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Systematic or Meta-analysis Studies

Risk of adverse events with the addition of targeted agents to endocrine therapy in patients with hormone receptor-positive metastatic breast cancer: A systematic review and meta-analysis

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ABSTRACT

Background: Combining targeted agents and endocrine therapy (ET) improves outcomes in hormone receptor-positive metastatic breast cancer patients but increases the risk of adverse events (AEs). This meta-analysis aims to estimate the comparative risk of AEs with ET in addition to targeted agents in this setting.

Methods: A systematic literature search of MEDLINE, EMBASE, Cochrane Library and conference proceedings up to July 17th 2017 was conducted to identify randomized controlled trials investigating ET with or without CDK4/6, mTOR, PI3K inhibitors and anti-HER2 agents. We calculated summary risk estimates (odds ratio, OR) and 95% confidence intervals (CI) for each AE within each class of targeted agents for each trial, and pooled analysis using the random and fixed effect models.

Results: Sixteen studies (n = 8529 patients) were included. The addition of targeted agents to ET was associated with a significant higher risk of grade 3–4 AEs: OR 2.86 (95% CI 2.49–3.27) for CDK4/6 inhibitors, 1.88 (95% CI 1.39–2.53) for mTOR inhibitors, 2.05 (95% CI 1.63–2.58) for PI3K inhibitors, and 2.48 (95% CI 1.09–5.66) for anti-HER2 agents. The highest class-specific risks were neutropenia grade 3–4 for CDK4/6 inhibitors (OR 40.77; 95% CI 19.52–85.19), stomatitis grade 3–4 for mTOR inhibitors (OR 11.92; 95% CI 3.68–38.57), hyperglycemia grade 3–4 for PI3K inhibitors (OR 40.93; 95% CI 10.08–166.22) and diarrhea for anti-HER2 agents (OR 9.93; 95% CI 4.71–20.95).

Conclusions: Adding targeted agents to ET is associated with a significant increased risk of AEs. The risk of developing different AEs varies largely according to the type of agent used.

Introduction

Hormone receptor-positive breast cancer represents close to 72% of the total number of breast cancers [1]. For more than 40 years, endocrine therapy has been recognized as a crucial part of the treatment of patients with hormone receptor-positive breast cancer [2]. In the metastatic setting, multiple approved endocrine agents have brought a significant improvement in clinical outcomes. As a consequence median survival in this setting now exceeds 50 months [3]. Nevertheless, primary and secondary resistance to endocrine therapy remain an important problem [2]. A considerable amount of research in the last decade has allowed to better understand, define and target the mechanisms of resistance to endocrine therapy. As a result, new endocrine and targeted agents have emerged and are available in daily clinical

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practice for patients with hormone receptor-positive metastatic breast cancer or are in the late stages of drug development [2]. The most promising classes of targeted agents include cyclin-dependent kinase 4/6 (CDK4/6) inhibitors, mammalian target of rapamycin (mTOR) inhibitors, phosphatidylinositol 3-kinase (PI3K) inhibitors, and anti-HER2 agents.

Multiple randomized trials have shown that combining targeted agents to endocrine therapy improves outcomes in women with hormone receptor-positive metastatic breast cancer [2]. Several of these agents are now recommended by international guidelines in association with endocrine therapy for these patients [4,5]. Four targeted agents have been approved by the Food and Drug Administration (FDA) in this context. Palbociclib and ribociclib, two CDK4/6 inhibitors, are approved in combination with letrozole for hormone receptor-positive/HER2-negative metastatic breast cancer as first-line treatment. Palbociclib and abemaciclib in combination with fulvestrant has also been approved after disease progression on prior endocrine therapy. The mTOR inhibitor everolimus in combination with exemestane is approved for the treatment of postmenopausal hormone receptor-positive/HER2-negative metastatic breast cancer after disease progression on a non-steroidal aromatase inhibitor. Activity and efficacy data have been demonstrated for pan-PI3K inhibitors, but no agents in this class have been granted registration by regulatory agencies so far. Finally, the combination of anti-HER2 agents and endocrine therapy is now considered a reasonable option in patients with hormone receptor-positive/HER2-positive disease [5].

Nowadays, the majority of metastatic breast cancer patients are candidates to receive at some point a combined treatment with targeted agents and endocrine therapy. When choosing the best treatment strategy, it is crucial for clinicians to have a clear understanding not only of the efficacy of available options but also of their potential added burden in terms of adverse events (AEs). So far, results from all the trials have not been necessarily consistent and not always easily translatable into clinical practice. Hence, it is not possible to clearly estimate the real impact on the risk of developing AEs when combining targeted agents and endocrine therapy. The present meta-analysis aimed to better understand the comparative safety profile of CDK4/6 inhibitors, mTOR inhibitors, PI3K inhibitors or anti-HER2 agents in addition to endocrine therapy in patients with hormone receptor-positive metastatic breast cancer.

