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ORIGINAL ARTICLE

Meta-analysis of pre-operative aromatase inhibitor versus tamoxifen in postmenopausal woman with hormone receptor-positive breast cancer

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Abstract
Purpose Clinical trials have reported conflicting results as to whether pre-operative aromatase inhibitors (AIs) improve outcome over pre-operative tamoxifen in postmenopausal women with hormone receptor-positive breast cancer.
Methods We performed a meta-analysis comparing primary and secondary end points of pre-operative AI and pre-operative tamoxifen. The event-based risk ratio (RR) with 95% confidence intervals (95% Cis) were derived, and a test of heterogeneity was applied.
Results Four studies (1,160 patients) met the inclusion criteria for the analysis. Meta-analysis showed that pre-operative AI was more effective than pre-operative tamoxifen. Pooled results of clinical efficacy were as follows: clinical objective response rate (RR, 1.29; 95% CI, 1.14–1.47; $P < 0.001$), ultrasound objective response rate (RR, 1.29; 95% CI, 1.10–1.51; $P = 0.002$), and breast conserving surgery (BCS) rate (RR, 1.36; 95% CI, 1.16–1.59; $P < 0.001$). Hot flashes, nausea, and fatigue were not different between the pre-operative AI and pre-operative tamoxifen groups. Although headache was more frequent in the pre-operative AI group ($P = 0.011$), it was a manageable toxicity and was not clinically relevant.
Conclusion Pre-operative AI has better BCS rate than tamoxifen and in terms of toxicities, is not inferior to tamoxifen; therefore, we could suggest pre-operative AI instead of tamoxifen for those postmenopausal patients with hormone receptor positive breast cancer, not eligible for chemotherapy.

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Introduction

The main goal of pre-operative endocrine therapy is to downstage hormone receptor-positive breast cancer to allow BCS instead of mastectomy, or to achieve operability in previously inoperable breast cancer [1]. Pre-operative endocrine therapy is a feasible treatment option for women with hormone receptor positive early stage breast cancers in whom immediate surgery would necessitate a mastectomy and who are unwilling or unfit to receive chemotherapy [2]. Pre-operative systemic chemotherapy regimens in primary breast cancer patients are associated with a relatively high frequency of toxicity related to myelosuppression, especially in postmenopausal woman [3]. Although pre-operative endocrine therapy has not been tried as frequently as pre-operative systemic chemotherapy, it might be equally efficacious and less toxic than pre-operative systemic chemotherapy, particularly in postmenopausal woman with a limited life span and co-morbid conditions [2].

Before the emergence of third generation AIs such as anastrazole, letrozole, and exemestane, tamoxifen was the main pre-operative endocrine therapy. AIs appear to be superior to tamoxifen as first-line endocrine option in postmenopausal women with metastatic breast cancer in terms of overall response rate (ORR) and time to progression (TTP), and survival [4, 5]. However, AIs as second-line endocrine therapy in postmenopausal women with metastatic breast cancer do not seem to add any significant benefit to megesterol acetate in terms of ORR and TTP [6]. Randomized studies comparing tamoxifen administered as primary therapy to surgery followed by adjuvant tamoxifen

have demonstrated an initial reduction in tumor size without an impact on survival. However, the long-term local disease control rate is poor in patients receiving primary tamoxifen therapy [7–9]. Furthermore, tamoxifen has various adverse effects including vaginal discharge, and the increased risk of endometrial cancer and higher incidence of thromboembolic events, although infrequent, are of important clinical consequence to the patient [10].

AI decreases the risk of thromboembolic and cerebrovascular events compared to tamoxifen, and the overall rate of cardiovascular events in patients treated with AIs is within the range seen in age-matched, placebo group [11], however, others are not [12, 13]. AIs are also associated with a lower incidence of endometrial cancer and fewer vaginal bleeding events than tamoxifen [14]. Generally, adverse events with AIs are predictable and manageable, whereas tamoxifen may be associated with life-threatening events in a minority of patients [15].

