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Review

The efficacy of lapatinib and capecitabine in HER-2 positive breast cancer with brain metastases: A systematic review and pooled analysis

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Abstract ***Introduction:*** Breast cancer (BC) with HER-2/neu overexpression or amplification (HER-2+) is associated with a higher prevalence of brain metastases (BMs) when compared to other subtypes. Among approved drugs for HER-2+ BC, lapatinib (L) is associated with single agent activity toward BMs. We conducted a systematic review to determine the efficacy of L, singly or in combination with capecitabine (C), as a treatment for HER-2+ BMs.
Material and methods: We searched PubMed, EMBASE, The Cochrane Library, SCOPUS, Web of Science, ClinicalTrials.gov, World Health Organization International Clinical Trials Registry Platform (ICTRP), and the European Union Clinical Trials Register for studies reporting data on L, singly or in combination with C, for the treatment of HER-2+ BC with BMs. Primary end-points were overall response rate (ORR) and disease control rate (DCR); these were pooled to provide an aggregate value. Progression-free survival (PFS) and overall survival (OS) were secondary end-points. Data were pooled using number of events/number of evaluable patients, according to a fixed or random effect model.
Results: Overall, 12 studies were included in the present meta-analysis, for a total of 799 patients with BMs. The pooled overall response rate (ORR) was 21.4% (95% CI 11.7–35.9). After exclusion of patients that received L alone, ORR reached 29.2% (95% CI 18.5–42.7). The pooled median PFS and OS were 4.1 (95% CI 3.1–6.7) and 11.2 (95% CI 8.9–14.1) months, respectively.

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Conclusions: Due to its activity on BMs, the L + C combination may be considered for HER-2+ BC that has progressed in the brain, when local therapy has been performed or failed and re-irradiation is not feasible.

1. Introduction

The brain is the least common site of metastasis of breast cancer (BC), coming after bone, lung and liver [1,2]; brain metastases (BMs) may possibly be diagnosed in 10–30% of cases of advanced disease [3]. Among BC patients with BMs, those with disease positive for human epidermal growth factor receptor (HER-2+) have a doubled to quadrupled risk of brain metastasis, when compared to HER-2 negative patients [4]. More specifically, the risk of BM development is higher for the hormonal receptor negative and HER-2 positive BC subtype than for the HR positive/HER-2 negative subtype (odds ratio: 1.978) [5]. The triple-negative subtype was also listed among the BM-predisposing subtypes [6].

Local treatment is usually the first option for treatment of BM, even if the blood–brain barrier (BBB) is potentially permeable to systemic drugs. The use of combination of the HER-2 inhibitors, trastuzumab and lapatinib (L), after diagnosis of BM, significantly increases survival when compared to the use of trastuzumab alone, L alone or no drugs [7]. In particular, L, as a small molecule that inhibits both EGFR and HER-2 targets, has a small molecular size and a high BBB penetrability [8]. Studies using a mouse preclinical model validated L as the first anti-HER-2 drug having a direct antitumour activity against BM of BC (a 50–53% reduction in the formation of large BMs) [9]. Two previous studies used L radiolabelled with carbon-11 (11C) and carbon-14 (14C) isotopes to evaluate its distribution across BBB [10,11]. Administration of 11C to six patients with HER-2+ BC and BM resulted in higher registered radioactivity levels in BM than elsewhere in the body, with no isotope uptake registered in normal brain tissue [10]. Conversely, variations in the BBB permeability were responsible for different distribution patterns of L when 14C was injected into experimental animals. The average concentration of L in BM exceeded the concentration in normal brain tissue by seven- to ninefold, but the average concentration was considerably lower than that registered in metastases outside the BBB (only 10–20% of the peripheral concentration) [11].

Lapatinib has shown some signals of activity in small early trials for HER-2+ BMs [12], but the labelled combination with capecitabine (C) has become the single most-evaluated regimen for CNS relapse in BC. The aim of this systematic review and pooled analysis was to determine the efficacy of L administration, singly or in combination with C, as a treatment for BMs from BC.

2. Material and methods

2.1. Search strategy and eligibility of studies

This systematic review and meta-analysis were performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The potentially eligible publications were retrieved from PubMed, EMBASE, SCOPUS, Web of Science, The Cochrane Library, ClinicalTrials.gov, World Health Organization International Clinical Trials Registry Platform (ICTRP) and European Union Clinical Trials Register using the search algorithm *('brain metastases' OR 'central nervous system metastases') AND (carcinoma OR carcinomas OR cancer OR cancers OR malignancy OR malignancies OR malignant OR tumour OR tumor OR tumours OR tumors OR neoplasm OR neoplasms) AND (breast) AND (lapatinib),* with an end of search date of 31st March 2017. Only papers published in English were included; reference lists were systematically searched for relevant articles. Eligible articles included prospective or retrospective studies reporting on the efficacy of L, singly or in combination with C, in patients with HER-2+ BC and BM [BM or metastasis to other central nervous system (CNS) sites]. Case reports or studies including <10 patients, concomitant L + C local treatment or other investigational therapies were excluded. Selection of studies was independently performed by two reviewers (FP and MG), and the final decision was reached after consultation with a third referee (SB) and team consensus.

2.2. Data extraction and statistical analysis

The extraction of data comprised author (year), type of study, number of patients, performance status, previous therapies including local therapies for BM, 6- and 12-month PFS rate, 1-year OS rate, 2-year OS rate, median time-to-progression (TTP), median overall survival (OS), BM overall response rate (BM ORR defined as rate of complete + partial response according to RECIST criteria), disease control rate (DCR) that reflects the proportion of patients with complete response, partial response or stable disease for at least 24 weeks;