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Everolimus plus endocrine vs endocrine therapy in treatment advanced ER+, HER2− breast cancer patients: A meta-analysis

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ABSTRACT

The purpose of this review was to compare the efficacy and safety of everolimus plus endocrine therapy with endocrine therapy for hormone receptor-positive, human epidermal growth factor 2 negative advanced breast cancer patients. We comprehensively searched the PubMed, the Cochrane Library, EMBASE, Web of Science, Chinese biomedicine literature database, WanFang Data, CNKI, and VIP database for relevant articles. The retrieval time limit is from building the database to July 2018. The computer search was supplemented with a manual search of reference lists for all available review articles. We scanned references of all included studies for additional studies. We included 7 randomized trials involving 1527 patients. Meta-analysis results are as follows: Everolimus plus endocrine therapy group is significantly better than endocrine therapy group in progression-free survival and clinical benefit rate, (hazard ratio [HR] = 0.48, 95% confidence interval [CI 0.42-0.55], $P < 0.00001$) and (risk ratio = 1.9, 95% CI [1.60-2.26], $P < 0.00001$). But there was no significant difference between the 2 groups in overall response rate and time to definitive deterioration (risk ratio = 4.37, 95% CI [0.79-24.27], $P = 0.21$) and (HR = 0.74, 95%

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CI [0.49-1.11], $P = 0.15$). In terms of safety, the incidence rate in everolimus plus endocrine therapy was higher than that in endocrine therapy group. Most frequently reported adverse events associated with everolimus treatment were stomatitis, rash, fatigue, diarrhea, decreased appetite, cough, dyspnea, and pneumonitis. The incidences of grade 3-4 adverse events were stomatitis, fatigue, diarrhea, pneumonitis, and hyperglycemia. Everolimus increased the efficacy of endocrine therapy in treatment advanced endocrine receptor-positive, human epidermal growth factor 2 negative breast cancer patients, and the safety profile of the combination is acceptable.

Introduction

Breast cancer is one of hormone-related tumors.[1] Hormone receptor-positive (HR+) breast cancer accounts for approximately 75% of all breast cancers, and almost 6%-10% of women with breast cancer present with advanced and/or metastatic disease, 20%-50% of the patients with early breast cancer eventually develop metastatic breast cancer, and their 5-year survival rate is about 26%. It is very urgent to improve the curative effect of advanced breast cancer.[2] Several guidelines recommend that endocrine therapy is the standard of care for advanced breast cancer with HR+ which only with bone and/or soft tissue metastasis or asymptomatic visceral metastasis.[3] However, resistance to endocrine therapy is quite common, leading to disease progression owing to either treatment failure or relapse and/or progression after initial response. Among them, 30% of HR+ breast cancer have primary endocrine resistance, and about 40% of patients were secondary endocrine resistance.[4] It was found that the mechanism of endocrine resistance and tumor progression is related to abnormal activation of several growth factor signaling pathways, especially the interaction between estrogen receptor (ER) pathway and PI3K/Akt/mammalian target of rapamycin (mTOR) pathway. Inhibiting the related targets of abnormal interaction with ER and reversing endocrine resistance is a new method to overcome endocrine resistance. Everolimus is an mTOR kinase inhibitor, it can block PI3K/Akt/mTOR pathway and restore the sensitivity of endocrine therapy in HR+ breast cancer patiens. [5,6] The antitumor effect of everolimus was observed in several phase I and II clinical studies in patients with breast cancer, the results suggesting that treatment with everolimus may enhance the efficacy of endocrine therapy and reverse hormone resistance in patients who are resistant to endocrine therapy.[7,8] However, some study showing that there was no difference in progression-free survival (PFS) between the combined treatment group and the control group, and there are more adverse reactions.[9] Therefore, the purpose of this meta-analysis including more randomized trials is to evaluate the efficacy and safety of everolimus combined with endocrine therapy group vs endocrine therapy group for HR+/HER2− breast cancer.

