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Efficacy and safety of endocrine monotherapy as first-line treatment for hormone-sensitive advanced breast cancer

A network meta-analysis

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Abstract

Background: Endocrine therapy was recommended as the preferred first-line treatment for hormone receptor-positive (HR+, i.e., ER+ and/or PgR+), human epidermal growth factor receptor-2-negative (HER2−) postmenopausal advanced breast cancer (ABC), but which endocrine monotherapy is optimal lacks consensus. We aimed to identify the optimal endocrine monotherapy with a network meta-analysis.

Methods: We performed a network meta-analysis for a comprehensive analysis of 6 first-line endocrine monotherapies (letrozole, anastrozole, exemestane, tamoxifen, fulvestrant 250 mg and 500 mg) for HR+ HER2− metastatic or locally advanced breast cancer in postmenopausal patients. The main outcomes were objective response rate (ORR), time to progression (TTP), and progression-free survival (PFS). Secondary outcomes were adverse events.

Results: We identified 27 articles of 8 randomized controlled trials including 3492 patients in the network meta-analysis. For ORR, the treatments ranked in descending order of effectiveness were letrozole > exemestane > anastrozole > fulvestrant 500 mg > tamoxifen > fulvestrant 250 mg. For TTP/PFS, the order was fulvestrant 500 mg > letrozole > anastrozole > exemestane > tamoxifen > fulvestrant 250 mg. We directly compared adverse events and found that tamoxifen produced more hot flash events than fulvestrant 250 mg.

Conclusions: Fulvestrant 500 mg and letrozole might be optimal first-line endocrine monotherapy choices for HR+ HER2− ABC because of efficacious ORR and TTP/PFS, with a favorable tolerability profile. However, direct comparisons among endocrine monotherapies in the first-line therapy setting are still required to robustly demonstrate any differences among these endocrine agents. Clinical choices should also depend on the specific disease situation and duration of endocrine therapy.

Abbreviations: 95% CI = 95% confidence interval, ABC = advanced breast cancer, AIs = aromatase inhibitors, DIC = Deviance information criteria, ER = estrogen receptor, HER2− = human epidermal growth factor receptor-2-negative, HR = hazard ratio, HR+ = hormone receptor-positive, I^2 = inconsistency statistic, IFs = inconsistency factors, LABC = locally advanced breast cancer, MBC = metastatic breast cancer, ORR = objective response rate, PFS = progression-free survival, PgR = progesterone receptor, PRISMA = Systematic Reviews and Meta Analyses, RCTs = randomized controlled trials, TTP = time to progression.

Keywords: breast cancer, endocrine therapy, first-line treatment, network meta-analysis

1. Introduction

Breast cancer is the most common cancer among women in the world; nearly 1.67 million new cancer cases were diagnosed (25% of all cancers) in 2012.[1] Advanced breast cancer (ABC) is a treatable but still generally incurable disease; most patients are postmenopausal women with hormone receptor-positive and human epidermal growth factor receptor-2-negative (HR+ HER2−) ABC. Current goals of therapy are to both optimize survival time and palliate symptoms to maintain quality of life. Endocrine therapy was recommended as the preferred first-line treatment to achieve these goals because of proven efficacy and generally favorable tolerability profile.[2–4]

Tamoxifen, a selective estrogen receptor modulator, was the most widely used first-line endocrine therapy for postmenopausal patients with HR+ HER2− locally advanced or metastatic breast cancer for many years.[5] In recent years, third-generation aromatase inhibitors (AIs) including anastrozole, letrozole, and exemestane have largely replaced tamoxifen as first-line endocrine therapy because of greater efficacy and tolerability.[6,7] Fulvestrant is an estrogen receptor (ER) downregulator distinct from other endocrine agents, and fulvestrant, 500 mg (high dose),

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has efficacy superior to fulvestrant 250 mg (low dose) for treating ER-positive ABC with progression after previous endocrine therapy.[8–10] A clinical trial found that high-dose fulvestrant was at least as effective as anastrozole in clinical benefit rate and ORR and was associated with significantly longer TTP in first-line ABC therapy.[11] So far, no study has directly compared first-line treatment with letrozole and the 2 other AIs or high-dose and low-dose fulvestrant. We have insufficient evidence from head-to-head clinical trials in the first-line treatment setting. The clinical significance and difference of these different endocrine therapies remain uncertain.

