Survival benefits from lapatinib therapy in women with HER2-overexpressing breast cancer: a systematic review

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Breast cancer is the second cause of cancer mortality worldwide and there is an unmet need for novel anticancer agents. Lapatinib is a novel tyrosine kinase inhibitor for treatment of breast cancer with human epidermal growth factor receptor 2 (HER2) amplification. Given promising results in clinical studies, we investigated the survival benefits of lapatinib use in patients with HER2-overexpressing advanced or metastatic breast cancer. We searched MEDLINE, EMBASE, American Society of Clinical Oncology Meeting proceedings, San Antonio Breast Cancer Symposia proceedings, and the Cochrane Library between 2000 and 2008 for randomized controlled trials where lapatinib was used as single agent or in combination with or following other therapies. Three trials ($n=704$) met the inclusion criteria. Study quality was assessed by two independent reviewers and meta-analyses were conducted. Significant differences were observed between lapatinib-containing treatments to those without lapatinib in terms of survival. Pooled estimates suggested the hazard ratios of 0.61 [95% confidence interval (CI): 0.50–0.74] for progression-free survival and 0.76 (95% CI: 0.60–0.97) for overall survival. Objective response rate and clinical benefit rate also showed significant differences in favoring the use of lapatinib with odds ratios of 2.15 (95% CI: 1.48–3.11) and 2.23 (95% CI: 1.59–3.12), respectively. Heterogeneity between studies was not observed. In conclusion, addition of lapatinib to conventional anticancer treatment might offer superior survival benefit to patients with advanced metastatic HER2-overexpressing breast cancer. Further investigations on the use of lapatinib in combination with anticancer agents are warranted. *Anti-Cancer Drugs* 21:487–493 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Breast cancer is the most common cancer and is the second cause of cancer mortality among women worldwide [1–3]. The global cancer incidence and mortality were estimated at 1.15 million new cases and 411 000 deaths, respectively in 2002 [1]. With the advancement in therapy, survival rate of breast cancer patients has been greatly improved. However, in developing countries, breast cancer incidence and mortality are similar possibly because of the diagnosis at a later stage in the absence of well-established screening programs and limited availability of adequate therapy [4]. Development of novel anticancer agents is one of the strategies to combat cancer.

Nowadays, breast cancer therapy is basically based on cancer subtypes identified by gene expression profiling. Cancer biomarkers such as estrogen receptor (ER), progesterone receptor (PgR), and human epidermal growth factor receptor (ErbB or HER) further classified breast cancer into four subtypes: luminal subtype A, characterized by ER+ and/or PgR+, HER2−; luminal subtype B, characterized by ER+ and/or PgR+, HER2+; ErbB2+ subtype, characterized ER−, PgR−, HER2+; basal-like subtype, characterized by ER−, PgR−, HER2−, cytokeratin 5/6+ and/or HER-1+ [5,6]. These subtypes were associated with different relapse-free survival and overall survival (OS) rates. The ErbB2+ subtype with HER2 overexpression was associated with poorly differentiated and high-grade tumors, lymph node involvement, and a relative resistance to certain types of chemotherapy [7]. Much research has therefore been conducted to block HER2 signaling pathways that were deemed as one of the important treatment strategies. With more understanding on other biomarkers such as Ki-67 proliferation index and BRCA gene mutation, in the future, the growing recognition of this molecularly heterogeneous disease would revolutionize cancer therapeutics.

Lapatinib is a tyrosine kinase inhibitor of HER2 and epidermal growth factor receptor (EGFR). It was proven to inhibit HER-driven tumor cell growth and can induce apoptosis *in vitro* and in animal models [8–10]. The single use of lapatinib has also shown promising efficacy in a phase II clinical trial [11]. The progression-free survival (PFS) rates at 4 and 6 months were 64 and 43%,

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respectively. The objective response rate (ORR) and clinical benefit rate (CBR) were 24 and 31% in the intent-to-treat (ITT) population, which were comparable with that of 26 and 35% in similar patient population treated with trastuzumab monotherapy, a currently widely used recombinant humanized monoclonal anti-HER2 antibody. As preliminary results from a single trial could not give any clue on how this drug could be best administered or illustrate any survival benefit, a systematic review was performed.

