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Review

Exemestane: One part of the chemopreventive spectrum for ER-positive breast cancer

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ABSTRACT

Development of drugs to prevent breast cancer has focused largely on anti-estrogenic agents, leading to approval by the US FDA of two such agents for this purpose: tamoxifen and raloxifene. However, the uptake of these drugs by high-risk women and their primary care physicians has been limited, due in large part to a perceived unfavorable risk:benefit balance. The current focus is on aromatase inhibitors, which appear to have more acceptable side effects in addition to being more efficacious in reducing breast cancer risk in high-risk women. The placebo-controlled phase III MAP.3 trial tested the AI exemestane in high-risk women and documented a 65% relative reduction in total and a 73% reduction in ER-positive breast cancers in the intervention compared to the placebo group. Toxicities centered around musculoskeletal side effects, but in the relatively short 35-month median follow-up period, these did not impair quality-of-life. A bone study nested within MAP.3 demonstrated significant decreases in bone mineral density (BMD) and in structural parameters of bone quality. The strengths and weaknesses of preventive exemestane as evaluated in the MAP.3 trial are discussed as are relevant areas for future consideration: influence of obesity, alternative dosing, and biomarker use in phase III prevention trials of aromatase inhibitors.

Introduction

As the most common cancer among women in the world,[1] breast cancer continues to pose a major challenge despite advances in therapy. Hence, increasing emphasis has been placed on preventing this disease. Extensive pre-clinical data support the notion that ER positivity is a marker that a cancer is fueled by estrogen's promotion of cell proliferation. The idea that anti-estrogens might prevent, as well as treat, breast cancer came from secondary outcomes in adjuvant trials for early-stage breast cancer. Specifically, new primary cancers in the contralateral breast (CLBCs) were shown to be reduced in women whose ER-positive breast cancers were treated with adjuvant anti-estrogens.[2] This efficacy in this secondary prevention setting encouraged the testing of these agents in high-risk but unaffected women.[3]

Anti-estrogenic agents fall into two major classes: selective estrogen receptor modulators (SERMs) and aromatase inhibitors (AIs). The SERMs resemble estrogen in being ligands of the ER. However, unlike estrogen, SERM binding to the ER downregulates ER activity in the breast, antagonizing the cancer-promoting effect of estrogen in this tissue. Aromatase inhibitors, in contrast, prevent estrogen synthesis so it is not available to bind the ER in target tissues.

Anti-estrogens in breast cancer prevention

Selective estrogen receptor modulators

Tamoxifen was suggested as having potential preventive activity in major adjuvant trials conducted in the 1980s demonstrating an approximately 35% decrease in incidence of CLBCs in women with early-stage disease.[2] Based on these data, four prevention trials were conducted to compare tamoxifen to placebo for breast cancer prevention (Table 1).

The study designs of these trials varied, with three of them limiting their participant cohort to high-risk women.[4–8] Although not all four trials yielded similarly positive outcomes, an overview

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Table 1
Baseline variables and outcomes in phase III primary prevention trials of SERMs and AIs.

