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Review

Aromatase inhibitors alone or sequentially combined with tamoxifen in postmenopausal early breast cancer compared with tamoxifen or placebo – Meta-analyses on efficacy and adverse events based on randomized clinical trials

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ABSTRACT

Tamoxifen (TAM) and aromatase inhibitors (AI) are adjuvant therapy options for postmenopausal women with estrogen receptor positive (ER+) breast cancer. This systematic review of seven randomized controlled studies comparing TAM and AI, and one study comparing extended therapy with an AI with placebo after about 5 years of tamoxifen, aims to assess long-term clinical efficacy and adverse events. The literature review was performed according to the principles of the Cochrane Collaboration. The search included common databases up to 2013-01-14. Studies of high or moderate quality were used for grading of evidence. Revman™ software was utilized for meta-analyses of published data. Disease free survival (DFS) and overall survival (OS) were improved with AI monotherapy compared to TAM with high and moderate quality of evidence respectively. Sequenced therapy with AI → TAM (or vice versa) improved DFS compared with TAM with moderate quality of evidence, but did not improve OS (low quality of evidence). However, if only studies on sequenced AI therapy with randomization before endocrine therapy were considered, no improvement of DFS could be found. Fractures are more frequently associated with AI whereas the risk of endometrial cancer and venous thromboembolism are higher with TAM. For cardiovascular events no difference was found between AI (mono- or sequenced therapy) and TAM, whereas sequenced therapy compared with AI had lower risk of cardiovascular events (moderate level of evidence).

AIs are superior to TAM as adjuvant hormonal therapy for postmenopausal ER-positive breast cancer. TAM can be considered for individual patients due to the different toxicity profile compared with AI. Cardiovascular events related to AI treatment deserve further attention.

Introduction

Hormonal therapy is the cornerstone of adjuvant systemic treatment for patients with ER- positive breast cancer. The efficacy of adjuvant tamoxifen (TAM) for 5 years, irrespective of menopausal status, compared to placebo has repeatedly been reported in terms of disease-free (DFS) and overall survival (OS) [1]. The side effects of TAM are well documented including increased risk of thromboembolic events and endometrial cancer [1]. For postmenopausal women, adjuvant endocrine therapy with TAM has

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been challenged during the last decade by third-generation AI showing improvement of DFS compared to TAM in ER-positive breast cancer [2,3].

Trials comparing adjuvant aromatase inhibitors (AI) with TAM have used different schedules: 5 years of monotherapy; sequenced therapy, i.e. TAM for 2–3 years followed by AI to a total of 5 years or vice versa with either TAM or an AI as the comparator; and extended therapy with AI compared to placebo after 5 years of TAM (Fig. 1) [2–9]. The adjuvant randomized controlled trials (RCT) of AI have included over 35,000 women worldwide and long-term follow-up data have been reported for some of the largest trials suggesting that AI also increases OS compared to TAM [2,4]. AI has consistently been reported to increase the risk of fractures compared to TAM [10,11], and to symptoms related to estrogen deprivation such as musculoskeletal- and genitourinary discomfort, whereas potentially negative effects on cardiovascular events are not fully elucidated.

In 2005 the Swedish Council on Health Technology Assessment and Assessment of Social Services (SBU) published a systematic review on the effects of AI in metastatic breast cancer together with data on adjuvant and neo-adjuvant treatment with AI in early breast cancer [12]. At that time point, no long-term data was available.

The aim of the present systematic review was to analyze long-term follow–up data from RCTs with AI (mono-, sequenced- and extended therapy) compared with TAM or placebo in order to provide a comprehensive update on efficacy (DFS and OS) and side effects including available data from ***on-*** and ***off-***treatment.