Methods

Literature search

The following data sources were searched: PubMed, The Cochrane Library, EMBASE, Web of Science, Chinese biomedicine literature database, WanFang Data, CNKI, and VIP database, we search for randomized controlled trials which comparing everolimus plus endocrine therapy (fulvestrant or exemestane or letrozole or anastrozole or tamoxifen or toremifene) with endocrine therapy alone in treatment advanced HR+, HER2− breast cancer patients. We used the

following terms: “everolimus,” “Afinitor,” “RAD-001,” “endocrine,” “breast cancer,” and “breast tumor.”

Inclusion and exclusion criteria

Studies were included if they were randomized controlled trials comparing everolimus plus endocrine therapy (fulvestrant or exemestane or letrozole or anastrozole or tamoxifen or toremifene) with endocrine therapy alone; all patients with histologically confirmed breast cancer; and patients were postmenopausal women with metastatic or locally advanced HR+, HER2− breast cancer that had recurred or progressed during or after endocrine therapy.

Evaluation method

Two evaluators independently screen and extract documents and cross-check them, with disagreements resolved by consensus opinion reached using the third reviewer. Both reviewers independently assessed the following domains: the information and characteristics of included trials, treatment methods, specific details, and follow-up time of the intervention measures; risk of bias, allocated concealment blinding, randomization, incomplete outcome data reporting, and selective outcome reporting. Discrepancies were resolved by discussion with the other investigator.

Statistical analysis

We planned to perform the meta-analysis according to the recommendations of the Cochrane Collaboration and analyzed the data using Review Manager (5.3). For dichotomous variables, we calculated the risk ratio (RR) with 95% confidence interval (CI). Continuous outcomes were analyzed by calculating weighted mean difference or standard mean difference. For analysis of survival index, we based on the method recommended by Parmar et al[10] to calculate the Log HR and standard error, then estimate and merge the HR and 95% CI using reciprocal of variance method. We used the I^2 statistic to assess heterogeneity between trials and the I^2 statistic to assess the extent of inconsistency. We used fixed effect model for calculations of summary estimates and their 95% CI unless there was significant heterogeneity, in which case chose a random effect statistical model. Subgroup analyses were intended to explore important clinical differences among trials that might be expected to alter the magnitude of treatment effect.

Results

Search results

We identified 592 potentially eligible trials, 58 were in Chinese and 534 in English. Of these, 585 trials were excluded for various reasons as follows: 17 studies were meta-analysis, 14 studies were letter, 41 studies were systematic reviews, 5 studies were editorial, 176 studies were review, 32 studies were case reports, 11 were comment, 13 studies were Phase I study, and others, such as, nonclinical research, not meet inclusion criteria, and so on. Finally, 7 trials[11-17] reported the effectiveness and safety for the comparison with everolimus plus endocrine therapy vs endocrine therapy alone in treatment advanced ER+, HER2− breast cancer patients.

Table 1
Characteristics of included studies.

Study	Country	Patients (*n*)(E/C)	Mean age (years)	Metastatic site	No. of metastatic sites (%) (≥3)(E/C)	Treatment (E/C)	follow-up (month)
Noguchi[11]	Japan	98/45	59.5/60	CNS Visceral (excluding CNS) Lung Liver Lung and liver Bone Bone only Other	42.8/33.3	EVE + EXE/PBO + EXE	18
Beck[12]	USA	100/37	62/61	Visceral Lung Liver Lung and liver Bone Bone only Other	42/43	EVE + EXE/PBO + EXE	18
Yardley[13]	global	485/239	62/61	Lung Liver Bone	36/37	EVE + EXE/PBO + EXE	18
Baselga[14]	Spain	138/132	68/66.9	Unclear	Unclear	EVE + letrozole/ PBO + letrozole	4
Bachelot[15]	France	54/57	63/66	Bone Bone only Visceral	24/28	EVE + tamoxifen/ tamoxifen	36.2
Guo[16]	China	23/23	57/59.5	Unclear	Unclear	EVE + EXE/EXE	9.5
Guo[17]	China	48/48	51/52	Lung Liver Brain Bone Soft tissue	24/28	EVE + ET/ ET	12