Methods

Procedures

We searched MEDLINE, EMBASE and the Cochrane breast cancer group with the terms 'breast cancer', 'randomized controlled trial', 'controlled clinical trial', 'lapatinib', 'GW572016', 'Tykerb' and 'tyrosine kinase inhibitor' between 2000 and 2008. The search strategy was also employed to obtain appropriate data from the online abstract databases of the American Society of Clinical Oncology meetings and the San Antonio Breast Cancer Symposia proceedings up to the year of 2008. Experts in breast cancer therapeutics were contacted to yield more potentially eligible trials. Trials were included if the following criteria were met: lapatinib therapy, in combination or alone, evaluated through a randomized controlled trial or through systematic review with or without statistical meta-analysis, results published as peer-reviewed articles or publicly available abstracts or presentations, outcome variables including but not limited to OS, PFS, mortality, time to disease progression, ORR, CBR or toxicity. PFS was defined as the time from randomization until the first documented sign of disease progression or death due to any cause; OS was defined as the time from randomization until death due to any cause; ORR was defined as the percentage of individuals achieving either a complete tumor response or partial tumor response; CBR was defined as the percentage of individuals with complete tumor response or partial tumor response or stable disease for more than or equal to 6 months. Trials published in a language other than English were excluded owing to the incapability of translation.

Two reviewers independently assessed the potential trials for inclusion, and disagreements were resolved by consensus. Unless compromise could not be made, discrepancies were resolved by a third reviewer about eligibility and quality of study inclusion. Methodological quality of all eligible randomized trials was assessed according to the criteria of the Cochrane Collaboration Reviewers' Handbook [12]. The criteria included sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective outcome reporting, and other potential threats to validity. A copy of the full article for each reference reporting a potentially eligible trial was obtained. Information of ongoing trials or unpublished trials was obtained from the trial protocol or the next best available source. The study was approved by the Chinese University of Hong Kong Ethics Committee in December 2008.

