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An evidence-based review of the outcome of fulvestrant plus a targeted agent versus fulvestrant alone in treating hormone receptor-positive endocrine therapy-resistant metastatic breast cancer

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Abstract

Background Fulvestrant is approved for the hormone receptor-positive advanced metastatic breast cancer (MBC) patients during or after prior endocrine treatment. The adding of a targeted agent to fulvestrant has improved the outlook for these patients from recent studies. However, these results were still under investigation, the analysis was undertaken to assess the clinical outcomes of the fulvestrant-based combination therapy compared with fulvestrant monotherapy.

Methods I systematically searched electronic databases to identify eligible literatures till January 2019. Randomized-controlled trials (RCTs) assessing the efficacy of a targeted agent to fulvestrant with fulvestrant mono-therapy in MBC patients who are refractory to or intolerant of prior endocrine therapy were included.

Results Six RCTs were included in this analysis. The group of a targeted agent to fulvestrant was significantly improved overall survival (OR = 0.86, 95%CI = 0.76–0.97, $P = 0.02$), progression-free survival (OR = 0.66, 95%CI = 0.54–0.81, $P < 0.0001$), as well with the objective response rate (OR = 2.30, 95%CI = 1.67–3.18, $P < 0.00001$), respectively. However, there are more adverse effects with the combination group (OR = 6.71, 95%CI = 5.58–8.06, $P < 0.00001$).

Conclusions Pooled results indicate that adding a targeted agent to fulvestrant prolonged OS, PFS and ORR in relapse or metastatic hormone receptor-positive breast cancer after prior endocrine therapy. Combination of fulvestrant with a targeted agent was associated with more frequent grade 3/4 toxicities. Further research is needed to develop a database of reliable biomarkers and their individual impact on the fulvestrant-based combination treatments.

Keywords Fulvestrant · Targeted agent · Endocrine resistance · Breast cancer · Meta-analysis

Introduction

Breast cancer is the leading cause of cancer-associated death in women and its incidence increases in postmenopausal individuals [1]. Despite many therapies have under progression, a large number of the breast cancer cases still developed into drug resistance with poor survival [2].

More than 70% of cases with metastatic breast cancer (mBC) present with hormone receptor-positive (HR+) disease and endocrine therapy (ET) are often the candidate regimen for these patients [3, 4]. However, even being highly initial response rates to endocrine therapy, virtually all the patients will develop drug resistance and lead to disease progression [5]. And the treatments for patients who failed endocrine therapy are still challenging without satisfied results.

Fulvestrant is a highly selective estrogen-receptor down-regulator,which is able to affect the estrogen receptor degradation [6]. Previous studies have demonstrated that it achieves benefit than tamoxifen and AIs [7, 8]. These evidences approved it for use in combination with other targeted pathways. Therefore, fulvestrant could be a second-line treatment for patients with disease progression following endocrine therapy [9].

The underlying biological mechanisms of endocrine resistance for metastatic breast cancer (MBC) remains under investigate, and numerous targeted agents in combination with fulvestrant are in clinical development, providing therapeutic options for these patients [10, 11]. Several trials have

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reported that fulvestrant as a combination therapy with targeted agents yielded a higher prolonged progression-free survival (PFS) and manageable toxicities than fulvestrant alone for endocrine resistance MBC [10–12]. However, some other studies failed to report a better efficacy of the fulvestrant-based combination strategies [13, 14]. Given these controversial and conflicting results, selecting the optimal therapeutic option for hormone receptor-positive metastatic breast cancer (MBC) patients who have progressed after endocrine therapy becomes complex and somewhat a challenge.

The aim of our meta-analysis is to compare the efficacy and toxicity of the fulvestrant-based combination therapy with fulvestrant monotherapy.

Methods and materials

Search strategy

I searched the electronic databases including PubMed, Embase and Cochrane library databases up to January 2019 with the keywords: "fulvestrant" AND "targeted agent" AND "endocrine resistance", AND "breast cancer", and no limitation was used during the literature search. Literature was also hand-searched using reference lists and materials.