Network meta-analysis can combine direct and indirect evidence from different studies simultaneously and compare all therapeutic methods to assess the relative efficacy of each treatment based on randomization,[12,13] so it can assess the relative effects of different endocrine therapies better than traditional head-to-head meta-analysis. Thus, we performed a network meta-analysis for a comprehensive analysis of 6 first-line endocrine monotherapies (letrozole, anastrozole, exemestane, tamoxifen, fulvestrant 250 and 500 mg) for HR+ HER2− ABC in postmenopausal patients.

2. Materials and methods

The reporting of this study adhered to the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidelines.[14] Two investigators (JZ and YH) independently performed the literature search, study selection, and data extraction. Discrepancies were resolved by discussion with a third investigator (KW). This study was performed with the approval of the institutional review board of Shantou University Medical College.

2.1. Literature search

ABC comprises both inoperable locally ABC (LABC) and metastatic breast cancer (MBC) or stage IV.[3] We identified randomized controlled trials (RCTs) of endocrine therapy for human HR+ HER2− ABC by searching MEDLINE via PubMed for articles published through May 2015 with the following MeSH terms and free text words: breast neoplasm, breast, mammary, cancer, carcinoma, neoplasm, tumor; advanced, metastatic; aromatase inhibitors, anastrozole, arimidex, letrozole, femara, exemestane, aromasin, tamoxifen, nolvadex, fulvestrant, selective estrogen receptor down regulator. In addition, reference lists of retrieved articles and the websites of American Society of Clinical Oncology, San Antonio Breast Cancer Symposium, and ClinicalTrials.gov were checked to identify further studies.

2.2. Study selection

Eligible studies were RCTs, blinded or not, assessing the efficacy and safety of anastrozole, letrozole, exemestane, tamoxifen, fulvestrant 250 and 500 mg, for first-line monotherapy of HR+ (ER+ and/or PgR+) postmenopausal women with metastatic or LABC who had no endocrine or cytotoxic chemotherapy for advanced disease, or had received no adjuvant endocrine therapy within 12 months before entry into the trials. We excluded studies that did not report the outcomes of interest, polyendocrine therapy studies, studies of endocrine monotherapy used as neoadjuvant treatment, abstracts from scientific meetings, and publications not in English or Chinese.

2.3. Data extraction and quality assessments

Two investigators independently extracted the first author, publication year, study location, study design, type of blinding, patient characteristics, and outcome measures from reports. We used the Cochrane Collaboration Risk of Bias tool to assess study quality, including the following potential biases: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias.[15] Any disagreements during extraction were resolved by consensus.

The primary outcome was efficacy, including objective response rate (ORR), time to progression (TTP), and progression-free survival (PFS). Secondary outcomes were adverse events. Because adverse events were inconsistently reported across studies, we selected the most frequently reported events (hot flashes, weight gain, nausea, and bone pain). For ORR and adverse events, dichotomous data were extracted as the number of patients with the outcome of interest and the total number of patients in the treatment groups. For TTP and PFS, survival data were extracted as the hazard ratio (HR) and 95% confidence interval (95% CI). Because the survival time in ABC is short, most deaths were assumed to be disease-specific. Each analyzed study included disease-specific death events as an endpoint; therefore, TTP and PFS were assumed to be similar.

2.4. Statistical analysis

The analysis of patients was based on intent-to-treat and that of efficacy on total number of randomly assigned patients. For ORR and adverse events, if only percentages were reported, the nearest whole number of events was estimated instead of the actual number.

For direct comparison of different treatments, we conducted pair-wise meta-analysis to synthesize studies comparing the same pair of treatments.[16] Odds ratios (ORs) and 95% CIs were calculated for dichotomous outcomes. Statistical heterogeneity among studies was assessed with the inconsistency statistic (I^2). $I^2 < 25\%$ was considered low heterogeneity and $I^2 > 50\%$ high heterogeneity.[17] Calculations involved use of STATA 12.0 (StataCorp, College Station, TX).