Several phase III, randomized, double-blind studies have been conducted with third generation AIs as a pre-operative endocrine therapy in postmenopausal woman with hormone receptor-positive breast cancer [16–19]. However, individually, these trials found that clinical objective response rate, ultrasound objective response rate, BCS rate, and toxicities were statistically inconsistent. These conflicting results recommend the conduct of a meta-analysis to verify the efficacy of AI versus tamoxifen as a pre-operative endocrine therapy in postmenopausal women with hormone receptor-positive breast cancer.

The purpose of this study was to perform a meta-analysis to examine whether AI is effective compared to tamoxifen as a pre-operative endocrine therapy for postmenopausal women with hormone receptor-positive breast cancer patients in terms of clinical objective response rate, ultrasound objective response rate, BCS rate, and toxicities.

Materials and methods

Outcomes

Analyses were conducted to determine significant differences in primary and secondary endpoints. The primary endpoint was clinical objective response rate, ultrasound objective response rate, and breast conserving surgery rate. Secondary endpoints were incidences of toxicities (hot flashes, nausea, headache, and fatigue).

Search strategy

We searched the literature from the MEDLINE and ISI Web of Knowledge databases to identify relevant available articles, and we limited our searches to randomized controlled trials. The following key words and subject terms were searched: “Pre-operative”, “Neoadjuvant”, “endocrine therapy”, “hormonal therapy”, “aromatase inhibitor”, “tamoxifen”, “postmenopausal” and “breast cancer”. The search was not language specific. References in the studies were reviewed to identify any additional studies that were not indexed by the electronic database.

Inclusion and exclusion criteria

Pre-operative tamoxifen was considered as the standard against preoperative AIs. A study was included in the analysis to find out the following: (1) if it was published or presented before November 2007; (2) if it was original data (independence among the studies); (3) if it was a phase III, randomized, double-blind trial; and (4) if it compared preoperative AI with tamoxifen in postmenopausal women with hormone receptor-positive breast cancer.

Data extraction

We followed a standard protocol for data extraction. For each study, the following data were recorded: first author’s name, year of publication, country in which the study was performed, name of the study (if given), study design, number of patients in each of the AI and tamoxifen groups, eligibility criteria, which AI the study used, duration of pre-operative endocrine therapy, and clinical objective response rate, ultrasound objective response rate, BCS rate, and the incidence of toxicities (hot flashes, nausea, headache and fatigue), which were reported in all trials and the incidence of more than 5% were selected in any treatment group.

Statistical analysis

The Q-statistic was used to investigate the degree of heterogeneity between trials. A P value of <0.1 was interpreted as evidence of greater heterogeneity among the combined trials than would be expected by chance alone. The I^2-statistical test was carried out to describe the proportion of total variation caused by situations in which there are few studies and excessive power to detect clinically unimportant heterogeneity when there are many studies. I^2 values of 25, 50 and 75% were used as evidence of low, moderate, and high heterogeneity, respectively. When there was no statistical heterogeneity, we used a fixed effect model. If heterogeneity was present, we used a random effect model (DerSimonian–Laird method) to account for interstudy heterogeneity instead of the fixed effect model [20]. The event-based risk ratio (RR) with 95% confidence intervals (95% Cis) were derived, and a test of heterogeneity was applied. All statistical analyses were carried out with the use of

STATA statistical software (version 10; Stata Corporation, College Station, TX). All statistical tests were two-sided.

Results

Of the 68 studies identified by the literature search, 61 studies were excluded because they were phase II studies, reviews, letters, comments, and case reports and 7 studies were chosen for detailed review. Among them, a total of four articles (P024 trial, IMPACT trial, PROACT trial and Exemestane trial) met the inclusion criteria. Table 1 shows the baseline characteristics of the studies.