Eligibility criteria

Studies were included in the meta-analysis if they met the following criteria: (1) the studies are designed as phase III random control trials (RCTs); (2) articles that enrolled patients harboring endocrine therapy -refractory hormone receptor-positive metastatic breast cancer (MBC) patients; (3) the studies were designed to compare fulvestrant monotherapy with a fulvestrant-based combination therapy with targeted agents; (4) studies with data of on clinical interested results, and HRs with 95% confidence interval (95%CI) were provided; Studies with most complete data on the outcomes were included.

Quality assessment

The quality of the retrieved studies was rated by choosing the risk of bias items (ROBI) for RCTs recommended by The Cochrane Handbook for Systematic Reviews of Interventions.

Data extraction

I extracted the following information from each study, and disagreement was resolved by consensus. From each of the eligible studies, the main categories based on the following: name of the first author, year of publication, trial name, treatment regimen, dose of fulvestrant, pathways inhibited, endpoint of interests. I extracted the corresponding variables adjusted and risk estimates of mortality with 95%CIs.

Data synthesis and analysis

A sensitivity analysis was based on the heterogeneity between-study, which was examined using I^2 statistic [15]. Studies with an $I^2 \geq 50\%$ was considered to indicate moderate and high heterogeneity, $I^2 < 50\%$ was considered to have low heterogeneity, respectively [16]. Only when there was low heterogeneity among studies, the fixed-effects model was used. Meanwhile, if the source of heterogeneity was not insignificant ($I^2 > 50\%$) uncertain, I used the random-effect model for further analysis. A P value less than 0.05 was identified as statistically significant. All analysis was conducted through the use of Review Manager version 5.3 software (Revman; The Cochrane collaboration Oxford, United Kingdom). Findings of our meta-analysis were shown in forest plots.

Results

Overview of literature search and study characteristics

A total of 346 articles were retrieved. Based on the eligibility criteria, 13 publications were evaluated by the intensive reading of the full texts, but some did not report data on detail of interesting results of two approaches. At last, a final total of 6 RCTs including 8 studies [10–14, 17–21] were included. The search process is described in Fig. 1. The characteristics of the included studies are depicted in Table 1.

Clinical and methodological heterogeneity

Pooled analysis of PFS comparing fulvestrant-based combination therapy with fulvestrant monotherapy

Six RCTs reported the PFS data, and the result showed that fulvestrant-based combination therapy did achieve PFS benefit (OR = 0.66, 95% CI = 0.54–0.81, $P < 0.0001$) compared with the fulvestrant monotherapy group (Fig. 2).

Pooled analysis of OS comparing fulvestrant-based combination therapy with fulvestrant monotherapy

There was low between-study heterogeneity in OS of studies; therefore, we used the fixed-effects model for merging. The pooled data showed that the combination group did