For the primary analysis, we conducted Bayesian network meta-analysis to synthesize direct and indirect treatment comparisons to assess the treatment effect between all interventions and rank the treatments graphically.[18–21] Analysis based on noninformative priors for effect sizes and precision involved the Markov chain Monte Carlo method with 10,000 initial iterations to burn in and the next 55,000 iterations for estimations.[20,22] We compared outcome variables with a fixed-effects model. The consistency between direct and indirect evidence is one important assumption of the network meta-analysis. We checked this assumption by the Bucher method to determine whether it was similar enough to combine the direct and indirect evidence.[23–25] That is, we calculated the difference between direct and indirect evidence in closed loops in the network. Inconsistent loops were identified with a 95% CI excluding 0, which could confirm the disagreement between direct and indirect evidence.[26] We also performed a sensitivity analysis repeating the main computations with a random-effects model. Deviance information criteria (DIC) was used to compare the fit of the fixed-effects and random-effects models .[23] Calculations involved use of R (http://www.R-project.org, the R Foundation for Statistical Computing, Vienna, Austria) and WinBUGS 1.4.3 (MRC Biostatistics Unit, Cambridge, UK).

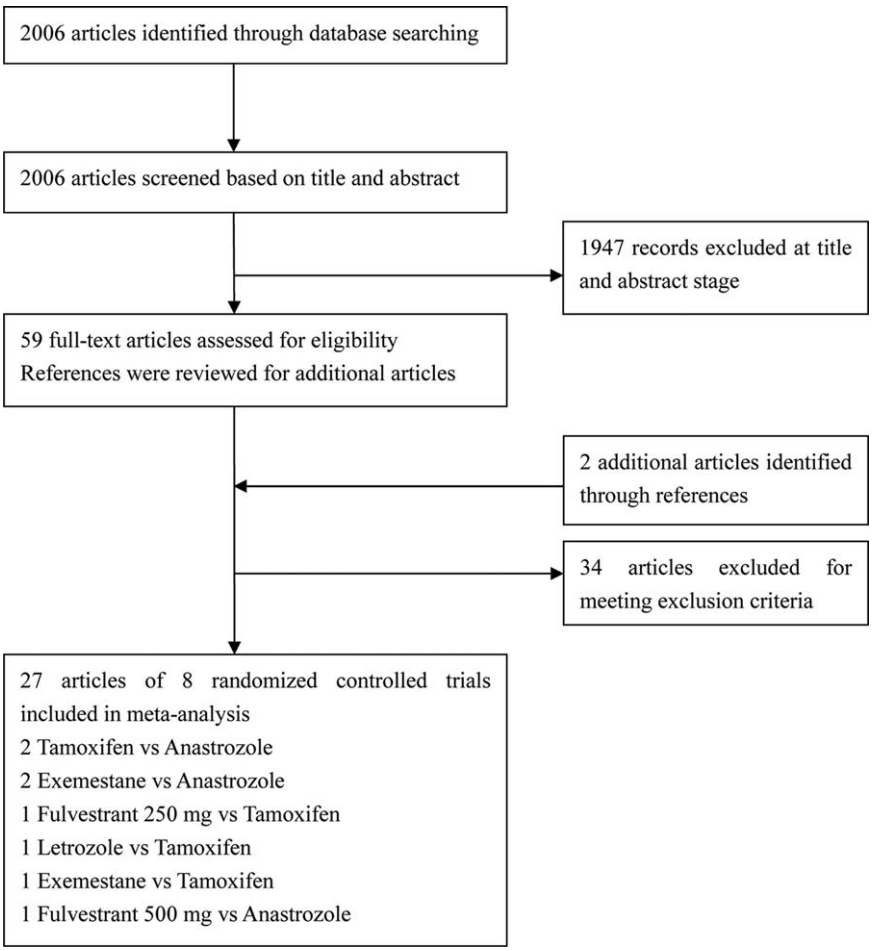

Figure 1. Flowchart for study selection.

3. Results

3.1. Characteristics of included trials

The literature search yielded 2006 records; 59 records remained after screening titles and abstracts. We added another 2 articles from reference lists, for 61 full-text articles assessed for eligibility; 34 articles were excluded. Finally, 27 articles of 8 RCTs were included (Fig. 1). All were 2-arm trials [11,27–52] with 3492 patients with ABC randomly assigned to receive 1 of the 6 first-line monotherapies: anastrozole, letrozole, exemestane, tamoxifen, fulvestrant, 250 and 500 mg. The main characteristics of the studies are in Table 1. The median ages of patients ranged from 63 to 72 years. The methodological quality of 5 double-blind studies was high and that of 3 other open-label studies [11,49,50] was moderate (Supplemental Data, S1 Fig, http://links.lww.com/MD/B834 S2 Fig, http://links.lww.com/MD/B834). All studies were considered to have no selective reporting bias or other bias, but most did not report the techniques for concealment.

