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Review

Management of aromatase inhibitor induced musculoskeletal symptoms in postmenopausal early Breast cancer: A systematic review and meta-analysis

Kate Roberts[a,*], Kirsty Rickett[b], Ristan Greer[b,c], Natasha Woodward[a,b,c]

[a] Department of Medical Oncology, Mater Health Services, Brisbane, Australia
[b] University of Queensland, Brisbane, Australia
[c] Mater Medical Research Institute Mater Health Services, Brisbane, Australia

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* Corresponding author at: Department Medical Oncology, Mater Health Services, South Brisbane, 4101, Australia.
E-mail address: Kate.Roberts@health.qld.gov.au (K. Roberts).

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ABSTRACT

Aromatase Inhibitors (AI) are widely used for the adjuvant treatment of hormone receptor positive breast cancers in the post-menopausal population. AI are often associated with significant joint and muscular symptoms; symptoms that are commonly referred to as aromatase inhibitor-associated musculoskeletal syndrome (AIMSS). AIMSS adversely impacts health-related quality of life of many patients, and reduces AI compliance. Although there are informal practice recommendations, the limited current level of evidence for management of AIMSS for breast cancer patients on aromatase inhibitors has made development of formal guidelines challenging, and remains an unmet need. This is the first systematic review to consider the evidence for all pharmacological and non-pharmacological interventions in the treatment of AIMSS, including physical therapy, acupuncture and complementary therapies.

1. Introduction

Aromatase Inhibitors (AI) are recommended for the adjuvant treatment of hormone receptor positive breast cancers in the post-menopausal population. These agents block the synthesis of oestrogen by inhibition of peripheral aromatase (Miller et al., 2003). Compared with Tamoxifen, third generation aromatase inhibitors have been shown to significantly improve disease free survival (DFS) (Cuzick et al., 2010; Regan et al., 2011; Ingle et al., 2006), and include the steroidal inhibitor exemestane, and the nonsteroidal inhibitors, anastrozole and letrozole. In the 2013 meta-analysis by Aydiner et al. (Aydiner, 2013), five years of adjuvant therapy with aromatase inhibitors improved DFS (HR 0.89, $p = 0.001$), and also overall survival (OS) (HR 0.92, $p = 0.046$) when compared to tamoxifen. Aromatase inhibitors have also demonstrated improvement in DFS, OS and distant metastasis rate when sequenced with tamoxifen (HR 0.70, $p < 0.001$; HR 0.81, $p = 0.003$, HR 0.74, $p < 0.001$ respectively), and an improvement in DFS as extended adjuvant treatment after 5 years of tamoxifen (HR 0.62, $p = 0.001$) (Aydiner, 2013). Recent evidence has revealed a benefit of continuing aromatase inhibitors for a period of 10 years, as reported in the MA.17R trial, which displayed significant improvement in breast cancer recurrence rates, and decreased contralateral breast cancer (Goss et al., 2016).

Aromatase inhibitors are associated with joint and muscular symptoms, commonly referred to as aromatase inhibitor-associated musculoskeletal syndrome (AIMSS) (Lintermans et al., 2013). AIMSS adversely impacts on the quality of life of many patients. Studies recently investigating AIMSS have shown incidence of musculoskeletal symptoms to be as much as 50% (Coleman et al., 2008; Laroche et al., 2014; Menas et al., 2012), higher than the pivotal aromatase inhibitor trials with rates of approximately 20–35% (Muss et al., 2008; Coates et al., 2007; Howell et al., 2005). The prevalence of musculoskeletal symptoms impacts the long-term care of these patients. Analysis of longitudinal claims data from three American commercial health programs revealed sub-optimal adherence to anastrozole in 19–28% of patients in their first year of treatment (Partridge et al., 2008). These statistics are consistent with other studies of aromatase inhibitor adherence (Hadji et al., 2014; Hershman et al., 2011; Presant et al., 2007; Henry et al., 2012), which report a significant percentage of patients displaying early discontinuation of treatment. There are important clinical implications of this data, as non-compliance with adjuvant endocrine therapies in early breast cancer has been shown to be detrimental to the patients' survival (Hershman et al., 2011).

AIMSS usually presents as symmetrical pain or soreness in the hands, knees, hips, lower back, shoulders, and/or feet. It is often associated with early-morning stiffness and difficulty sleeping (Burstein, 2007). There may be additional extra-articular symptoms present, such as myalgia, fibromyalgia, neuropathy and carpal tunnel syndrome (Sestak et al., 2009). MRI studies conducted on patients taking aromatase inhibitors have shown the development of tenosynovial changes and increased intra-articular fluid in patients with AIMSS (Lintermans et al., 2013). Most of the symptoms will develop within the first two to three months of AI treatment (Burstein, 2007; Mao et al., 2009a). This systematic review aims to summarise the recent literature on the symptom management intervention strategies for AIMSS. Meta-analyses have been conducted where feasible.

2. Methods

2.1. Search strategy

A systematic search of the electronic literature was designed and conducted by an information specialist (KR) to identify the relevant evidence. The following databases were searched: PubMed, EMBASE, CINAHL and CENTRAL. Controlled terminology (MESH, EMTREE, CINAHL headings) and free text words were used. Google scholar was also searched for unpublished literature. The final search of all the databases was conducted on 24th February 2016. Reference lists of relevant review articles and of the full text reviewed papers were also cross checked and any relevant papers included for review. The complete search strategies for all the databases can be found in Appendix A.

2.2. Study selection: inclusion and exclusion criteria

2.2.1. Type of studies

Although the best type of study to assess the efficacy of an intervention is a randomised controlled trial (RCT), the scope of studies for inclusion in this review has been expanded. This is to reflect the recognition that there are very few RCT in the area, and to be inclusive of as many intervention types as possible to inform clinical practice and respond to patient enquiries. Therefore, all clinical trials (prospective and retrospective), cohort and case control studies and preventative trials were considered. Conference abstracts were included, but where a later full paper has been published, the abstract was excluded and replaced with the full paper. Letters to the editor detailing clinical trial results were also included. Conference abstracts and letters to the editor were only considered in the narrative analysis and were not included in the risk of bias assessment or meta-analysis as there was not enough infor-