E, experimental group; C, control group.
EVE + EXE/PBO + EXE: everolimus 10 mg/d + exemestane 25 mg/d vs placebo+ exemestane 25 mg/d.
EVE + letrozole/PBO + letrozole: everolimus 10 mg/d + letrozole 2.5 mg/d vs placebo + letrozole2.5 mg/d.
EVE + tamoxifen/tamoxifen: everolimus 10 mg/d + tamoxifen 20 mg/d vs tamoxifen 20 mg/d alone.
EVE + ET/ET: tverolimus 5 mg/d + endocrine therapy vs endocrine therapy (fulvestrant 250 mg/4 week or exemestane 25 mg/d or letrozole 2.5 mg/d or anastrozole 1 mg/d or tamoxifen 20 mg/d or toremifene 60 mg/d).

The Characteristics and Quality of Included Studies are shown in Tables 1 and 2.

Meta-analysis results

PFS

Five studies reported the PFS. No heterogeneity was observed ($I^2 = 0\%$, $P = 0.56$). So, fixed effects model was used, and significant statistical difference was observed (HR, 0.48; 95% CI, 0.42-0.55, $P < 0.00001$). The results are shown in Figure 1.

The complete response

Five studies reported the complete response. No heterogeneity was observed ($I^2 = 0\%$, $P = 0.57$). So, fixed effects model was used, but there were no significant differences between the 2 groups (RR, 1.54; 95% CI, 0.79-3.02, $P = 0.21$). The results are shown in Figure 2.

Table 2
Quality assessment of included studies.

Study	Randomization	Blinding	Allocated concealment
Noguchi[11]	Adequate	Adequate	Adequate
Beck[12]	Adequate	Adequate	Adequate
Yardley[13]	Adequate	Adequate	Adequate
Baselga[14]	Adequate	Adequate	Adequate
Bachelot[15]	Adequate	Adequate	Adequate
Guo[16]	Adequate	Adequate	Adequate
Guo[17]	Unclear	Unclear	Unclear

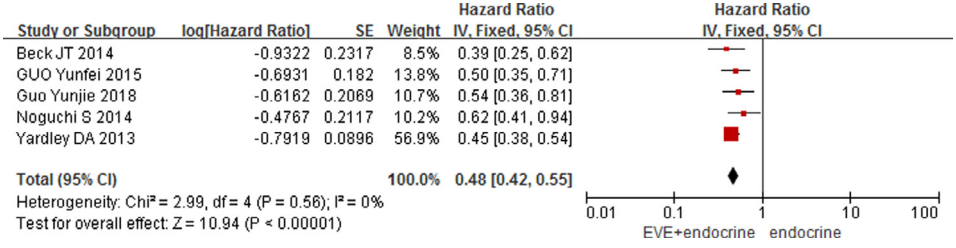

Fig. 1. The PFS of EVE + endocrine group vs endocrine group. EVE, everolimus; progression-free survival.

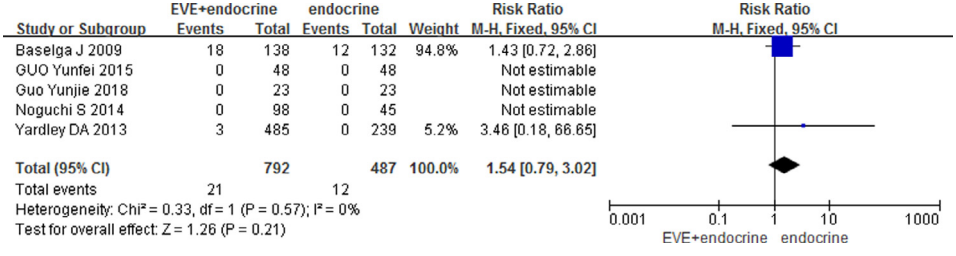

Fig. 2. The CR of EVE + endocrine group vs endocrine group. CR = complete response; EVE, everolimus.