Material and methods

Study objectives

The present study was a quantitative synthesis of randomized phase II and phase III trials with the primary objective of determining the comparative risk of AEs occurrence during treatment with CDK4/6 inhibitors, mTOR inhibitors, PI3K inhibitors and anti-HER2 agents plus endocrine therapy in comparison to endocrine therapy alone. For all targeted agents, the following AEs were considered (non-specific AEs): overall incidence of grade 1–4 AEs, overall incidence of grade 3–4 AEs, grade 3–4 fatigue, grade 3–4 rash, grade 3–4 nausea, grade 3–4 diarrhea and grade 3–4 aspartate aminotransferase (AST) and grade 3–4 alanine aminotransferase (ALT) elevation at first occurrence. Also, class-specific grade 3–4 AEs of special interest were considered for each of the targeted agent analyzed: leukopenia, neutropenia, febrile neutropenia, thrombocytopenia and anemia for CDK4/6 inhibitors; stomatitis, hyperglycemia, non-infectious pneumonitis, hypertension and hypercholesterolemia for mTOR inhibitors; stomatitis, hyperglycemia, non-infectious pneumonitis, hypertension, depression and anxiety for PI3K inhibitors; as well as cardiac AEs and first occurrence decrease in left ventricular function (LVEF) $\geq$15% for anti-HER2 agents.

Data sources and search strategy

A systematic literature search of the electronic databases MEDLINE, EMBASE, and Cochrane Library was conducted to identify randomized controlled trials investigating CDK4/6 inhibitors, mTOR inhibitors, PI3K inhibitors, or anti-HER2 agents plus endocrine therapy compared to endocrine therapy alone in patients with hormone receptor-positive metastatic breast cancer. No language restriction nor restriction in terms of year of publication were applied; the final date for the database running searches was July 17th 2017.

The search strategy was developed using the patient, intervention, comparator and outcome (PICO) framework. The terms used for the search strategy were related to "breast cancer", "endocrine therapy", "cyclin-dependent kinases", "mTOR", "phosphatidylinositol 3-kinase", "HER2", "protein kinase inhibitors", "side effects" and "adverse reactions". Boolean operators were used to connect specific search keywords for each database and other free text terms. The specific rules and vocabulary of each database were used and the search strategy was designed by one reviewer (SM) and discussed with two other reviewers (ML and CM).

The titles and abstracts retrieved from the search strategy were evaluated independently by two reviewers (SM and ML) and a third author (CM) reviewed the search results to apply the eligibility criteria. A review of proceedings from major conferences, in specific the American Society of Clinical Oncology (ASCO) annual meetings, the European Society for Medical Oncology (ESMO) annual meetings and the San Antonio Breast Cancer Symposium (SABCS) was also conducted to include unpublished studies. Finally, the references found in all the identified studies were tracked to locate and include any additional eligible studies. The present study was done accordingly to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [6]. This meta-analysis is registered with the PROSPERO registration number CRD42017058278 and the full protocol is freely available on the PROSPERO website.

Article selection

The eligible trials for this analysis were those with the following characteristics: (a) phase II or III randomized clinical trials with published, presented or otherwise publicly available data; (b) trials conducted in patients with locally advanced inoperable/metastatic hormone receptor-positive breast cancer; (c) studies with at least two comparator arms constituted of targeted therapy (i.e. CDK4/6 inhibitor, mTOR inhibitor, PI3K inhibitor or anti-HER2 agents) plus endocrine therapy versus endocrine therapy alone; (d) studies with available information on incidence of AEs in the targeted therapy plus endocrine therapy and in the endocrine therapy alone arms; (e) studies with sufficient information to estimate the odds ratio (OR) and 95% confidence intervals (CI) for treatment safety profiles.

The studies excluded from this analysis were those with the following characteristics: (a) randomized trials designed to evaluate the efficacy of targeted therapies plus endocrine therapy but with no endocrine therapy alone control arm; (b) non-randomized studies conducted to evaluate the role of targeted therapies plus endocrine therapy; (c) studies currently ongoing and for which no and/or insufficient results where available at the time of the literature search.

Two investigators (SM and ML) carefully and independently extracted the data from all the eligible studies. In case of multiple

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