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Systematic or Meta-analysis Studies

Efficacy of extended adjuvant therapy with aromatase inhibitors in early breast cancer among common clinicopathologically-defined subgroups: A systematic review and meta-analysis

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ABSTRACT

Background: Randomized controlled trials (RCTs) have shown improvements in breast cancer outcomes from extending treatment with aromatase inhibitors (AIs) beyond the initial 5 years after diagnosis. Consistency of this effect in common clinicopathologically defined subgroups was not been reported systematically.

Methods: We identified RCTs comparing extended AIs to placebo or no treatment using a systematic search of MEDLINE and a review of abstracts from key conferences between 2013 and 2016. Hazard ratios (HRs) and 95% confidence intervals (CI) for disease-free survival (DFS) were included in a meta-analysis using generic inverse variance and random effects modelling. Pre-specified subgroups included: age (<60 ± 5 years versus ≥60 ± 5 years), tumor size (>2 cm versus ≤2 cm), nodal status (positive versus negative), hormone receptor status (double versus single receptor expression) and receipt of adjuvant chemotherapy (yes versus no).

Results: Seven trials comprising 16,349 patients were analyzed. Overall, the effect of extended AIs was similar in all subgroups. Non-significantly greater effect sizes were seen in patients with larger tumors (HR for DFS 0.77 versus 0.88, p for difference = 0.44), nodal involvement (HR = 0.72 versus 0.83, p for difference = 0.22), double hormone receptor expression (HR = 0.68 versus 1.01, p for difference = 0.31) and receipt of adjuvant chemotherapy (HR = 0.71 versus 0.80, p for difference = 0.51).

Conclusions: Extended treatment with AIs is associated with similar relative improvements in DFS in all subgroups analyzed. The combination of greater effect size and higher absolute risk of recurrence in node positive and larger tumors will likely translate to higher absolute benefits from extended AIs in these groups.

Introduction

The role of adjuvant endocrine therapy for women with hormone receptor positive early breast cancer is well established [1]. Aromatase inhibitors (AIs) have been shown to improve breast cancer outcomes for postmenopausal women, and their use in this population is a gold standard [1]. The risk of recurrence persists for more than a decade after the initial 5 years of adjuvant hormonal therapy [2]. This suggests a potential benefit from extended endocrine treatment. While extending treatment beyond 5 year of tamoxifen appears beneficial [3], there remains uncertainty regarding the optimal duration of adjuvant AIs treatment. Some data indicate benefit from extending adjuvant endocrine treatment beyond 5 years [4–6], the literature is inconsistent [7,8].

Although extended treatment with AIs is associated with a 20–25% relative improvement in disease free survival (DFS) in

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Table 1
Characteristics of included studies.

Trial/Median follow-up	Study arm (num patients)	Control arm (num patients)	Median Age (years)	Tumour size[a]	Node positive (%)	Grade 3 (%)	Dual receptor expression (%)	Prior chemotherapy (%)	Prior endocrine therapy
ABCSG 6a, Jakesz et al. [4] (62 months)	Anastrozole 3 years (387)	None (469)	68.2	T1 62.7% T2 35.4% T3 1.9%	32.5%	20%	78%	NR	Tamoxifen alone 5 years: 52.6% Tamoxifen 5y+ aminoglutethimide first 2 years with tamoxifen: 47.4%
MA.17R, Goss et al. [5] (76 months)	Letrozole 5 years (959)	Placebo (959)	65.1	T1-2 90.5% T3-4 8.7%	51.4%	NR	80.4%	58.3%	Tamoxifen: 79.3% AIs[b]: 100%
MA 17, Goss et al. [6] (30 months)	Letrozole 5 years (2572)	Placebo (2577)	62	NR	45.6%	NR	NR	45.3%	Tamoxifen: 100%, median duration usage 5 years AI: 0%
NSABP B-33, Mamounas et al. [7][c] (30 months)	Exemestane 5 years (783)	Placebo (7 7 9)	60	T1 61% T2-4 38%	48%	NR	81%	55%	Tamoxifen: 100%, duration 57-67 months AIs: 0%
Dutch DATA, Tjan-Heijnen et al. [8] (49 months, adapted)	Anastrozole 6 years (827)	Anastrozole 3 years (833)	57	T1 45.5% T2 47.4% T3-4 7%	66.2%	28.1%	75.9%	68.4%	Tamoxifen: 100%, 2–3 years AIs: 0%
IDEAL, Blok et al. [17,18] (78 months)	Letrozole 5 years (903)	Letrozole 2.5 years (898)	55–65[d]	NR	73.1%	NR	NR	NR	Five years of endocrine therapy: -Tamoxifen: 11.6% -AIs: 24% -Sequence of tamoxifen and AIs: 60% -Unknown: 4.4%
NSABP B-42, Mamounas et al. [16] (83 months)	Letrozole 5 years (1959)	Placebo (1964)	≥60[d]	NR	42.6%	NR	NR	NR	Five years of endocrine therapy: -AIs: 60.9% -Sequence of tamoxifen and AIs: 39.1%

Abbreviations: AIs- aromatase inhibitors, NR- not reported.
[a] Tumor size: T1 ≤ 2 cm, T2 > 2 cm ≤ 5 cm, T3 > 5 cm
[b] 99% received prior AIs for 4.5–6 years.
[c] Study required early accrual termination and unblinding in October 2003 in view of the results of the MA.17 [5].
[d] Median age not reported, but estimated from reported age ranges.