Efficacy and Safety of Everolimus as a Combination Therapy in the Treatment of Metastatic Breast Cancer: A Systemic Review and Meta-analysis

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INTRODUCTION

- Metastatic breast cancer (mBCa) is the most advanced stage of breast cancer affecting the women worldwide.
- The incidence rate of breast cancer is highest in non-Hispanic white women (125.4 per 100,000 women per year) and lowest for Asian-Americans/Pacific Islander (6.4 cases per 100,000 females).1

Everolimus, a derivative of sirolimus, when combined with endocrine therapy (ET) shows anti-tumor activity in the patients suffering from mBCa. This drug is orally active and has a more favorable pharmacological profile than its predecessors.2,3

- A combination of everolimus and trastuzumab is considered as a first line drug for human epidermal growth factor receptor-2 (HER-2) overexpressing advanced breast cancer.3 In addition, it is a USFDA-approved drug for the treatment of renal cell carcinoma.

- While the safety of everolimus is debatable as clinicians are feared to recommend due to the negative outcomes of BOLERO-2 studies,6 the current systematic review scrutinizes the available literatures on safety and efficacy of this drug as a combination therapy.

OBJECTIVE

To evaluate the efficacy and safety of everolimus as a combination therapy in the treatment of patients with mBCa.

MATERIALS AND METHODS

- All the randomized controlled trials (RCTs) examining the efficacy and safety of everolimus as a combination therapy in mBCa patients were included in the study.

Our primary outcomes were overall survival (OS) and progression free survival (PFS). Local assessment is

Secondary outcomes were response rate (RR), complete response (CR), partial response (PR), stable disease (SD), clinical benefit (CB), stable response (SD), progressive disease (PD) and overall discontinuation.

- Literature searches were conducted using MEDLINE, Cochrane Library, and clinicaltrials.gov. The references of the included studies were considered. No language or data restrictions were imposed.

- Two authors independently selected the papers, extracted the data and assessed the quality of the included studies.

- The study quality of included trials were assessed using the Cochrane Risk of Bias Tool.

RESULTS

- A total of 18 RCTs involving a total of 17,252 patients were included in the meta-analysis.

- Everolimus regimen showed significant improvement in OS and PFS when compared to control. However, no significant difference was observed in response including RR (RR=1.02, 95% CI 0.93-1.12, N=17,192), CR (RR=1.00, 95% CI 0.90-1.12, N=1,401), PR (RR=1.01, 95% CI 0.90-1.12, N=1,401), and CB (RR=1.03, 95% CI 0.99-1.08, N=1,401), SD (RR=1.01, 95% CI 0.91-1.23, N=1,401), and stable disease (SD) (RR=1.00, 95% CI 0.91-1.23, N=1,401) between two groups.

- The overall discontinuation for experimental group was lower than control group.

- Overall, the risk of bias of the included trials was unclear (N=7) to high (N=7).

- Most common adverse events of everolimus are stomatitis, diarrhea, rash, and neutropenia, pneumonia, pyrexia, and arthralgia.

- Further analysis on more RCTs with adequate power is needed to support the current finding.

DISCUSSION

- Everolimus is a derivative of natural macrocyclic lactone sirolimus that binds to immunophilin FK Binding Protein-12 (FKBP-12) generating an immunosuppressive complex which inhibits the activation of mammalian target of rapamycin (mTOR), a key regulatory kinase in cell cycle and tumorigenesis.4

- Inhibition of mTOR results in the inhibition of T lymphocytes and prevents the proliferation associated with antigen and cytokine (IL-2, IL-4, and IL-15) stimulation.

- The BOLERO-2 trials on the drug efficacy demonstrated a significant benefit in PFS (72.9%, total N=724) for the combination therapy in the patients with estrogen receptor-positive advanced breast cancer who relapse or progress during or shortly after non-stereoidal antiestrogen therapy.3

- Patients with HER-2 positive advanced breast cancer having tumors with PIK3CA mutations, PTK7 (tumor suppressor gene) loss, or hyperactive PI3K/mTOR pathway could derive PFS benefit from everolimus.

- However, clinicians unfamiliarity to everolimus treatment for breast cancer might be the reason of previous discontinuations.6,7

- A number of studies showed that addition of everolimus to ET did not significantly affect the safety profile.8,9,10

- In addition, the efficacy and safety of everolimus plus trastuzumab and paclitaxel as a first-line treatment for HER-2 positive advanced breast cancer in Asian patients was consistent with this previous reports.5

CONCLUSION

- Everolimus showed significant improvement in OS and PFS in patients with mBCa when compared to control. In addition, everolimus was associated with lower overall discontinuation compared to control.

- The data supports the safety and efficacy of everolimus in the combination therapies, such as with ET or trastuzumab.

REFERENCES