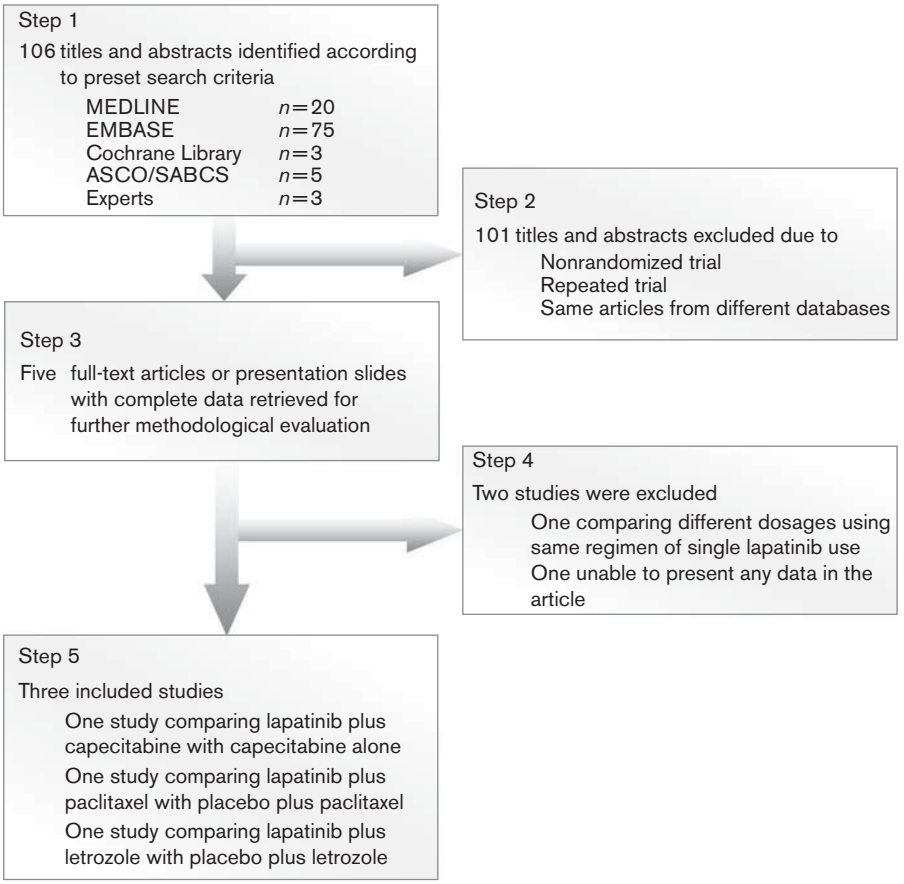
Statistical analysis

Primary outcome measures were estimated as hazard ratio (HR) and secondary outcome measures were estimated as odds ratio (OR) for each trial. Associated variances and 95% confidence interval (CI) were obtained for each study, and the pooled estimate was calculated from an inverse-variance-weighted average of the individual studies using Review manager software from the Cochrane collaboration (Review manager version 5.0.20) [13]. Considering different regimens with different combination therapies of lapatinib that might vary in treatment effects, a random effects model was applied. The I^2 statistic, described as the percentage of variability because of heterogeneity between studies rather than sampling error, was used to assess statistical heterogeneity. All statistical tests were two-sided and the level of significance was set at 5%. Safety outcomes were not pooled, but results were assessed qualitatively and presented in a narrative form. As only a small number of trials could be selected and pooled, a funnel plot was not performed to assess for the publication bias.

Results

The flowchart of studies from initial search to the final decision made on the inclusion of eligible studies is shown in Fig. 1. Of the five studies [11,14–17] that met the inclusion criteria, two were excluded. One randomized study [11] on locally advanced or metastatic breast cancer patients receiving either 1500 mg once daily or 500 mg twice daily was excluded considering that the comparator in this study was a cohort of the same drug but in different dosages. Hence the study was unsuitable for meta-analysis to evaluate the overall estimate of survival benefit. Although another randomized controlled trial regarding preoperative chemotherapy plus trastuzumab, lapatinib or both in the HER2-positive operable breast cancer study (CHER-LOB trial) [14] was also eligible for inclusion as suggested by the two reviewers; compromise has been made not to include such a trial after the full article was obtained and reviewed because it only described the methodology of the trial and the relevant data was unavailable in the paper. Of the three eligible studies included in the systematic review, two included the subgroups of patients with HER2-negative and HER2-postive breast cancer in the individual studies. We extracted the subgroup of patients with HER2-positive breast cancer for meta-analysis. These three studies compared the effect of the combination use of lapatinib with chemotherapy (capecitabine or paclitaxel) or with endocrine therapy (letrozole) against the comparator of chemotherapy or endocrine therapy,

Fig. 1



Flowchart of study selection.

and the latter has already been widely used in clinical practice. Details of the selected studies including treatment and the study population are described in Table 1. In conclusion, only three randomized controlled trials [15–17] with a total of 704 patients with HER2-positive breast cancer were identified to compare the effect of comparing lapatinib in combination with conventional treatments with conventional treatment alone.

Quality of selected studies

All selected studies as of February 2009 were randomized trials of high quality. Two independent reviewers assessed the quality of the selected three studies. Both had the same quality ratings for the first two studies [15,16]. Discussion was made on disagreements between reviewers regarding a methodological criterion, allocation concealment, of the third study [17]. The second reviewer has checked the study protocol (EGF30008) from the pharmaceutical company's website [18] and suggested that adequate allocation concealment could be made. Compromise was finally made between reviewers.

From the preliminary appraisal of the study quality, three trials [15–17] were of good quality to be included in the meta-analysis. The study by Johnston *et al.* [17] had two features unclear about the risk on the bias, but data was accepted and presented at a well-received San Antonio Breast Cancer Symposia. From the presentation slides, it briefly described the placebo-controlled study design and showed balanced baseline patient characteristics. Notwithstanding a mild risk of bias, the quality of the study was good enough. Meta-analysis was then carried out for the selected three studies as listed in Table 1.