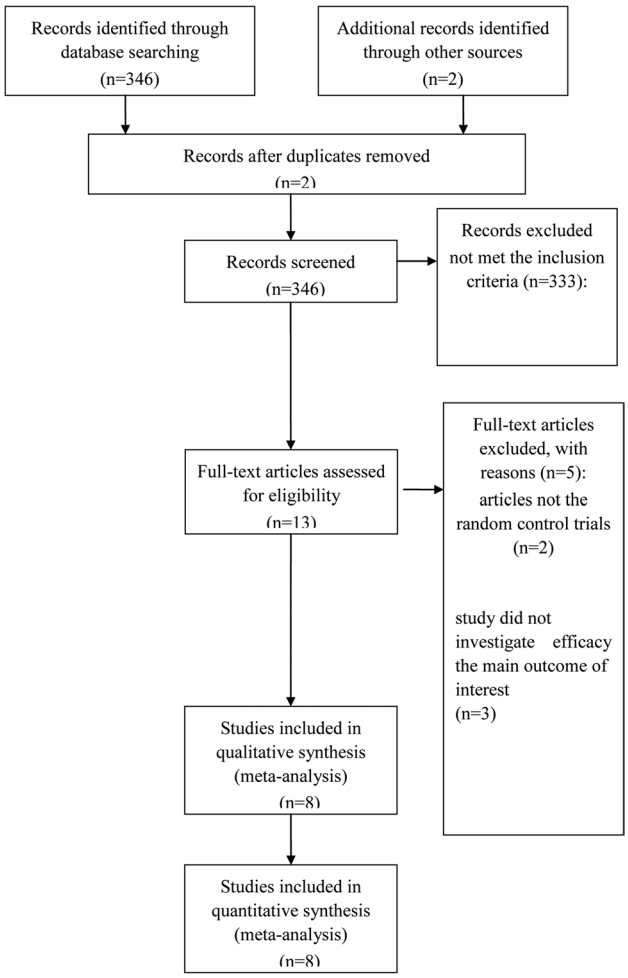

Fig. 1 PRISMA flow chart of selection process to identify studies eligible for pooling

improve OS (OR = 0.86, 95% CI = 0.76–0.97, $P = 0.02$) than monotherapy group (Fig. 3).

Pooled analysis of ORR comparing fulvestrant-based combination therapy with fulvestrant monotherapy

The pooling ORR data were available for 6 studies. Results showed that there was a benefit with fulvestrant-based combination therapy (OR = 2.30, 95% CI = 1.67–3.18, $P < 0.00001$) (Fig. 4).

Pooled analysis of SAEs comparing fulvestrant-based combination therapy with fulvestrant monotherapy

SAEs data were available for five studies. Results showed that there were much worse grade 3–5 adverse events in the fulvestrant-based combination therapy than that in the monotherapy group (OR = 6.71, 95% CI = 5.58–8.06, $P < 0.00001$) (Fig. 5).

Discussion

Fulvestrant was introduced to treat the postmenopausal advanced breast cancer patients after recurrence or progression after endocrine therapy [21, 22]. Recently, a number of targeted therapies for hormone-receptor-positive advanced breast cancer have derived benefit from the PI3K/mTOR pathway inhibitor everolimus and the cyclin-dependent kinase 4/6 (CDK4/6) inhibitors palbociclib and ribociclib, while a benefit with abemaciclib treatment [12, 23]. Previous studies evaluating fulvestrant in combination with these targeted agents have been conducted [10, 11]. However, the genetic backgrounds, comorbidities and demographics are different from each patient, studies performed made the various survival findings with uncertain adverse effect. Thus, in the current meta analysis, we aim to offer conclusive clinical evidence on the controversial results.

Our findings confirm the better efficacy but worse tolerability when compare fulvestrant in combination with a targeted agent than fulvestrant alone.

To improve the efficacy of patients with disease progression after previous exposure to ET, it is necessary to understand and overcome mechanisms of resistance to endocrine therapy. Preclinical data have indicated the basic role of signalling-pathway crosstalk with different oestrogen receptors and acquisition of oestrogen-receptor mutations in therapeutic resistance [24, 25].

Additional fulvestrant to targeted agents to block cell signaling pathways that interact with the ER increased

Table 1 Basic characteristics of included studies

Author, year	Trial	Targeted agents	Dose of fulvestrant	Pathways inhibited
Sledge GW 2017	MONARCH 2	Abemaciclib	500 mg	CDK4/6
Cristofanilli M 2016/Turner NC 2018	PALOMA-3	Palbociclib	500 mg	CDK4/6
Burstein HJ 2014	CALGB 40302	Lapatinib	250 mg	HER1, HER2
Baselga J 2017/Campone M 2018	BELLE-2	Buparlisib	500 mg	PI3 K
Di Leo A 2017	BELLE-3	Buparlisib	500 mg	PI3 K
Slamon DJ 2018	MONALEESA-3	Ribociclib	500 mg	CDK4/6

