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Review

Phosphoinositide 3-kinase inhibitors in advanced breast cancer: A systematic review and meta-analysis

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Abstract Phosphoinositide 3-kinase (PI3K) inhibitors may overcome drug resistance and improve advanced breast cancer (ABC) outcomes. We conducted a systematic review and meta-analysis to assess the efficacy and safety of adding a PI3K inhibitor to the standard of care (SOC) treatment in ABC. The electronic databases Ovid, PubMed, Cochrane Central Register of Controlled Trials and Embase, were searched for relevant randomised trials. Pooled hazard ratios (HRs) for progression-free survival (PFS) and pooled risk ratios (RRs) for objective response rates (ORRs), disease control rates (DCRs) and toxicity were meta-analysed using the Mantel–Haenszel method and generic inverse variance. Five studies were included. In unselected patients, the addition of a PI3K inhibitor decreased the risk of progression by 21% (2329 participants, HR = 0.79; 95% confidence interval [CI], 0.71–0.88). A marginal improvement in ORR (2329 participants, RR = 1.26; 95% CI, 1.01–1.57) and no improvement in DCR (2146 participants, RR = 1.05; 95% CI, 0.94–1.18) were achieved with a significant increase in toxicity of any grade (2386 participants, RR = 1.05; 95% CI, 1.03–1.06) and of grade III and higher (2386 participants, RR = 1.91; 95% CI, 1.76–2.08). A PFS benefit was seen in patients with and without PI3K pathway activation assessed on tumour and only in patients with an activated PI3K pathway when it was assessed from the plasma using circulating tumour DNA (ct-DNA) analysis. The addition of a PI3K

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inhibitor decreases the risk of progression in unselected ABC patients and particularly in patients with an activated PI3K pathway detected on ct-DNA analysis. However, their significant dose-limiting toxicity is a limiting factor. Selective PI3K inhibitors are being tested to assess whether these better-tolerated agents have a role in ABC treatment.

1. Introduction

Patients with advanced breast cancer (ABC) experience disease progression after a median time of 1–2 years of first-line therapy [1–4]. In the majority of cases, due to incurability, they succumb to their disease [2–4], indicating an unmet need to develop therapies that overcome treatment resistance and extend ABC patients' survival.

The phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) pathway is activated in approximately 30–40% of BC cases [5–8]. The most common known aberrations include the *PIK3CA* gene mutation and the loss-of-function mutations or epigenetic silencing of phosphatase and tensin homologue (PTEN) [5–7]. They induce cell proliferation and tumour growth, and they confer resistance to endocrine therapy, human epidermal growth factor receptor 2 (HER2)–directed therapy and cytotoxic therapy in BC [8–13]. However, the frequency and type of PI3K pathway aberration can vary among the different BC subtypes, resulting in different clinical manifestations and therapeutic impact [14–17]. While hormone receptor–positive and HER2-positive tumours can harbour *PIK3CA* mutations, triple-negative tumours are found to have PI3K pathway aberrations through PTEN loss and a combined signature of PTEN loss and PIK3CA mutation in HER2-positive tumours can be a strong predictor of trastuzumab resistance [15].

Over the last decade, several targeted therapies have been developed to improve outcomes of ABC and delay disease progression. These include pan-PI3K inhibitors targeting all four isoforms of the catalytic subunit p110 and isoform-selective PI3K inhibitors. Randomised trials have been conducted to assess whether the addition of a PI3K inhibitor to the standard of care (SOC) treatment improves response rates and survival or not. While some of these trials showed benefit in terms of extending the median progression-free survival (PFS) (i.e. the BELLE-2 trial with a hazard ratio [HR] for PFS of 0.78; 95% confidence interval [CI], 0.67–0.89) [18], other trials showed no difference in PFS (i.e. the FERGI trial with an HR for PFS of 0.74; 95% CI, 0·52–1·06) [19]. Furthermore, these medications were associated with significant dose-limiting toxicities that led to treatment delays and interruptions such as elevated transaminase levels in about 40% of patients, depression and anxiety in about 20% of patients as well as mucosal (stomatitis), skin (rash) and metabolic (hyperglycemia) toxicities [20]. Thus, our objective was to systematically review and meta-analyse the efficacy and safety of PI3K inhibitors in combination with the SOC compared with the SOC alone or with placebo in the treatment of ABC administered at any line of treatment.

2. Methods

This review was conducted using methods of the Cochrane Database of Systematic Reviews [21] and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [22].

2.1. Inclusion criteria

We included phase II and phase III randomised controlled clinical trials. The trials had to have at least two arms: an experimental arm (including a PI3K inhibitor) and a control arm (SOC ± placebo). The experimental arm was any PI3K inhibitor (pan-PI3K inhibitors targeting all four isoforms of class I PI3K, as well as isoform-selective PI3K inhibitors) added to the SOC treatment in ABC. The PI3K inhibitor should be administered until disease progression, unacceptable toxicity, study withdrawal, study completion or termination. The control arm included the SOC treatment in ABC ± placebo. The SOC was either endocrine therapy or chemotherapy. Endocrine therapy included selective oestrogen receptor modulators (i.e. tamoxifen), aromatase inhibitors (i.e. anastrozole, letrozole, exemestane) or selective oestrogen receptor downregulators (i.e. fulvestrant) [23,24]. Chemotherapy included any chemotherapy regimen considered SOC in the advanced setting (i.e. anthracyclines, taxanes) [23,24]. The SOC treatment should have been given until disease progression, unacceptable toxicity, study withdrawal, study completion or termination. Studies that assessed PI3K inhibitors in the (neo)adjuvant setting were excluded. We also excluded cohort studies, case series, reviews, case reports and letters to editors.

The population of interest included women aged ≥18 years with advanced or metastatic BC as per the American Joint Committee on Cancer criteria [1] with any disease phenotype (hormone receptor status, HER2 status) and treated with any line of therapy.