Methods

Literature search and selection of articles

This article is based on a Health Technology Assessment reported by *The Swedish Council of Health Technology Assessments and Assessment of Social Services*, SBU [13], whose methods are in line with the Cochrane Collaboration Handbook for Systematic Reviews (http://handbook.cochrane.org/). The methods used in this review article are essentially the same as recommended in the Prisma Checklist (http://www.prisma-statement.org/statement.htm). The search strategy along with the text words (TW) and MeSH terms used are listed in Appendix C. Languages were restricted to English and Nordic languages. The electronic literature search included the databases PubMed, the Cochrane Library and Embase up to 2013-01-14. We also consulted the reference lists of the articles found in the electronic search and thus identified relevant articles manually.

Inclusion and exclusion criteria

This study was based on the PICO criteria (Population, Intervention, Control and Outcomes [14] (Table 1)). All abstracts were assessed independently by two of the authors (LR and JA). Only RCTs were used for the analyses of efficacy outcomes (OS, DFS), systematic literature reviews and meta-analyses were also considered. Follow-up had to be $\geq$ 5 years. Serious adverse events in this study are those that have been reported in the large RCTs, i.e. endometrial cancer, fractures, venous thromboembolic-, cardiovascular- and cerebrovascular events as well as death without recurrence. Surrogate variables such as lipid alterations and osteoporosis were disregarded. We included two systematic reviews [10,11] with data on adverse events but if data with a longer follow-up were available from individual studies these were used. In some cases, toxicity data from ***on***- and ***off***-treatment were reported.

Rating quality of individual studies

The quality of each study was rated independently by two of the authors (JA and LR) as high, moderate or low according to a standard checklist [13] adopted from The Cochrane Handbook. This checklist identifies the risk of different types of bias, such as

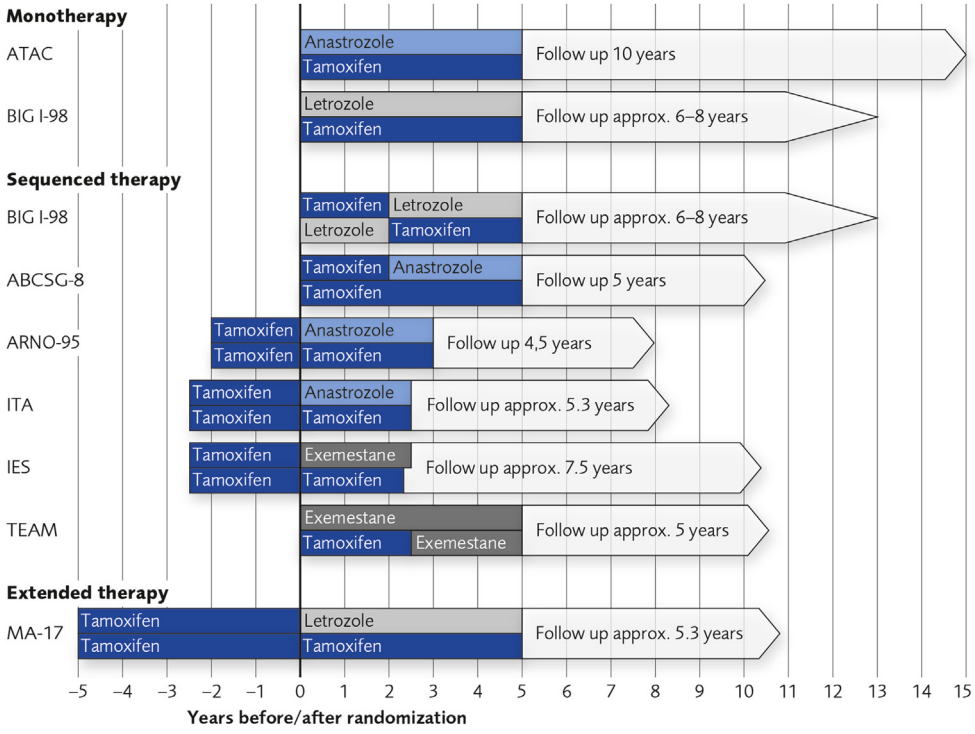

Fig. 1. Flow chart of the literature selection process of included studies [13].