Clinical objective response rate

The Q-statistic showed the presence of heterogeneity among different trials included in our meta-analysis ($P = 0.005$) and the I^2-statistic indicated heterogeneity (77%). The P024 and Exemestane trials reported a statistically significant increase in clinical objective response rate for patients receiving pre-operative AI treatment compared to tamoxifen, whereas the IMPACT and PROACT trials found the opposite trend. The pooled results by random effect model demonstrated a statistical difference in the clinical objective response rate between patients who had pre-operative AI treatment and those who had pre-operative tamoxifen treatment (RR, 1.29; 95% CI, 1.14–1.47; $P < 0.001$) (Table 2).

Ultrasound objective response rate

The Q-statistic showed the presence of homogeneity among different trials included in our meta-analysis ($P = 0.203$) and the I^2-statistic detected the presence of homogeneity (34.8%). Only the Exemestane trial reported a statistically significant increase in ultrasound objective response rate for patients receiving pre-operative AI treatment compared to tamoxifen, whereas the P024, IMPACT, and PROACT trials found the opposite trend. The pooled results by fixed effect model demonstrated a statistical difference in the ultrasound objective response rate between patients with pre-operative AI treatment and pre-operative tamoxifen treatment (RR, 1.29; 95% CI, 1.10–1.51; $P = 0.002$) (Table 2).

Breast conserving surgery rate

The Q-statistic showed the presence of homogeneity among different trials included in our meta-analysis ($P = 0.627$) and the I^2-statistic detected the presence of homogeneity (0%). The IMPACT and Exemestane trials reported a statistically significant increase in BCS rate for patients receiving pre-operative AI treatment compared to tamoxifen, whereas the P024 and PROACT trials found the opposite trend. The pooled results by fixed effect model demonstrated a statistical difference in the BCS rate between patients with pre-operative AI treatment and pre-operative tamoxifen treatment (RR, 1.36; 95% CI, 1.16–1.59; $P < 0.001$) (Table 2; Fig. 1).

Toxicities

The Exemestane trial did not report adverse event data, so we were only able to include the P024, IMPACT, and PROACT trials in the adverse events meta-analysis. Among the

Table 2 Pooled meta-analysis results of clinical ORR, ultrasound ORR, BCS rate, and toxicities (hot flashes, nausea, headache, and fatigue)

Meta-analysis	Heterogeneity (P value)	I^2 (%)	RR (95% CI)
Outcomes			
Clinical OR	0.005	77	1.29 (1.14, 1.47)
Ultrasound OR	0.203	34.8	1.29 (1.10, 1.51)
BCS rate	0.627	0	1.36 (1.16, 1.59)
Toxicities			
Hot flashes	0.454	0	0.84 (0.63, 1.11)
Nausea	0.743	0	1.10 (0.79, 1.53)
Headache	0.579	0	2.02 (1.18, 3.45)
Fatigue	0.169	43.7	0.63 (0.34, 1.17)

Table 1 Summary of the included clinical trials comparing pre-operative AIs with tamoxifen

Study	Arms	No. of patients		Duration of treatment	Reference
P024	Letrozole versus tamoxifen	Letrozole	162	For 4 months	Eiermann et al. [17]
		Tamoxifen	175		
IMPACT	Anastrazole versus tamoxifen	Anastrazole	113	For 12 weeks	Smith et al. [18]
		Tamoxifen	108		
PROACT	Anastrazole versus tamoxifen	Anastrazole	228	For 3 months	Cataliotti et al. [16]
		Tamoxifen	223		
Exemestane	Exemestane versus tamoxifen	Exemestane	76	For 3 months	Semiglazov et al. [19]
		Tamoxifen	75		