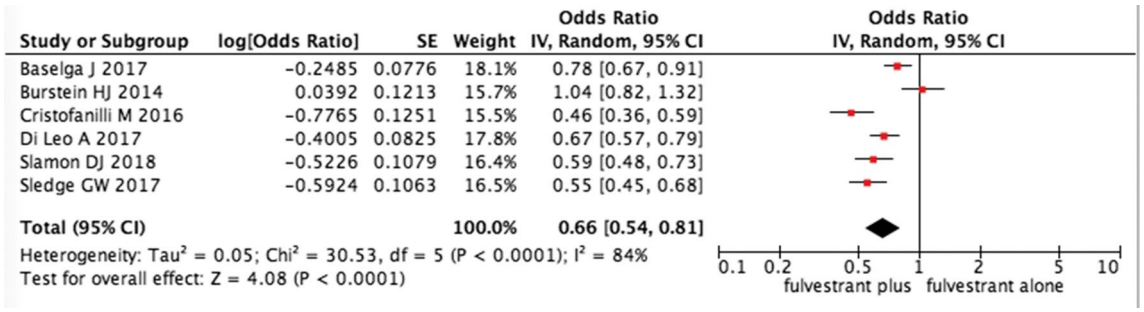

Fig. 2 Pooled analysis of PFS comparing fulvestrant-based combination therapy with fulvestrant monotherapy

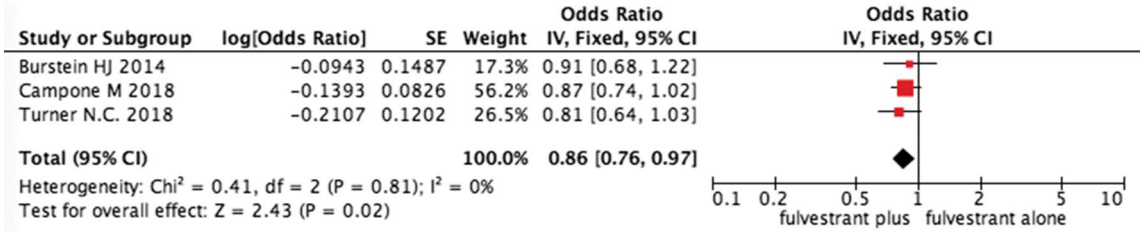

Fig. 3 Pooled analysis of OS comparing fulvestrant-based combination therapy with fulvestrant monotherapy

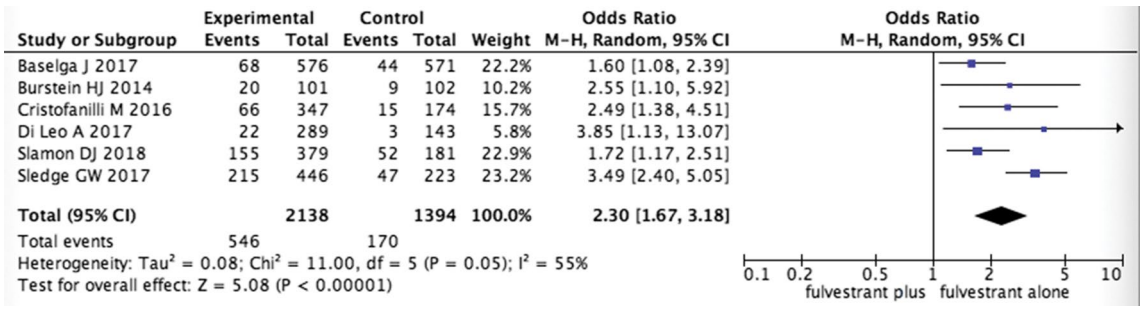

Fig. 4 Pooled analysis of ORR comparing fulvestrant-based combination therapy with fulvestrant monotherapy

