European Journal of Cancer 68 (2016) 11–21

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

The risk of myocardial infarction with aromatase inhibitors relative to tamoxifen in post-menopausal women with early stage breast cancer

Husam Abdel-Qadir [a,b,c,d], Eitan Amir [a,c,e], Hadas D. Fischer [b], Longdi Fu [b], Peter C. Austin [b,c], Paula J. Harvey [a,d,f,g], Paula A. Rochon [a,b,c,d,f], Douglas S. Lee [a,b,c,g,1], Geoffrey M. Anderson [b,c,f,*,1]

[a] *Department of Medicine, University of Toronto, Suite RFE 3-805, 200 Elizabeth Street, M5G 2C4, Toronto, Ontario, Canada*
[b] *Institute for Clinical Evaluative Sciences, G1 06, 2075 Bayview Ave, M4N 3M5, Toronto, Ontario, Canada*
[c] *Institute of Health Policy, Management and Evaluation, University of Toronto, 155 College Street, Suite 425, M5T 3M6, Toronto, Ontario, Canada*
[d] *Women's College Hospital, 76 Grenville Street, M5S1B2, Toronto, Ontario, Canada*
[e] *Princess Margaret Cancer Centre, 610 University Ave, M5G 2M9, Toronto, Ontario, Canada*
[f] *Women's College Research Institute, 7th Floor, 790 Bay Street, M5G 1N8, Toronto, Ontario, Canada*
[g] *Peter Munk Cardiac Centre and Joint Department of Medical Imaging, University Health Network, 585 University Ave, M5G 2N2, Toronto, Ontario, Canada*

Received 16 March 2016; received in revised form 22 June 2016; accepted 25 August 2016
Available online 30 September 2016

KEYWORDS
Hormonal therapy;
Endocrine therapy;
Anastrozole;
Letrozole;
Exemestane;
Coronary artery disease;

Abstract ***Background:*** Aromatase inhibitors (AIs) may increase cardiovascular risk relative to tamoxifen in post-menopausal women with breast cancer. This risk has not been well-quantified outside of clinical trials.
Methods: Observational population-based cohort study of women aged >55 years diagnosed with stage I–III breast cancer between 2005 and 2010. Women treated with AIs or tamoxifen were followed to March 2012. The primary outcome was hospitalisation for myocardial infarction (MI). Cause-specific hazards were compared using tamoxifen as the reference group. Inverse probability of treatment weighting using the propensity score was used to

* *Corresponding author*: 4th Floor, Health Sciences Building, 155 College Street, Suite 425, Toronto, Ontario, M5T 3M6, Canada.
E-mail address: geoff.anderson@utoronto.ca (G.M. Anderson).
[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.ejca.2016.08.022

Cardio-oncology;
Survivorship

reduce confounding due to measured baseline covariates. Results were confirmed using two cause-specific hazards models. Subgroup analyses included women aged ≥66 years, those with prior ischaemic heart disease, and a 'lower-risk group' aged <74 years with stage I–II cancer and no prior ischaemic heart disease.

Results: In 7409 aromatase inhibitor-treated and 1941 tamoxifen-treated women, the median age was 71 versus 74 years, respectively ($p < 0.001$). Baseline prevalence of ischaemic heart disease was similar (17.0% versus 16.9%, $p = 0.96$). Over a mean of 1184 d of follow-up, there were 123 hospitalisations for MI; the cause-specific hazard was higher with AIs (hazard ratio 2.02; 95% confidence interval 1.16–3.53 in the weighted sample). We observed comparable patterns within pre-defined subgroups and when adjusted using cause-specific hazards models.

Conclusion: Aromatase inhibitors are associated with a higher risk of MI compared with tamoxifen. This risk should be accounted for when managing aromatase inhibitor-treated women.

1. Introduction

Cardiovascular disease shares multiple risk factors with breast cancer [1–6] and is a recognised adverse effect of cancer therapy [7]. This makes cardiovascular disease a leading cause of death among older breast cancer survivors [8,9]. Thus, there is growing interest in reducing the adverse cardiovascular impact of breast cancer therapy [7,10–14].

Aromatase inhibitors (AIs) have become preferred to tamoxifen for adjuvant endocrine therapy of postmenopausal women with breast cancer [15] since they improve both disease-free and overall survival (OS) [16–18]. There has been enthusiasm for longer durations of aromatase inhibitor therapy beyond the 5 years tested in clinical trials [17]. However, the prolonged duration of endocrine therapy also mandates consideration of the expected adverse event profile in a given patient [17,19]. A recent meta-analysis demonstrated a small but significant increase in the risk of cardiovascular events among patients receiving AIs compared with tamoxifen [20]. This concern is heightened by the United States Food and Drug Administration's (FDA) warning of a higher incidence of cardiovascular events among anastrozole-treated women with pre-existing heart disease [21]. The data prompting this warning remain unpublished in peer-reviewed literature.

Observational studies may be used to assess the safety of interventions when administered outside the setting of a clinical trial. We designed a retrospective population-based cohort study to evaluate the cause-specific hazard of hospitalisations for myocardial infarction (MI) associated with AIs relative to tamoxifen to better inform treatment decisions and follow-up care. We hypothesised that there would be a higher cause-specific hazard of MI among aromatase inhibitor–treated women.

2. Methods

2.1. Data sources

The Ontario Health Insurance Plan (OHIP) provides universal health insurance coverage of medically-necessary care for residents of Canada's most populous province. Patients' encoded health insurance numbers were used to link multiple administrative health databases. The Ontario Cancer Registry is a passive registry of invasive cancer diagnoses among Ontario residents since 1964 [22]. Breast cancer stage data were obtained using Cancer Care Ontario's best stage data algorithm [23].

The Ontario Drug Benefit program provides reimbursement of prescription medications for Ontario residents aged >65 years, for individuals receiving long-term care, governmental financial assistance, disability support, or those with high-prescription drug costs relative to their income [24]. This database was used to determine exposure to tamoxifen or AIs after breast cancer diagnosis, as well other medications in the year preceding endocrine therapy initiation. We used the New Drug Funding Program to identify women receiving trastuzumab.

The Canadian Institute for Health Information Discharge Abstract Database includes a record of all discharges from acute care hospitals in Ontario. The National Ambulatory Care Reporting System contains data for emergency department and ambulatory hospital-based care, whereas physician services were captured from billing claims in the OHIP database. Baseline co-morbidities were identified by searching the Canadian Institute for Health Information Discharge Abstract Database and National Ambulatory Care Reporting System for the corresponding International Classification of Diseases codes in the 10 years preceding the index date. Diagnoses of baseline ischaemic heart