3.2. Direct comparisons

For direct comparison of different treatments (Supplemental Data, S1 Table, http://links.lww.com/MD/B834), the results suggested that letrozole was more efficacious for both ORR and TTP/PFS than tamoxifen; exemestane was more efficacious for ORR than tamoxifen; and fulvestrant 500 mg was more efficacious for TTP/PFS than anastrozole. In side-effect analysis, fulvestrant 250 mg produced fewer hot flash events than tamoxifen, with no difference between other adverse event types.

3.3. Network meta-analysis

The full network of comparisons is illustrated in Fig. 2. We found one closed loop of comparisons connecting anastrozole, exemestane, and tamoxifen. We assessed the difference between direct and indirect estimates for this loop by inconsistency factors (IFs) with corresponding 95% CIs. IFs were compatible with zero (ORR, IF = 0.61, 95% CI −0.17 to 1.39; TTP/PFS, IF = 0.18, 95% CI −0.21 to 0.58), which indicated that the loops were consistent.

The network meta-analysis results were based on a fixed-effects model because of better goodness of fit than random-effect models. Overall, the model fit was relatively robust. The efficacy of the 6 first-line monotherapies in the network meta-analysis is presented in Table 2. For ORR, letrozole was more efficacious than tamoxifen and fulvestrant 250 mg (OR = 0.59, 95% CI 0.43–0.80 and OR = 0.54, 95% CI 0.34–0.85, respectively) and exemestane was more efficacious than tamoxifen and fulvestrant 250 mg (OR = 0.67, 95% CI 0.48–0.91 and OR = 0.61, 95% CI 0.37–0.97, respectively). Most studies reported TTP; only 1 study reported PFS.[49] For TTP/PFS, anastrozole and letrozole were more efficacious than tamoxifen (HR = 0.84, 95% CI 0.72–0.99

Table 1

Characteristics of included studies.

Study	Comparison	Design	No. of patients randomized	Median age, years (range)	WHO performance status, (%) (0/1/2)	HR+ unknown (%)	HER2− (%)	Bone metastases (%)	Visceral disease (%)
Bonneterre et al, 2000[28]	Anastrozole (1 mg/d) vs. Tamoxifen (20 mg/d)	Randomized, double-blind, multicenter study	668	67 (34–92)	100 (0–2)	55	NR	47	34
Nabholtz et al, 2000[29]	Anastrozole (1 mg/d) vs. Tamoxifen (20 mg/d)	Randomized, double-blind, multicenter study	353	67 (30–92)	100 (0–2)	11	NR	59	48
Howell et al, 2004[42]	Fulvestrant (250 mg/mo) vs. Tamoxifen (20 mg/d)	Randomized, double-blind, double-dummy, parallel-group study	587	67 (43–93)	100 (0–2)	19	NR	30	NR
Mouridsen et al, 2001[33]	Letrozole (2.5 mg/d) vs. Tamoxifen (20 mg/d)	Phase III, randomized, double-blind, double-dummy, parallel-group study	907	65 (31–96)	57 (90–100)/35 (70–80)/8 (50–60) (Karnofsky)	34	NR	30	44
Paridaens et al, 2008[49]	Exemestane (25 mg/d) vs. Tamoxifen (20 mg/d)	Phase II/III, randomized, multicenter, open-label study	371	63 (37–87)	44/44/12	7	NR	35	47
Robertson et al, 2012[51]	Fulvestrant (HD) (500 mg/mo plus 500 mg on day14 of month 1) vs. Anastrozole (1 mg/d)	Phase II, randomized, multicenter, open-label study	205	66 (40–89)	100 (0–2)	0	48	8	56
Llombart-Cussac et al, 2012[50]	Exemestane (25 mg/d) vs. Anastrozole (1 mg/d)	Phase II, randomized, open-label, cross-over study	103	72 (45–94)	44/26/19	2	NR	NR	52
Iwata et al, 2013[52]	Exemestane (25 mg/d) vs Anastrozole (1 mg/d)	Phase III, randomized, double-blind study	298	64 (44–95)	82/18	NR	NR	27	49

HD = high dose, HER− = human epidermal growth factor receptor-2-negative, HR+ = hormone receptor-positive, NR = not reported, WHO = World Health Organization.

