American Pain Society
RESEARCH
EDUCATION
TREATMENT
ADVOCACY
PUBLISHED BY ELSEVIER

The Journal of Pain, Vol 15, No 3 (March), 2014: pp 293-303
Available online at www.jpain.org and www.sciencedirect.com

Classification of and Risk Factors for Estrogen Deprivation Pain Syndromes Related to Aromatase Inhibitor Treatments in Women With Breast Cancer: A Prospective Multicenter Cohort Study

Francoise Laroche,* Joël Coste,† Terkia Medkour,‡ Paul Henri Cottu,§ Jean-Yves Pierga,§ Jean-Pierre Lotz,|| Karine Beerblock,|| Christophe Tournigand,¶ Xavier Declèves,** Patricia de Cremoux,†† Didier Bouhassira,‡‡ and Serge Perrot‡,‡‡

**Pain Clinic, Saint Antoine Hospital, Paris, France.*
†Biostatistics, Hôtel Dieu Hospital, Paris, France.
‡Pain Clinic and Internal Medicine Department, Hôtel Dieu Hospital, Paris Descartes University, Paris, France.
§Medical Oncology Department, Institut Curie, Paris, France.
||Oncology Department, Tenon Hospital, Paris, France.
¶Oncology Department, Saint Antoine Hospital, Paris, France.
***Pharmacology Department, Hôtel Dieu Hospital, Paris, France.*
††Molecular Oncology, APHP and Paris-Diderot University, Saint Louis Hospital, Paris, France.
‡‡INSERM U 987, Paris, France.

Abstract: **Aromatase inhibitors (AIs) are the first-line treatment in women with breast cancer for total estrogen depletion. Half the treated women may develop pain, and this condition may therefore be seen as a clinical model of pain related to estrogen deprivation. In this prospective multicenter study, we classified AI-related pain syndromes and identified their predictors. A 1-year, prospective, multicenter cohort study, with 6 visits, was carried out on 135 women with early-stage breast cancer and no pain at the start of AI treatment. At initial assessment, we investigated clinical (demographic and psychosocial, cancer characteristics and treatment, sleep, quality of life), biological (sex hormones, vitamin D, bone biomarkers, oxidative stress, immunologic and inflammatory markers), environmental, and genetic (polymorphism for pain mechanisms) risk factors for pain. During 1 year of follow-up, 77 women (57%) developed pain, leading to AI discontinuation in 12 cases. Five pain syndromes were identified: joint pain (36%), diffuse pain (22%), tendinitis (22%), neuropathic pain (9%), and mixed pain (11%), which are mostly persistent (57%), with diffuse and joint pains the most intense. Risk factors for the development of pain included higher levels of anxiety and impaired quality of life at the initial assessment, whereas cancer characteristics, genetic background, inflammation, and immunologic and hormonal status at baseline were not significant predictors.**

Perspective: ***This article presents a classification of AI–related pain syndromes induced by estrogen deprivation that were previously described as arthralgia, but not as neuropathic, diffuse, and mixed pain. This estrogen deprivation–related condition represents a clinical model of pain, and our study identified mostly psychological risk factors for pain development.***

Key words: *Breast cancer, pain, estrogen deprivation, aromatase inhibitors, arthritis.*

Aromatase inhibitors (AIs) are the first-line treatment for hormone-dependent breast cancers in postmenopausal women.[1,17] The aim of AI treatment is to induce total estrogen deprivation and prevent breast cancer recurrence. In relation to this estrogen deprivation, data from clinical trials and prospective surveys indicate that up to 50% of patients may develop pain following AI treatment.[1,5,13-15,20,21,30-32,34,35,37,38] Several symptoms are described, including joint pain, stiffness, myalgia, tendinitis, carpal tunnel syndrome, and bone pain.[20,22,36,37] However, AI-related pain problems

Received September 30, 2013; Accepted November 20, 2013.
This study received financial support from the CNP foundation, the API-CIL foundation and IUD-Institut Upsa de la Douleur.
None of the authors have any conflicts of interest related to this study.
Address reprint requests to Serge Perrot, MD, PhD, Internal Medicine Department and Pain Clinic, Hôpital Hôtel Dieu, 1 Place du Parvis Notre Dame, 75004 Paris, France. E-mail: serge.perrot1@gmail.com
1526-5900/$36.00

http://dx.doi.org/10.1016/j.jpain.2013.11.004

have not yet been systematically classified. Thus, AI-related pain syndrome represents a clinical model of pain related to estrogen deprivation that could shed light on the links between pain development and estrogen modifications.