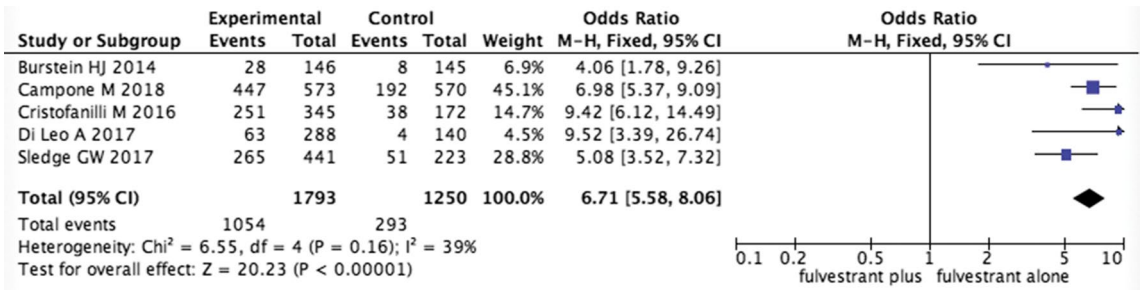

Fig. 5 Pooled analysis of SAEs comparing fulvestrant-based combination therapy with fulvestrant monotherapy

clinical benefits compared with single fulvestrant treatment. Cyclin dependent kinases 4 and 6 (CDK 4 and 6) inhibition and a direct PI3 K inhibitor are accepted as an effective strategy to restore therapy sensitivity and inhibit the growth of endocrine therapy-resistant tumors [26, 27]. Moreover, findings of previous trials have reported that CDK4/6

inhibitors might sensitise *PIK3CA*-mutant breast cancer to agents that target the PI3 K/mTOR pathway, result in investing the combination use of CDK4/6 and PI3 K inhibitor in this setting [28]. Other genomic alterations have been found in the PI3 K/AKT/mTOR pathway that influenced breast cancer including PTEN loss and *AKT* mutations. The loss of PTEN activity and mutations of *AKT* lead to aberrant signalling and have associate with *t* primary and metastatic malignancies, [29, 30].

With respect to the OS analysis, results from PALOMA-3 trial and BELLE-2 trial slightly in favor of fulvestrant-based combination therapy than fulvestrant mono-therapy, albeit without statistical significance. In our OS analysis, fulvestrant-based combination therapy improved OS in the overall population with significant statistical difference. To our knowledge, crossover therapy after disease progression may negatively influence the overall survival [31] and probably lead to prolong the overall survival in the control group in inverse, thereby more comprehensive evaluation of selective inhibitors is in-need in future.

In terms of the safety profile, we found the grade 3/4 AEs were more common in the combination group irrespective of the targeted agents included.

The toxicities of the combination group was broadly consistent with previous studies of its safety when given as a single agent [32], and were not severe and none led to death. While there are little data to predict which patients will suffer from these toxicities beyond a past medical history of endocrine therapy-resistant MBC. This is clearly an area that needs to be explored further to improve the safety of these combination agents.

The results contribute to the growing evidence that supports combination group in endocrine therapy-resistant MBC. However, there are limitations to our study. First, although the experimental methods of the included studies were similar, they were not identical. The heterogeneity due to varying different treatment regimens cannot be discounted entirely. Furthermore, due to the lack of data, we did not analysis the subgroup of the different pathway inhibitor or menopausal status, and further investigation should be given to rapid evaluation.

Conclusion

In conclusion, the combination of a targeted agent with fulvestrant for hormone receptor-positive metastatic breast cancer (MBC) patients progressed after prior endocrine therapy was generally well tolerated, showing promising activity with a better efficacy profile. However, more randomized controlled trials with larger sample sizes are still needed to detect relevant biomarkers that have sufficient sensitivity and specificity to choose the patient population that would achieve advantage from the combination therapy.

Author contribution Y-MH: protocol/project development, data collection and management, manuscript writing/editing.

Compliance with ethical standards

Conflict of interest The authors declare there is no conflict of interest.

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