mitigate this associated toxicity both by development of novel therapies and by better identification and prediction of fracture risk.

Results Preliminary results indicate that parenteral oestrogen can mitigate associated osteoporotic risk and that CT scans could provide a more accurate indicator of overall bone quality and hence fracture risk.

Conclusions As healthcare costs increase globally, cheap and effective alternatives that achieve ADT, but mitigate or avoid such bone toxicities, will be needed. More so, innovative techniques to improve both the measurement and the extent of this toxicity, by assessing bone health and prediction of fracture risk, are also required.

Key Words: prostate cancer • androgen deprivation therapy • luteinising hormone releasing hormone agonist • osteoporosis • fracture imaging

INTRODUCTION

The discovery by Huggins in the 1940s that prostate cancer is androgen-sensitive led to the development of therapies, with differing mechanisms of action, to achieve castrate levels of androgen (ADT). Unfortunately, these agents often also had major unwanted side effects, such as osteoporosis and fractures, with ADT achieved with contemporary LHRH agonists (LHRHa) [1]. As both the clinical and financial burden surrounding prostate cancer grows [2], cheap and effective alternatives that achieve ADT but mitigate such bone toxicities are required.

Mechanisms of action and toxicity with contemporary hormonal treatment of prostate cancer

Prostate cancer cell growth is usually androgen-dependent [3], through stimulation of androgen receptors for growth and proliferation [4]. ADT in men, either medically (LHRHa) or by surgical orchiectomy, suppresses serum concentrations of both androgens and oestrogen to less than 5% and 20% of normal values respectively (oestradiol is synthesised in males by the aromatisation of testosterone) [5]. These very low sex hormone levels result in potentially major toxicities, including hot flushes, sarcopenia, erectile
dysfunction and osteoporosis (the latter and related fragility fracture risk specifically are most likely a consequence of oestrogen deficiency) [6].

**Osteoporosis, fracture risk and ADT**

Susceptibility to bone fractures arises following an imbalance in the activity of cells involved in bone turnover, namely osteoblasts and osteoclasts [7]. This results in reduced bone formation with increased bone resorption. As such, bone mineral density (BMD) is reduced and susceptibility to bone fracture increases. Following initiation of ADT, accelerated bone resorption ensues, leading to both a reduced bone mass, as well as structural changes with perforation of trabeculae [8] accounting, therefore, for the greater risk of developing osteoporosis [9]. Shahinian et al. demonstrated a direct link between ADT and fracture risk [10], whilst Shao et al. confirmed this and reported it to be directly proportional to the number of LHRHa doses received [11]. Importantly, Shao et al. reported that if a fracture occurred, it was associated with an overall 40% higher relative risk of mortality compared to if no fracture occurred (mortality was 6.27% higher within 6 months and 9.87% within 12 months of experiencing a fracture). There is, therefore, an unmet need for new and effective alternative interventions that achieve ADT, but avoid bone toxicities and the related morbidity, mortality and cost.

**Alternative therapies: revisiting the past**

Oral oestrogen (diethylstilbestrol – DES) was originally one of the main therapeutic options for treating prostate cancer. While many studies confirmed its efficacy of androgen suppression, and even improved overall survival, thorough analyses revealed it was associated with life-threatening cardiovascular toxicity [12]. Importantly, these early studies were conducted using a relatively high dose of DES (5 mg) and further work has elucidated that a lower dose, either 3 mg or 1 mg may avoid or reduce such cardiovascular toxicity [13, 14]. This is now known to be due directly to the hepatic first-pass of oestrogen, which results in induction of pro-coagulant proteins increasing the risk of thromboembolism and cardiovascular events. More recently, there is evidence that parenteral administration of oestrogen (either by intramuscular injection or transcutaneously) is able to circumvent this cardiovascular toxicity [15, 16]. Furthermore, the administration of parenteral (exogenous) oestrogen returns serum (endogenous) oestrogen to levels that may mitigate contemporary ADT toxicities that are caused by endogenous oestrogen depletion. Such mitigations of toxicities include osteoporosis, by improving the BMD [17].