Study: agents	NSABP P-1:BCPT: tamoxifen[a] vs placebo[o]	IBIS-I: tamoxifen[a] vs placebo[p]	Royal Marsden: tamoxifen[a] vs placebo[q]	Italian tamoxifen trial: tamoxifen[a] vs Placebo[r]	NSABP P-2: STAR: raloxifene[b] vs tamoxifen[s]	NCIC MAP.3: exemestane vs placebo[t]
Mean or median follow-up	74 mos Mean FU	96 mos Median FU	13 yrs Median FU	11 yrs Mean FU	81 mos Median FU	35 mos Median FU
Number randomized/ mean or median age at randomization	13,388/NA	7145/50.7 yrs Mean	2494/2471 Analyzed/ 47 yrs median[n]	5408/51 Yrs Median	19,747/58.5 yrs Mean (postmenopausal)	4560/62.5 yrs Median (postmenopausal)
Risk level of participants (% participants at a given risk score level)	5-yr Risk[c]: ≤2% (~25%) 2.01–3% (~31%) 3.01–5% (~26.6%) ≥5% (~17.3%)	10-yr Risk[d]: <2% (~1.5%) 2–3% (~3.5%) 35% (~24%) 5–10% (~55%) >10% (~16%)	NA[e]	NA[f]	Mean 5-yr risk[c]: = 4.03%	Median 5-yr risk[c]: = 2.3%
1° Endpoint[l]: incidence	Invasive BC: RR = 0.57 (95% CI, 0.46–0.70; $p < 0.001$)	BC (invasive + DCIS):RR = 0.73 (95% CI, 0.58–0.91; $p = 0.004$)	Invasive BC: HR = 0.78 (95% CI, 0.58–1.04; $p = 0.1$)	BC: RR = 0.84 (95% CI, 0.60–1.17)	Invasive BC: RR = 1.24 (95% CI, 1.05–1.47; $p = 0.01$)	Invasive BC: HR = 0.35 (95% CI, 0.18-.0.70; $p = 0.002$)
2° Endpoints[l]: incidence						
Noninvasive BC	Total noninvasive (DCIS + LCIS): RR = 0.63 (95% CI, 0.45–0.89; $p = 0.008$)	DCIS: RR = 0.63 (95% CI, 0.32–1.20)	DCIS: OR = 1.56 (95% CI, 0.67–3.61; $p = 0.4$)	Noninvasive: OR = 1.51 (95% CI, 0.54–4.24; $p = 0.4$)	Total noninvasive (DCIS + LCIS + mixed): RR = 1.22 (95% CI, 0.95–1.59; $p = 0.12$); DCIS: RR = 1.22 (95% CI, 0.95–1.69)	DCIS: HR = 0.65 (95% CI, 0.28–1.51; $p = 0.31$)
BC ER status: ER + BC	RR = 0.38 (95% CI, 0.28–0.50)	RR = 0.66 (95% CI, 0.50–0.87)	HR = 0.61 (95% CI, 0.43–0.86; $p = 0.005$)	RR = 0.77 (95% CI, 0.51–1.16)[j]	RR = 0.93 (95% CI, 0.72–1.24)[g]	HR = 0.27 (95% CI, 0.12–0.60; $p < 0.001$)
BC ER status: ER- BC	RR = 1.31 (95% CI, 0.86–2.01)	RR = 1.00 (95% CI, 0.61–1.65)	HR = 1.4 (95% CI, 0.7–2.6; $p = 0.3$)	RR = 1.10 (95% CI, 0.59–2.05)[j]	RR = 1.15 (95% CI, 0.75–1.77)[g]	HR = 0.80 (95% CI, 0.21–2.98; $p = 0.74$)
Adverse events:						
Endometrial cancer	Invasive: RR = 3.28 (95% CI, 1.87–6.03) ≤49 yrs: RR = 1.42 (CI, 0.55–3.81) ≥50 yrs: RR = 5.33 (CI, 2.47–13.17) In situ: RR = 0.35 (CI, 0.01–4.36)	RR = 1.55 (95% CI, 0.68–3.65)	HR = 2.69 (95% CI, 0.96–7.55; $p = 0.06$)	NA	RR = 0.55 (95% CI, 0.36–0.83; $p = 0.003$)	NA[h]
Thromboembolic: overall	NA	RR = 1.72 (95% CI, 1.27–2.36)	OR = 2.55 (95% CI, 0.68–9.67; $p = 0.2$)	RR = 1.63 (95% CI, 1.02–2.62; $p = 0.04$)	RR = 0.75 (95% CI, 0.60–0.93; $p = 0.007$)	OR = 1.58 (95% CI, 0.61–4.08; $p = 0.3$)
Thromboembolic: pulmonary emboli	RR = 2.15 (95% CI, 1.08–4.51)	[DVT/PE: RR = 1.84 (95% CI, 1.21–2.82)][m]	NA	NA	RR = 0.80 (95% CI, 0.57–1.11)	NA
Thromboembolic: deep vein thrombosis	RR = 1.44 (95% CI, 0.9–2.30)	[DVT/PE: RR = 1.84 (95% CI, 1.21–2.82)][m]	NA	NA	RR = 0.72 (95% CI, 0.54–0.95)	NA
Cardiovascular events and stroke or all CVA events	Stroke: RR = 1.42 (95% CI, 0.97–2.08) TIA: RR = 0.91 (95% CI, 0.54–1.52) Ischemic heart disease: RR = 1.03 (95% CI, 0.79–1.36)	Stroke/CVA: RR = 1.25 (95% CI, 0.55–2.93) All cardiac events: RR = 0.99 (95% CI, 0.77–1.29)	Stroke: OR = 0.74 (95% CI, 0.28–2.00; $p = 0.6$)	Cerebrovascular events total: RR = 1.78 (95% CI, 0.70–4.52; CV events: RR = 1.04 (95% CI, 0.30–3.58); CV-arrhythmia: RR = 1.73 (95% CI, 1.01–2.98)	NA	Stroke/TIA: OR = 1.19 (95% CI, 0.53–2.66; $p = 0.7$) CV events: (95% CI, 0.72–1.26; $p = 0.78$)
Endocrine: hot flashes (bothersome), vasomotor	NA in reference 8; TAM: 45.7% vs Placebo: 28.7%[i]	[Combined gynecologic and vasomotor: RR = 1.08 (95% CI, 1.06–1.10)][m]	OR = 1.99 (95% CI, 1.69–2.35; $p < 0.001$)	RR = 1.78 (95% CI, 1.57–2.00)	NA	Vasomotor symptoms in MENQOL: OR = 1.49 (95% CI, 1.31–1.69; $p < 0.001$)[k]