Studies have identified previous hormone replacement therapy, time since menopause, obesity,[14,26,34,35] and poorer quality of life[38] as risk factors for the development of AI-related pain. However, no study has yet considered psychological factors, such as anxiety, depression, personality traits, and coping strategies. Furthermore, no study has considered all these potential risk factors together in a single prospective analysis.

The aims of this study were 1) to describe and classify all the AI-related pain symptoms developing within 1 year of estrogen deprivation related to the initiation of AI treatment in pain-free women and 2) to investigate extensive predictors of pain development in an estrogen deprivation clinical model of pain: clinical predictors (demographic, psychological) and biological predictors (inflammation, oxidative stress, autoimmune disorders, bone metabolism, genetic pain polymorphism, hormones).

The subtyping of pain syndromes and its specific predictors should help to improve the management of AI-related pain and to reduce the number of women stopping their AI treatment.

Patients and Methods

Design

We carried out a 1-year observational multicenter prospective cohort study with recruitment at 4 medical oncology departments and extensive pain assessment at 1 pain clinic, all these centers being located in university hospitals in Paris, France.

Ethics Statement

This study was carried out in accordance with the Helsinki Declaration. Informed consent was obtained from each subject before enrollment. Institutional review board and French data protection agency approvals (CCTIRS, CNIL) were obtained before subject enrollment.

Study Population

Consecutive women treated for early breast cancer at 4 medical oncology departments were eligible to participate if free of pain and starting AI treatment from June 2009 to March 2011, and each participant was followed for 12 months. Exclusion criteria were pain conditions interfering with pain assessment, patient not able to follow the protocol, other treatment for cancer scheduled for the next 12 months, previous AI treatment, and estimated survival of less than 12 months.

AI Treatments and Other Drugs Prescribed During the Study Period

All postmenopausal women with hormone-dependent breast cancer recruited for this study began oral treatment with AI (anastrozole, letrozole, exemestane). All other treatments, including analgesics, were permitted and their use was monitored.

Measurements

Baseline and follow-up measurements were carried out under the supervision of a research nurse (T.M.) and rheumatologists specializing in pain medicine. Visits were scheduled for 1, 3, 6, and 12 months after the start of AI treatment.

Baseline Measurements

The initial visit occurred just before the start of AI treatment, with a complete medical examination carried out by a rheumatologist (F.L. or S.P.).

Demographic and Cancer History Data

The demographic data collected included age, body mass index (BMI), menopause duration, and history of hormone replacement therapy. Cancer history variables included pathologic subtype of breast cancer, type of surgery, history of chemotherapy, and history of radiotherapy.

Pain Assessment and Subclassification

Pain intensity was assessed with a 100-mm visual analog scale (VAS),[19] and we considered pain as clinically significant for VAS scores of at least 30 mm. Affective and sensorial domains of pain were assessed with the short-form McGill Pain Questionnaire, which has been validated for cancer and arthritis.[19] The extent to which pain interfered with daily life was assessed with the Brief Pain Inventory,[9] which has also been validated for use in populations with and without cancer.[2] Pain duration was assessed, at each visit, in months since the start of pain. We included 4 subclasses of pain: joint pain, diffuse pain, neuropathic pain, and tendon pain. This classification was made in 3 steps: 1) the body diagram included in the Brief Pain Inventory for pain localization and classification of diffuse pain, 2) by specific questions when localized pain: first 7 items from the DN4 questionnaire[4] to detect neuropathic component, and specific questions on pain location (around the joint, inside the joint), and 3) confirmation by clinical examination.

We also defined 2 types of pain: transient pain, observed at 1 visit, and persistent pain, observed on at least 2 consecutive visits.

On the basis of previous studies on AI-related pain, and according to the International Association for the Study of Pain pain taxonomy,[28] we included patients developing pain during the study in the following categories: joint pain, diffuse pain, neuropathic pain, tendon pain, and mixed pain combining at least 2 of the previous categories of pain.

Psychological and Clinical Assessment

Anxiety and depression were assessed with the Hospital Anxiety and Depression Scale.[3] Personality traits and pain catastrophizing were assessed with the Temperament and Character Inventory[33] (TCI–French version) and the Pain Catastrophizing Scale.[42]