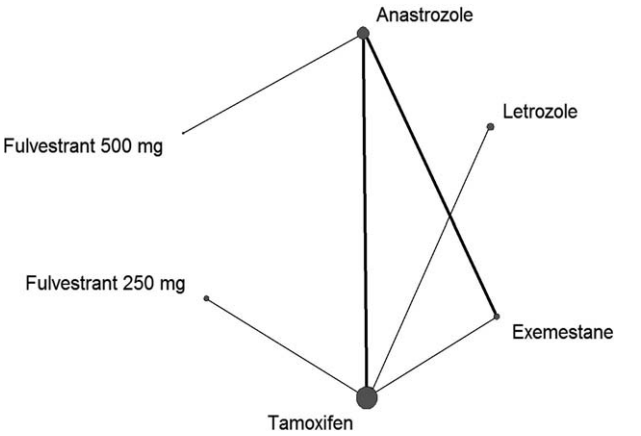

Figure 2. Network of eligible comparisons for the network meta-analysis for efficacy. The size of the nodes is proportional to the number of randomized participants (sample size), and the width of the lines is proportional to the number of trials comparing each pair of treatments.

and HR = 0.70, 95% CI 0.60–0.81, respectively); anastrozole, letrozole, and exemestane were more efficacious than fulvestrant 250 mg (HR = 0.72, 95% CI 0.56–0.93; HR = 0.60, 95% CI 0.46–0.76; HR = 0.75, 95% CI 0.57–0.97, respectively); and fulvestrant 500 mg was more efficacious than the other treatments except letrozole (HR = 1.54, 95% CI 1.09–2.11; HR = 1.61, 95% CI 1.08–2.25; HR = 1.84, 95% CI 1.24–2.55; HR = 2.17, 95% CI 1.35–3.11 for anastrozole, exemestane, tamoxifen, and fulvestrant 250 mg, respectively).

According to the Bayesian framework, we ranked treatments and estimated the cumulative probabilities of being the best treatment (Supplemental Data, S2 Table, http://links.lww.com/MD/B834). For TTP/PFS, the order was fulvestrant 500 mg > letrozole > anastrozole > exemestane > tamoxifen > fulvestrant 250 mg. For ORR, the treatments ranked in descending order of effectiveness were letrozole > exemestane > anastrozole > fulvestrant 500 mg > tamoxifen > fulvestrant 250 mg.

A sensitivity analysis of efficacy with random-effects model revealed no significant difference among the 6 endocrine therapies (Supplemental Data, S3 Table, http://links.lww.com/MD/B834), but the rank orders are consistent with the fixed-effects model.

4. Discussion

Our network meta-analysis of the efficacy of 6 first-line endocrine monotherapies for HR+ HER2− postmenopausal women with ABC was based on 8 studies including 3492 patients randomly assigned to receive 6 endocrine therapies. TTP/PFS was significantly longer with fulvestrant 500 mg, versus the other endocrine therapies except letrozole; for ORR, fulvestrant 500

Table 2

Network meta-analysis comparison of the efficacy of 6 first-line endocrine monotherapies for ORR and TTP/PFS.

Anastrozole	1.47 (0.99–2.16)	1.29 (0.93–1.77)	0.85 (0.66–1.09)	0.78 (0.50–1.18)	1.02 (0.55–1.79)	
1.21 (0.97–1.48)	**Letrozole**	0.91 (0.57–1.38)	0.59 (0.43–0.80)	0.54 (0.34–0.85)	0.72 (0.32–1.36)	
0.96 (0.80–1.15)	0.81 (0.62–1.01)	**Exemestane**	0.67 (0.48–0.91)	0.61 (0.37–0.97)	0.81 (0.39–1.54)	
0.84 (0.72–0.99)	0.70 (0.60–0.81)	0.88 (0.74–1.04)	**Tamoxifen**	0.91 (0.64–1.28)	1.22 (0.62–2.18)	ORR
0.72 (0.56–0.93)	0.60 (0.46–0.76)	0.75 (0.57–0.97)	0.86 (0.71–1.04)	**Fulvestrant 250 mg**	1.38 (0.64–2.72)	
1.54 (1.09–2.11)	1.29 (0.85–1.86)	1.61 (1.08–2.25)	1.84 (1.24–2.55)	2.17 (1.35–3.11)	**Fulvestrant 500 mg**	
			TTP/PFS			