Meta-analyses

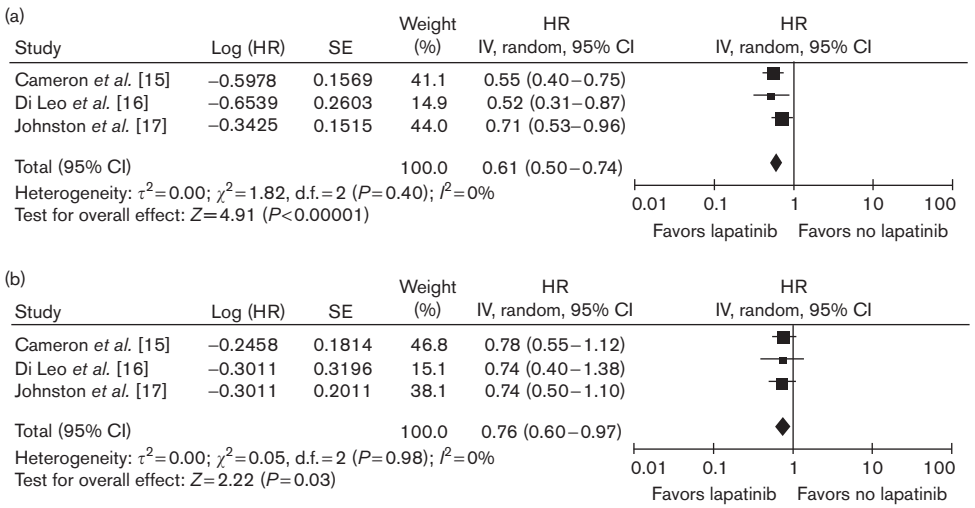
All patients had HER2-positive advanced or metastatic breast cancers and all results from these studies were analyzed on an intent-to-treat principle. Pooled estimates of PFS, OS, ORR, and CBR were calculated to illustrate their overall effect estimates. As the toxicity profile for HER2 subpopulation was described only in Cameron's study [15] and no additional data was available, pooled results were unavailable in this review.

Table 1 Selected studies for systematic review

Study	Interventions	Number of randomized patients	Patient eligibility	Primary outcomes	Secondary outcomes	Analysis	Power and sample size
[15]	Lapatinib plus capecitabine versus capecitabine	399 (198 vs. 201)	HER2-positive, locally advanced breast cancer (T4 primary tumor and stage IIIB or IIIC disease) or metastatic breast cancer having progressed after treatment with anthracycline, taxane and trastuzumab	TTP	PFS, OS, ORR, CBR, safety	ITT	266 TTP events required to achieve 90% β at α 0.05 to detect a 50% increase in the median TTP (from 3 months of capecitabine alone to 4.5 months in lapatinib plus capecitabine)
[16]	Paclitaxel plus lapatinib versus paclitaxel plus placebo	579 (291 vs. 288)[a]	First-line metastatic breast cancer	TTP	Objective response rate, CBR, response duration, event-free survival, OS safety	ITT	580 patients to achieve 374 disease progression or death events providing the study with 90% β at α 0.05 to detect a 40% increase in the median TTP (from 6 months of paclitaxel-placebo group to 8.4 months in paclitaxel-lapatinib group)
[17]	Letrozole plus lapatinib versus letrozole plus placebo	1286 (642 vs. 644)[b]	First-line hormone receptor-positive advanced or metastatic breast cancer	PFS	OS, ORR, CBR, safety	ITT	218 patients with HER2+MBC needed and 173 events to have 80% β at α 0.05 to detect a 55% increase in median PFS; 1280 patients needed for ITT population to recruit 218 HER2+ patients at power > 90% to detect a 30% increase in median PFS

CBR, clinical benefit rate; HER, human epidermal growth factor receptor; ITT, intent-to-treat; MBC, metastatic breast cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TTP, time-to-progression.
[a]Subpopulation: HER2-positive patients (49 vs. 37).
[b]Subpopulation: HER2-positive patients (111 vs. 108).

