European Journal of Cancer 56 (2016) 31–36

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Genetic variant in the osteoprotegerin gene is associated with aromatase inhibitor-related musculoskeletal toxicity in breast cancer patients

A. Lintermans [a,*], K. Van Asten [b], L. Jongen [b], T. Van Brussel [c,d], A. Laenen [e], J. Verhaeghe [a,f], D. Vanderschueren [g,h], D. Lambrechts [c,d], P. Neven [a,b]

[a] *Department of Gynecology & Obstetrics, University Hospitals Leuven, Leuven, Belgium*
[b] *Department of Oncology, KU Leuven, Leuven, Belgium*
[c] *Vesalius Research Center, VIB, Leuven, Belgium*
[d] *Laboratory for Translational Genetics, Department of Oncology, KU Leuven, Leuven, Belgium*
[e] *Leuven Biostatistics and Statistical Bioinformatics Centre, KU Leuven, Leuven, Belgium*
[f] *Department of Development and Regeneration, KU Leuven, Leuven, Belgium*
[g] *Department of Clinical and Experimental Medicine, KU Leuven, Leuven, Belgium*
[h] *Department of Endocrinology, University Hospitals Leuven, Leuven, Belgium*

Received 13 July 2015; received in revised form 27 November 2015; accepted 14 December 2015
Available online xxx

KEYWORDS
Breast cancer;
Aromatase inhibitor;
Tamoxifen;
SNP;
OPG;
Musculoskeletal pain;
AIMSS;
Hot flashes

Abstract ***Background:*** Aromatase inhibitor (AI) therapy is associated with musculoskeletal (MS) toxicity, which adversely affects quality of life and therapy adherence. Our objective was to evaluate whether genetic variants may predict endocrine therapy-related MS pain and hot flashes in a prospective observational cohort study.

Patients & methods: 254 early breast cancer patients starting AI (n = 159) or tamoxifen therapy (n = 95) were included in this genetic biomarker study. MS and vasomotor symptoms were assessed at baseline and after 3, 6 and 12 months of therapy. AI-induced MS pain was defined as an increase in arthralgia or myalgia relative to baseline. Single nucleotide polymorphisms (SNP) in candidate genes involved in oestrogen signalling or previously associated with AI-related MS pain or oestrogen levels were selected.

Results: Overall, 13 SNPs in *CYP19*, *CYP17*, osteoprotegerin (*OPG*) and *oestrogen receptor 1* exhibited an allele frequency >0.05 and were included in the analysis. Patients carrying the G allele of rs2073618 in *OPG* experienced significantly more AI-induced MS toxicity compared to the wildtype allele, after correction for multiple testing ($P = 0.046$). Furthermore, this SNP

* *Corresponding author:* Department of Gynecology & Obstetrics, University Hospitals Leuven, Herestraat 49, 3000 Leuven, Belgium, Tel.: +32 16344634.
E-mail address: anneleen.lintermans@uzleuven.be (A. Lintermans).

http://dx.doi.org/10.1016/j.ejca.2015.12.013

was associated with severity of pain ($P = 0.018$). No association was found with regard to the other SNPs, both in AI and tamoxifen-treated patients. Neither could an association with vasomotor symptoms be demonstrated.
Conclusion: The SNP rs2073618 in *OPG* is associated with an increased risk of MS symptoms and pain with AI therapy, which has not been reported previously. Validation of this finding in larger cohorts and further functional studies are required.

1. Introduction

The use of aromatase inhibitors (AIs) in the treatment of early hormone receptor positive breast cancer has been well established and continues to rise, with various studies investigating their use in the extended setting and in premenopausal patients. As more and more patients will be exposed to these agents and for an increasing duration, the importance of ensuring an adequate quality of life and acceptable side-effect profile grows.

AIs are associated with multiple menopausal symptoms, particularly with hot flashes and musculoskeletal (MS) symptoms. The AI-induced musculoskeletal syndrome (AIMSS), which comprises joint and muscle pain, stiffness, carpal tunnel syndrome (CTS) and tingling, has been reported in up to 60% of patients and accounts for the majority of premature discontinuations [1]. However, a large variability in the magnitude of adverse events between patients exists. The identification of patients more susceptible for AI-related MS toxicity could result in personalised treatment decision making when starting adjuvant therapy.

Oestrogen deprivation evoked by AI therapy is considered the triggering factor in the occurrence of AIMSS although the exact mechanisms responsible remain to be determined.

Various clinical predictors have been suggested, like previous use of hormone replacement therapy, young age and recent menopausal transition, baseline pain, obesity, low body mass index and prior chemotherapy, almost all of which can be explained by an overall decrease in oestrogen levels [2–6]. Besides these clinical factors, genetic host variants affecting oestrogen and AI levels, transport and metabolism may be of importance to inter-patient and intra-patient AI tolerability differences.

Several associations between genetic variants and the presence of AIMSS have been reported so far. In particular, variants in *CYP19A1*, which is the gene encoding for aromatase, have been linked with altered serum oestrogen levels and increased risk of MS toxicity in several studies [7–10]. Furthermore, Henry et al. [11] showed that an intronic variant of oestrogen receptor 1 (*ESR1*), which encodes oestrogen receptor (ER) alpha, is associated with increased risk of AI discontinuation due to MS toxicity.

However, the validation of these associations in independent cohorts is of great importance. The objective of this study was to evaluate whether single nucleotide polymorphisms (SNPs) in selected genes, based on literature review, were associated with MS or vasomotor symptoms during the first year of treatment with an AI or tamoxifen. Therefore, well-characterised longitudinal patient-reported outcome data of our prospective cohort study, which were published previously, were used [1].

2. Patients and methods

2.1. Study design

Early postmenopausal breast cancer patients starting AI or tamoxifen therapy were included in our prospective observational cohort study, as described previously [1]. MS and menopausal symptoms were assessed at baseline and at 3, 6 and 12 months thereafter. AI-induced MS pain was defined as an increase in arthralgia or myalgia relative to baseline. AIMSS was set as the presence of $\geq$3 features (arthralgia, myalgia, joint stiffness, tingling, CTS) that were probably-definitely associated with AI therapy, according to the patient. Furthermore, the presence of vasomotor symptoms under endocrine therapy was recorded. Of the 293 patients included in the observational cohort, DNA samples were available for 255 patients in the Multidisciplinary Breast Center biobank. The study was approved by the Ethical Committee for Clinical Studies of University Hospitals Leuven, Belgium and conducted according to the Belgian guidelines and the ethical standard of the Helsinki Declaration [12].

2.2. Selection of polymorphisms

A detailed literature search in PubMed was performed to identify genetic variants in *CYP19A1* that were associated with either oestrogen levels or MS symptoms. Also SNPs located in other genes and previously linked with MS health in breast cancer patients treated with endocrine therapy were included. Overall, 40 variants in 11 genes were selected: rs10046, rs727479, rs6493497, rs7176005, rs10459592, rs4775936, rs1062033, rs700518, rs700519, rs749292, rs936308, rs60271534, rs56658716,