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Original Research

Arthralgia induced by endocrine treatment for breast cancer: A prospective study of serum levels of insulin like growth factor-I, its binding protein and oestrogens

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Abstract ***Background:*** Aromatase inhibitors (AIs) frequently induce or enhance musculoskeletal problems (AI-induced musculoskeletal syndrome (AIMSS)) which sometimes are debilitating. Apart from low oestrogen levels, underlying mechanisms are unknown and likely multiple. We previously hypothesised a role for the growth hormone/insulin like growth factor-I (IGF-I) axis. Here, we report the effect of tamoxifen and AI on IGF-I, IGF binding protein-3 (IGFBP-3) and oestrogen levels from a prospective study.
Materials and methods: Postmenopausal women with an early breast cancer scheduled to start adjuvant endocrine therapy with an AI or tamoxifen were recruited. A rheumatologic questionnaire was completed and serum was collected for assessment of IGF-I, IGFBP-3 and oestrogen levels. Re-evaluation was done after 3, 6 and 12 months of therapy.

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Results: 84 patients started on tamoxifen ($n = 42$) or an AI ($n = 42$). 66% of the latter group experienced worsening of pre-existing or *de novo* complaints in joint and/or muscle, compared to 29% of tamoxifen-treated patients. AI therapy resulted in elevated IGF-I levels with a statistically significant increase at 6 months ($p = 0.0088$), whereas tamoxifen users were characterised by a decrease in IGF-I levels at all follow-up times ($p < 0.0004$). No effect on IGFBP-3 was seen in the latter group. AI-users, however, showed decreased IGFBP-3 levels at 12 months ($p = 0.0467$). AIMSS was characterised by a decrease in IGFBP-3 levels ($p = 0.0007$) and a trend towards increased IGF-I/IGFBP-3 ratio ($p = 0.0710$).
Conclusion: These findings provide preliminary evidence that AI-induced musculoskeletal symptoms are associated with changes in the growth hormone (GH)/IGF-I axis.

1. Introduction

Over the last decade, breast cancer related mortality has decreased mainly because of an earlier detection of the disease and improved adjuvant systemic treatment. However, in postmenopausal women with an oestrogen receptor (ER)-positive breast cancer, patients' willingness and ability to adhere to oral aromatase inhibitors (AI) is low due to frequently encountered side-effects. Arthralgia, myalgia, joint stiffness, paresthesia and carpal tunnel syndrome (CTS), symptoms enclosed in the AI-induced musculoskeletal syndrome (AIMSS) are most commonly reported by AI-users. This syndrome hampers quality of life in over half of the patients, considering early discontinuation of therapy which threatens the excellent breast cancer outcome.

Despite its clear clinical significance, the aetiology behind AIMSS remains poorly defined. Oestrogen deprivation caused by AI is considered a key factor, but the exact pathophysiology, likely multifactorial, remains unclear.

Numerous hypotheses have been proposed, such as an anti-nociceptive effect of oestrogens, underlying autoimmune processes, systemic and local inflammation, vitamin D deficiency, changes in circulating androgen levels and susceptibility to AIMSS through genetic differences based on single nucleotide polymorphisms (SNP's). However, none of these theories could be established or have resulted in strong evidence so far. It is therefore of great importance to further evaluate AIMSS as aetiological mechanisms might lead to better therapy since treatment modalities are scarce.

We previously hypothesised an underlying involvement of the growth hormone (GH)/insulin like growth factor-I (IGF-I) axis in AIMSS, with a more pronounced loss of grip strength and premature AI discontinuation in lean and obese than in normal weight women [1,2]. Several lines of evidence underlie this hypothesis. AIs as opposed to oral oestrogens and tamoxifen increase IGF-I levels [3]. In addition, higher IGF-I levels are associated with arthralgia and other conditions known to affect the GH/IGF-I axis, like pregnancy, acromegaly, diabetes, perimenopause and obesity are linked with arthralgia [4].

To test this hypothesis, we conducted a prospective cohort study in postmenopausal breast cancer patients starting on tamoxifen or a non-steroidal AI to evaluate a potential association between changes in IGF-I levels and musculoskeletal symptoms through a 12 month period.

2. Materials and methods

2.1. Study design and sample (NCT01223833)

Consecutive postmenopausal women with an early ER-positive breast cancer scheduled to start adjuvant hormonal therapy with any of the third generation AIs or tamoxifen were recruited at University Hospitals Leuven between November 2010 and December 2011. The decision to treat with an AI or tamoxifen was based on our institution's in-house protocol for the use of either therapy [5]; there was no self-selection of patients based on age or pre-existing joint symptoms. Patients were requested to provide written informed consent. Demographic data, including body mass index (BMI) and waist-to-hip ratio (WHR), were collected at baseline. Women with severe rheumatologic disorders such as severe rheumatoid arthritis, or recent use of hormone replacement therapy were excluded. Patients were requested to complete a musculoskeletal questionnaire and donate a blood sample at baseline and during follow-up visits at 3, 6 and 12 months after start of endocrine therapy. In cases wherein discontinuation of the drug was warranted, a repeat evaluation was performed 3 months after termination of the initial endocrine treatment.

Serum was apportioned into 0.5 ml aliquots and stored at –80 °C until biomarker assessment.

2.2. Biomarker assessment

Serum samples were analysed in batch to minimise interassay variation. IGF-I levels, after acid ethanol