ORR = objective response rate, PFS = progression-free survival, TTP = time to progression. Results are represented by the odds ratio and 95% confidence interval for ORR (upper right quadrant) and by the hazard ratio and 95% confidence interval for TTP/PFS (lower left quadrant). For ORR, odds ratio > 1 favour the column-defining treatment. For TTP/PFS, hazard ratio < 1 favour the column-defining treatment.

mg was not differed from the other therapies. Over all, fulvestrant 500 mg may be the best option for first-line treatment of HR+ HER2− ABC to prolong TTP/PFS. We found no significant difference among the 3 AIs for ORR or TTP/PFS. However, we identified a class effect for the 3 AIs because they were generally more efficacious than fulvestrant 250 mg and tamoxifen. Among AIs, letrozole may be preferred because it was significantly more efficacious than tamoxifen and fulvestrant 250 mg for both ORR and TTP/PFS. In addition, for TTP/PFS, it was the only therapy with no significant difference from fulvestrant 500 mg, and letrozole was ranked higher in efficacy than the 2 other AIs.

All studies indicated that the 2 monotherapies they compared were well tolerated. Direct comparisons revealed no significant difference among the 6 regimens except that tamoxifen produced more hot-flash events than fulvestrant 250 mg.[42] However, fulvestrant 250 mg was used more as second-line treatment for MBC with progression after antiestrogen therapy because it was approved by the US Food and Drug Administration for this purpose.[53]

Ferretti et al[54] conducted a traditional meta-analysis to evaluate the effectiveness and safety of AIs compared with tamoxifen as first-line endocrine therapy in postmenopausal MBC women. AIs were significantly better than tamoxifen for ORR, TTP, and clinical benefit in a fixed-effects but not random-effects model. In terms of safety, tamoxifen was associated with more thromboembolic and vaginal bleeding events when compared with AIs. Rob et al[55] conducted a systematic review of 3 first-line AIs for hormone-sensitive ABC. The authors indirectly compared 3 AIs in a network meta-analysis and found that letrozole and exemestane were better than anastrozole for ORR. Our study included 2 RCTs that directly compared exemestane and anastrozole [50,52] and found no significant difference between the AIs. However, the study by Rob et al found no significant difference with the more clinically relevant outcome of TTP/PFS, which was consistent with our findings. Mustafa et al[56] conducted a traditional meta-analysis to copare the relative efficacy and safety of fulvestrant to other endocrine therapy options (including anastrozole, exemestane, tamoxifen) in ABC and found that first-line monotherapy with fulvestrant 500 mg may delay progression when compared with AIs, which was also consistent with our findings.

To our knowledge, this is the first comparison of 6 endocrine monotherapies for first-line treatment of HR+ HER2− ABC that incorporated both direct and indirect evidence in a network meta-analysis. To compare trials with similar clinical features, we included only first-line treatment studies to avoid potential confounders from prior treatments and also excluded studies of different doses.[57] Our findings are consistent with the suggestions of prior published reviews,[54–56,58] indicating that some of the endocrine monotherapies differed both statistically and clinically. Thus, our results confirmed previous conclusions.

Our study has some limitations. First, we used published data rather than individual patient information, which contains more detailed appraisal of outcomes. Second, some included studies did not report randomization and allocation concealment adequately, which might undermine the validity of the overall findings.

5. Conclusion

In conclusion, our study found that fulvestrant 500 mg and letrozole might be the preferred first-line endocrine monotherapy choices for HR+ HER2− postmenopausal women with ABC because of their more efficacious ORR and TTP/PFS with favorable tolerability profiles. However, direct comparisons among first-line endocrine monotherapies are still required to robustly demonstrate the possible differences among these endocrine agents, especially fulvestrant 500 mg and letrozole. Clinical choices should also depend on the specific disease situation and duration of endocrine therapy.

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