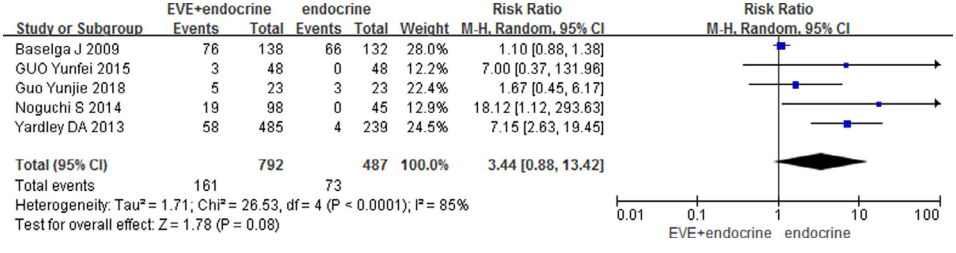

Fig. 3. The PR of EVE + endocrine group vs endocrine group. EVE, everolimus; PR = partial response.

The partial response

Five studies reported the partial response. Heterogeneity was observed ($I^2 = 85\%$, $P < 0.0001$). So, random effects model was used, but there were no significant differences between the 2 groups (RR, 3.44; 95% CI, 0.88-13.42, $P = 0.08$). The results are shown in Figure 3.

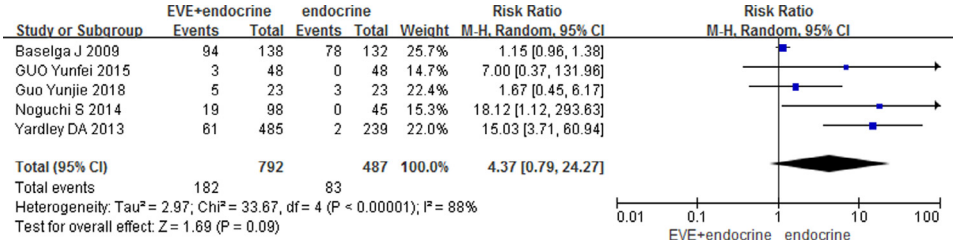

Fig. 4. The ORR of EVE + endocrine group vs endocrine group. ORR = overall response rate.

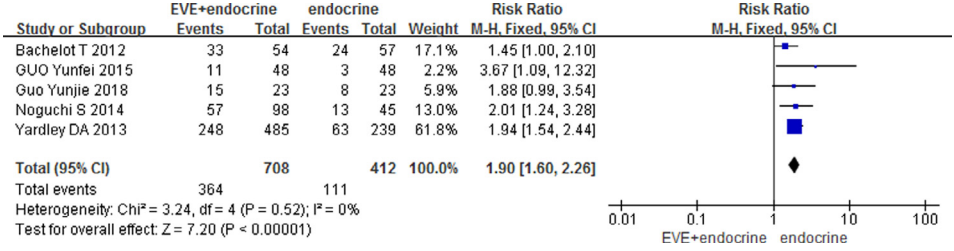

Fig. 5. The CBR of EVE + endocrine group vs endocrine group. CBR = clinical benefit rate; EVE, everolimus.

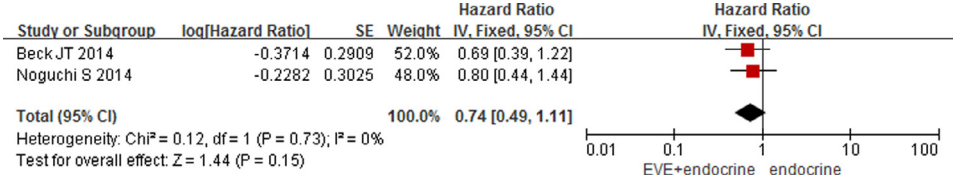

Fig. 6. The TTD of EVE + endocrine group vs endocrine group. EVE, everolimus; TTD, time to definitive deterioration.