Fig. 2



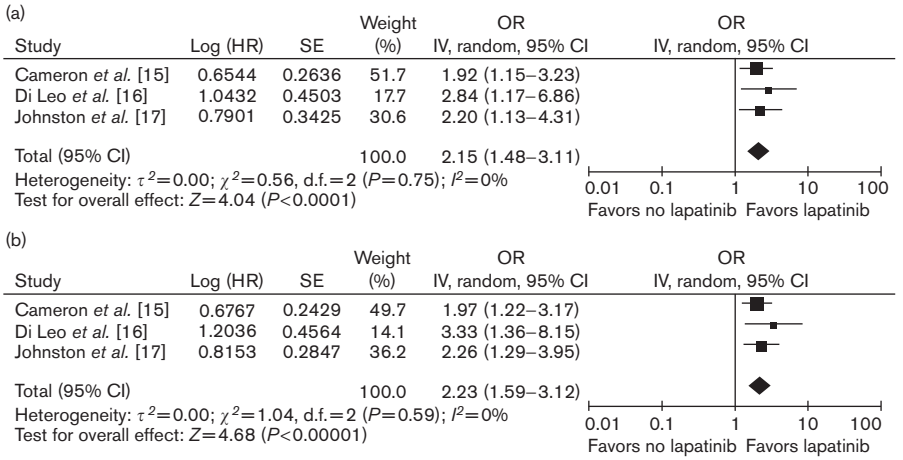
Survival outcomes. (a) Progression-free survival. (b) Overall survival. CI, confidence interval; d.f., degrees of freedom; HR, hazard ratio; SE, standard error.

The HRs and 95% CIs of PFS for the lapatinib-containing regimen and the regimen without lapatinib, together with the pooled estimate, are shown in Fig. 2a. The estimate of effect favored the regimen containing lapatinib and the pooled result showed a significant reduction in risk [HR 0.61 (95% CI: 0.50–0.74), $P < 0.00001$]. The HRs and 95% CIs of OS with the pooled estimate are shown in Fig. 2b. The estimate of effect again favored the regimen containing lapatinib and the pooled result showed a significant reduction in risk [HR 0.76 (95% CI: 0.60–0.97), $P < 0.03$]. Figure 3 showed the ORs and 95% CI for ORR and CBR that assessed the lapatinib-containing regimens. Both outcome measures showed statistically significant overall effects. The overall estimate for ORR favored lapatinib [OR 2.15 (95% CI: 1.48–3.11), $P < 0.0001$]. Equally, the overall effect for CBR was also in favor of the lapatinib-containing regimen [OR 2.23 (95% CI: 1.59–3.12), $P < 0.00001$]. No evidence of heterogeneity was observed in the above overall effect estimates with I^2 statistics of 0%.

Discussion

HER2 overexpression, occurring in about 20–30% of invasive breast cancer, is associated with poor prognosis

Fig. 3



Response rate and clinical benefit rate. (a) Objective response rate. (b) Clinical benefit rate. CI, confidence interval; d.f., degrees of freedom; OR, odds ratio; SE, standard error.

and confers a more aggressive phenotype of breast cancer [19–22]. Therefore, anti-HER2 has long been studied to improve survival in advanced or metastatic breast cancer. Trastuzumab, a recombinant humanized monoclonal antibody, is the first molecular targeted agent approved by United States Food and Drug Administration for treatment of HER2-overexpressing breast cancer since 1998. However, the agent only benefits approximately 30% of metastatic breast cancer patients with HER2 overexpression in first-line treatment and disease progression was also observed within 1 year even for those responsive to the treatment [23,24]. Cross-talk between HER family receptors is recognized as one of possible mechanisms for resistance to HER2-targeted therapy [25,26]. Lapatinib is an orally administered, small molecule, dual tyrosine kinase inhibitor of EGFR and HER2 that reasonably overcomes the potential resistance mechanism by interrupting the intracellular signals downstream of HER2 receptors and the cross-talk between HER family receptors inside the cell.

The combination of lapatinib and capecitabine for the treatment of trastuzumab-refractory HER2-positive metastatic breast cancer was approved by the US Food and Drug Administration in 2007. The latest data on the use of the combination treatment did not show a significant survival benefit [HR 0.78 (95% CI: 0.55–1.12), $P = 0.177$] although an improvement in time to disease progression from 4.3 to 6.2 months [HR 0.75 (95% CI: 0.43–0.77), $P < 0.001$] was observed [15]. In this review, the meta-analysis showed a significant survival benefit from the lapatinib-containing regimen for patients with locally advanced or metastatic HER2-overexpressing breast cancer. The HRs for PFS and OS were 0.61 (95% CI: 0.50–0.74) and 0.76 (95% CI: 0.60–0.97), respectively. The addition of lapatinib to currently available treatment obviously brings significant improvements in PFS and OS. However, McArthur [27] has mentioned the possible confounder of different capecitabine doses in each arm of the study by Cameron *et al.* [15] on the interpretability of the study results. Nevertheless, the investigators of this review have noted the important effect of this trial and a significant weight contributed by this trial in the meta-analysis. A loss of significance of the overall estimate would result if the trial was excluded.