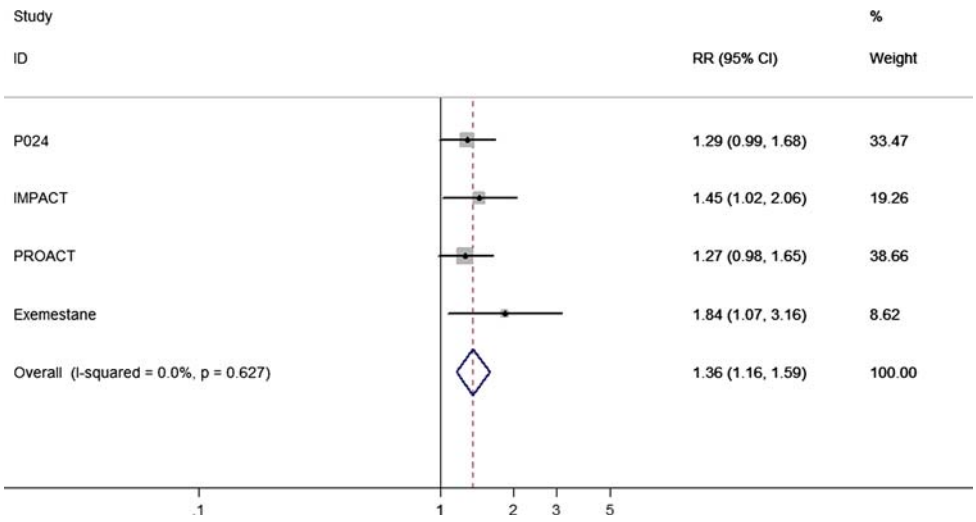

Fig. 1 Meta-analysis evaluating the breast conserving surgery rate of pre-operative AIs compared to pre-operative tamoxifen in postmenopausal women with hormone receptor-positive breast cancer

adverse events, we compared hot flashes, nausea, headache, and fatigue. Q-statistics of all adverse events showed the presence of homogeneity (hot flashes $P = 0.454$, nausea $P = 0.743$, headache $P = 0.579$, fatigue $P = 0.169$). We obtained pooled results by a fixed effect model. The pooled results were as follows: hot flashes (RR, 0.84; 95% CI, 0.63–1.11; $P = 0.221$), nausea (RR, 1.10; 95% CI, 0.79–1.53; $P = 0.565$), headache (RR, 2.02; 95% CI, 1.18–3.45; $P = 0.011$) (Fig. 2), and fatigue (RR, 0.63; 95% CI, 0.34–1.17; $P = 0.169$) (Table 2). Hot flashes, nausea, and fatigue were not different between the pre-operative AI and pre-operative tamoxifen groups. However, headache was significantly more frequent in the pre-operative AI group ($P = 0.011$). Among the four trials, only the IMPACT trial showed clinically significant adverse events. Vaginal discharge was not reported in any patient on pre-operative AI (0%) compared with 6% of patients on tamoxifen, and thromboembolic events (e.g., deep vein thrombosis and pulmonary embolism) were recorded only in the pre-operative tamoxifen group (2%) [18].

Discussion

In current clinical practice, pre-operative endocrine therapy is generally offered to postmenopuasal patients with hormone receptor positive tumors that are either inoperable or would require a mastectomy. Actually, most of clinical trials about pre-operative endocrine therapy enrolled patients were considered unfit for primary systemic chemotherapy [2]. One of the main goal of pre-operative endocrine therapy is to allow BCS instead of mastectomy because BCS was equivalent to mastectomy in terms of survival. Fisher et al. [21] reported that BCS with or without irradiation of the breast resulted in rates of disease-free survival, distant-disease-free survival, and overall survival that were not significantly different from those observed after total mastectomy.