The overall response rate

Five studies reported the overall response rate. Heterogeneity was observed ($I^2 = 88\%$, $P < 0.00001$). So, random effects model was used, but there were no significant differences between the 2 groups (RR 4.37; 95% CI, 0.79-24.27, $P = 0.09$). The results are shown in Figure 4.

The clinical benefit rate (CBR)

Five studies reported the CBR. No heterogeneity was observed ($I^2 = 0\%$, $P = 0.52$). So, fixed effects model was used, and significant statistical difference was observed (RR, 1.90; 95% CI, 1.60-2.26, $P < 0.00001$). The results are shown in Figure 5.

The time to definitive deterioration (TTD)

Two studies reported the TTD. TTD of the Global Health Status was defined as a

5% decrease in Health-related quality of life relative to baseline, with no subsequent increase above this threshold.[18] No heterogeneity was observed ($I^2 = 0\%$, $P = 0.73$). So, fixed effects model was used, but there were no significant differences between the 2 groups (HR, 0.74; 95% CI, 0.49-1.11, $P = 0.15$). The results are shown in Figure 6.

Table 3
Most common adverse events (all grades).

Adverse event	I^2(%)	*P*	Statistical method	Effect estimate	Z(*P*)
Stomatitis	0	0.61	RR(fixed effects model)	4.98[3.89,6.36]	12.8($P < 0.00001$)
Rash	57	0.04	RR(random effects model)	3.76[2.23,6.34]	4.95($P < 0.00001$)
Fatigue	0	0.57	RR(fixed effects model)	1.46[1.22,1.74]	4.12($P < 0.0001$)
Diarrhea	0	0.58	RR(fixed effects model)	1.92[1.51,2.43]	5.37($P < 0.00001$)
Decreased appetite	0	0.66	RR(fixed effects model)	2.28[1.69,3.09]	5.34($P < 0.00001$)
Nausea	0	0.85	RR(fixed effects model)	1.04[0.84,1.28]	0.33($P = 0.74$)
Cough	0	0.70	RR(fixed effects model)	2.32[1.65,3.26]	4.86($P < 0.00001$)
Pneumonitis	19	0.29	RR(fixed effects model)	20.45[7.07,59.12]	5.57($P < 0.00001$)
Decreased weight	0	0.81	RR(fixed effects model)	3.66[2.45,5.48]	6.32($P < 0.00001$)
Dyspnea	1	0.37	RR(fixed effects model)	2.28[1.56,3.34]	4.25($P < 0.00001$)
Anemia	72	0.01	RR(random effects model)	3.55[1.11,11.36]	2.14($P = 0.03$)
Hyperglycemia	0	0.59	RR(fixed effects model)	5.16[2.85,9.34]	5.42($P < 0.00001$)

RR, risk ratio.

Table 4
Most common adverse events (grades 3-4).

Adverse event (grade 3-4)	I^2(%)	*P*	Statistical method	Effect estimate	Z(*P*)
Stomatitis	0	0.76	RR(fixed effects model)	14.32[3.99.51.47]	4.08($P < 0.0001$)
Rash	0	0.95	RR(fixed effects model)	4.60[0.80,26.57]	1.71($P = 0.09$)
Fatigue	0	0.83	RR(fixed effects model)	3.03[1.33,6.88]	2.65($P = 0.008$)
Diarrhea	0	0.80	RR(fixed effects model)	5.81[1.06,31.97]	2.02($P = 0.04$)
Pneumonitis	33	0.22	RR(fixed effects model)	5.61[1.69,18.58]	2.82($P = 0.005$)
Decreased weight	0	0.58	RR(fixed effects model)	5.35[1.03,27.67]	2.00($P = 0.05$)
Dyspnea	0	0.45	RR(fixed effects model)	10.67[1.97.57.70]	2.75($P = 0.006$)
Anemia	56	0.13	RR(random effects model)	8.99[0.68,119.25]	1.66($P = 0.10$)
Hyperglycemia	10	0.35	RR(fixed effects model)	7.57[2.43,23.63]	3.49($P = 0.0005$)

RR, risk ratio.