New and encouraging preliminary data reveals oestrogen to be a cheap and safe option. Moreover with outcomes at least equivocal to contemporary ADT, the question of why oestrogen in parenteral form has yet to reclaim a role in prostate cancer therapy, remains a mystery. The ongoing UK National PATCH (Prostate Adenocarcinoma TransCutaneous Hormones) randomised clinical trial comparing transdermal oestradiol with LHRHa in locally advanced and metastatic prostate cancer has shown preliminary data to support the potential offered by oestrogen to deliver ADT and mitigate associated bone toxicity, as well as other adverse events of LHRHa ADT [18]. PATCH, which includes a total of 686 men, compares oestrogen patches (EP; FemSeven 100 µg/24 hr, 4 patches changed twice-weekly reducing to 3 after 4 weeks) versus LHRHa for locally advanced or metastatic prostate cancer (allocation ratio 2:1 before 21/2/2011, 1:1 after). Early Phase II data showed equivalence of safety and efficacy between trial arms [15]. A recent PATCH sub-study evaluating bone health further highlighted the osteoprotective potential of transdermal oestrogen whilst avoiding the associated cardiovascular toxicity of oral oestrogen. Compared to baseline, lumbar spine BMD declined following LHRHa treatment at both year 1 and year 2 (-2.11% and -6.09% respectively), while it increased with oestrogen patch treatment at year 1 (+6.43%) and was maintained at year 2 (+4.58). These early results encourage the hypothesis that exogenous oestrogen suppresses testosterone to castrate levels whilst appearing to improve BMD values (Table 1) [17].

**Predicting fracture risk: is the current gold standard accurate enough?**

The current gold standard for measuring osteoporotic risk is assessment of BMD [19], This is assessed by comparing arms

**Table 1. Early data from the bone sub-study of the PATCH trial: Changes in lumbar spine bone mineral density at 1 and 2 years from baseline (Langley et al. 2014 [17])**

|                  | Mean percentage change | p-value  |
|------------------|------------------------|----------|
| **LHRHa arm**    |                        |          |
| Year 1           | -2.11% (n=21)          | <0.001*  |
| Year 2           | -6.09%, n=10           | <0.001*  |
| **Transdermal oestrogen arm** | +6.43%, (n=39) |          |
| Year 1           | +6.43%, (n=39)         | <0.001*  |
| Year 2           | +4.58%, n=20           | <0.001*  |

*Comparing arms
using Dual Energy X-ray Absorptiometry (DEXA) and the diagnostic tool: Fracture Risk Assessment Tool (FRAX) [20]. FRAX integrates the BMD of the femoral neck along with multiple clinical risk factors to calculate both the 10-year probability of a hip fracture and a major osteoporotic fracture [21]. Whilst originally it was thought that bone strength was almost entirely explained by density, clinical observations did not support the data [22]. It was subsequently found that densitometry failed to take into account the importance of cortical geometry and trabecular architecture for bone strength. In fact, BMD only accounts for about 40–50% of the in vitro compressive strength of bone, whilst structure contributes as much as 30–40% of the remainder [23]. Following these discoveries, a new understanding of bone strength-based bone quality, operationally defined as the structural and mechanical basis of bone strength, was developed [24].

Bone quality is an amalgamation of all the factors that determine how well a skeleton can resist fracturing, including the micro-architecture, accumulated microscopic damage, quality of collagen, size of mineral crystals and the rate of bone turnover [19]. The current challenge is to find a suitable and non-invasive method of measuring bone quality in clinical practice, which can predict the risk of bone fracture in individual patients. Whilst advanced technologies such as computerised tomography (CT) and magnetic resonance imaging (MRI) have been considered, it is difficult to balance factors such as radiation risk to the patient, technical matters including image resolution and the inescapable costs of healthcare.

CONCLUSIONS

There is an unmet need to improve management of patients requiring treatments that may diminish bone quality, as well as instruments that will predict this, and hence osteoporotic and fracture risk to patients. This is particularly important for those already at an increased risk of bone loss, including the elderly or prostate cancer patients undergoing ADT. Patients enrolled on the PATCH trial offer a unique opportunity to study these bone quality changes by comparing directly between prostate cancer therapies that either decrease (LHRHa) or increase (oestrogen) bone quality, and thus to assess the methods by which these changes may be more easily monitored and speedily diagnosed.

CONFLICT OF INTEREST

Professor Paul Abel as editorial member at Central European Journal of Urology.

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