Most published evidence regarding pre-operative therapy has focused on pre-operative systemic chemotherapy rather than endocrine therapy [22–26]. However, pre-operative endocrine therapy might be effective and feasible in postmenopausal women with hormone receptor-positive

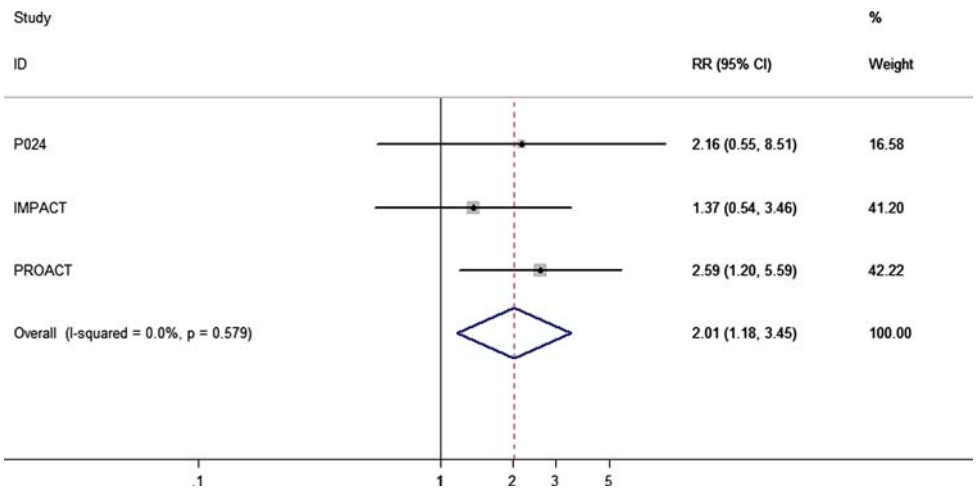

Fig. 2 Meta-analysis evaluating the incidence of headache of pre-operative AIs compared to pre-operative tamoxifen in postmenopausal women with hormone receptor-positive cancer

breast cancer. Endocrine therapy is less toxic than any systemic chemotherapy, and its efficacy is not inferior to systemic chemotherapy, especially in postmenopausal women with hormone receptor-positive breast cancer. Postmenopausal women usually have relatively poor performance and more co-morbid diseases. Pre-operative endocrine therapy can provide an alternative treatment measure.

Our meta-analysis indicated that pre-operative AI was more effective than pre-operative tamoxifen in terms of BCS rate with homogeneity. Furthermore, there was no difference in clnically relevant toxicities betweent the two treatments.

The four trials we included used several AIs. One trial (P024) [17] used letrozole, two trials (IMPACT and PROACT) [16, 18] used anastrazole, and one trial (Exemestane) [19] used exemestane. This meta-analysis included three published articles about the P024, IMPACT, and PROACT trials and one presented article about the Exemestane trial. The outcomes (clinical objective response rate, ultrasound objective response rate, and BCS rate) and the incidence rate of toxicities (hot flashes, nausea, headache and fatigue) of each study were inconsistent, leading to controversies about treatment preference. We attempted to identify which agent is more effective and less toxic as a pre-operative endocrine therapy. Although there was no difference between therapies in the incidence of hot flashes, nausea, or fatigue, the incidence of headache was statically significant. However, headache is a manageable toxicity and not clinically relevant. And other cardiovascular events were not reported at all in both treatment groups. However, clinically significant vaginal discharge (5.6%) and thromboembolic events (1.9%) were reported only in the pre-operative tamoxifen group in the IMPACT trial. Therefore, we could carefully suggest that pre-operative AI is not inferior to tamoxifen in terms of toxicities.

There are some limitation to our approach. First, our meta-analysis is potentially limited due to the small number of trials. Second, most of clinical trials about pre-operative endocrine therapy enrolled patients were considered unfit for primary systemic chemotherapy. Although our meta-analysis is potentially limited due to limitations, we believe it to be the first meta-analysis about pre-operative endocrine therapy in postmenopausal women with hormone receptor-positive breast cancer. Until now, there has been no standard recommendation regarding pre-operative endocrine therapy in postmenopausal women with hormone receptor-positive breast cancer.

In conclusion, pre-operative AI has better BCS rate than tamoxifen and in terms of toxicities, is not inferior to tamoxifen; therefore, we could suggest pre-operative AI instead of tamoxifen for those postmenopausal patients with hormone receptor-positive breast cancer, who are not eligible for chemotherapy.

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