The most common adverse events between 2 groups are shown in Tables 3 and 4.

Discussion

Endocrine therapy is the standard of care in these women with early and/or advanced HR+, HER2− breast cancer. Currently available endocrine drugs include tamoxifen, aromatase inhibitor, fluvastatin, and progestin, etc.[19] Endocrine therapy has similar efficacy to first-line chemotherapy for HR+ advanced breast cancer, which can improve prognosis and survival rate.[20] Once endocrine therapy is effective, its remission period is generally long, and it can change other endocrine therapeutic drugs when treatment ineffective. Therefore, endocrine therapy has become the first choice for the treatment of HR+ advanced breast cancer patients with slow progress.[21] But acquired endocrine resistance often occurs. PI3K/Akt/mTOR is a canonical intracellular signaling pathway with a well-established role in tumor cell growth and proliferation.[22] Akt-induced activation of the endocrine receptor (ER) pathway, it is a known mechanism of resistance to endocrine therapy.[23] Everolimus is a new type of oral mTOR kinase inhibitor with a chemical structure of 42-o-(2-hydroxyethyl)-rapamycin. Several studies assessing that treatment with everolimus can enhance the efficacy of endocrine therapy and overcome this resistance in metastatic breast cancers.[24,25] BOLERO-2 trial is confirmed that the efficacy of mTOR inhibitor everolimus in patients with endocrine-resistant breast cancer. Based on the results of BOLERO-2 trial, in July 2012, the US Food and Drug Administration-approved everolimus combined with exemestane to treat HR+ postmenopausal advanced breast cancer patients who failed endocrine therapy. The drug was the first mTOR inhibitor which approved for HR+ breast cancer. At the same time, the European drug administration also approved everolimus for breast cancer pa-

tients with advanced HR+ postmenopausal women. In addition, everolimus combined with endocrine therapy has been recommended by the latest clinical practice guidelines of national comprehensive cancer network.

The aim of this meta-analysis was to determine whether everolimus combined with endocrine therapy is efficacy and safety in the treatment of patients with postmenopausal HR+, HER2− advanced breast cancer. There were 7 RCTs included in this meta-analysis, the results are as follows: the addition of everolimus to endocrine therapy significantly prolonged PFS, and it is significantly superior to endocrine therapy group in CBR. In terms of safety, adverse events occur more frequently with the everolimus combination group. However, it is common in grades 1-2, the incidences of grades 3-4 adverse events were stomatitis, fatigue, diarrhea, pneumonitis and hyperglycemia. In general, the safety profile of the everolimus plus endocrine therapy combination was manageable.

The meta-analysis has some limitations, which are as follows: (1) there is heterogeneity in this meta-analysis, which may be related to different endocrine therapy. (2) The amount of literature reported is still small, and the main data came from BOLERO-2 clinical trial. (3) The selection of Chinese and English documents in the language, not including documents in other languages, it may result in incomplete search of documents.

The included studies also have several limitations, which are as follows: (1) the outcomes were incomplete. Only 5 studies report the results of PFS, and 2 studies report the TTD. Most studies have not report the overall survival (OS). (2) There were no reports about cost-benefit analysis. (3) The follow-up time was short and no subgroup analysis was carried out in the follow-up cross treatment.

In conclusion, everolimus combined with endocrine may be more efficacious in patients with HR+, HER2− advanced breast cancer. However, combination therapy was associated with a higher risk of adverse events than with endocrine therapy alone. Therefore, we need to carefully select suitable patients and observe their adverse reactions. If well tolerated, combination therapy with everolimus and endocrine therapy may be a useful treatment option in patients with HR+, HER2− advanced breast cancer refractory to nonsteroidal AIs.

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