In addition to the pooled estimates of survival benefit from lapatinib therapy, ORR and CBR are also concerned outcome measures of the tumor burden and the likelihood of benefit from the therapy in metastatic settings [28]. The OR of 2.15 (95% CI: 1.48–3.11) for ORR and the OR of 2.23 (95% CI: 1.59–3.12) for CBR are altogether in favor of the use of lapatinib-containing regimen in metastatic setting. Improvements in both ORR and CBR are expected to offer survival advantage and better quality of life (QoL) although formal QoL assessment was unavailable for meta-analysis. One of the selected studies in this review, the phase III randomized trial (EGF100151) has conducted the QoL assessment using the Functional Assessment of Cancer Therapy-Breast (FACT-B) and EuroQoL (EQ-5D) questionnaires [29]. The assessments showed no statistical significance between two arms, but a slightly better QoL was observed in patients receiving lapatinib plus capecitabine as illustrated by between-group differences ranging from 0.7 to 2.2 (FACT-B total) and 0.3 to 1.8 (EQ-5D Visual Analog Scale). It is noteworthy that a greater proportion of patients receiving lapatinib plus capecitabine reported

no problems in performing usual activity than those receiving capecitabine alone (49 vs. 39%), but a lower proportion of patients receiving lapatinib plus capecitabine reported no problems with pain or discomfort than those receiving capecitabine alone (23 vs. 30%). Interestingly, a correlation between reduction in tumor size and change in QoL was also observed. This is important clinical information in the treatment of advanced metastatic breast cancer using lapatinib.

There is a concern over cardiotoxicity because many HER2-positive breast cancer patients were treated with anthracycline-based chemotherapy followed by trastuzumab and could therefore be at increased risk of cardiotoxicity [30–32]. From the selected studies, lapatinib-containing treatment might cause a low level of cardiotoxicity in the form of asymptomatic, reversible decreases in left ventricular ejection fraction although neither a statistical test nor a meta-analysis was available. Perez *et al.* [33] have conducted a review on the cardiac safety of lapatinib on 3689 patients enrolled in clinical trials. A very low rate of symptomatic congestive heart failure (0.2%) or asymptomatic cardiac event (1.4%), which was comparable with contemporary controls of 1301 patients who did not receive lapatinib. Further follow-up was suggested to investigate the long-term adverse effects of lapatinib on cardiac function. Physicians are therefore recommended to perform a serial cardiac monitoring if lapatinib is prescribed to a patient, although consensus has not been made on the frequency of left ventricular ejection fraction assessments.

The review has several limitations which made our overall results better viewed as hypothesis generating and further investigations of this drug in combination with OS as a significant end-point of analysis are warranted. First, results were limited by the small number of trials that might mask the publication bias and the possible heterogeneity between studies. A systematic review is likely to be vulnerable to publication bias, which is a threat to validity of research reviews [34]. The undetermined bias indicates that the results of this review should be treated with caution. Although some unknown potential confounders might affect the overall estimates, the included studies are of good methodological quality and, therefore, the pooled results were suggestive of survival benefits contributed by the addition of lapatinib into the conventional treatment for patients with HER2-overexpressing advanced metastatic breast cancer; however, further investigations are warranted.

Second, pooling trials using different combination regimens of lapatinib might induce heterogeneity and the problem of generalizing the clinical application. A random effects model was employed to produce a more conservative estimate [35] considering the possible variation in treatment effects among studies. The overall estimates supported the use of a lapatinib-containing regimen and heterogeneity was absent among pooled trials. Nevertheless, there is biological evidence suggesting the interaction between ER and EGFR/HER2 giving rise to inhibition of apoptosis, stimulation of cell proliferation, enhancement of cell motility and invasion, and induction of angiogenesis [36]. Subgroup analysis for patients with breast cancer of luminal subtype B might give another picture of survival benefit using lapatinib because this particular subtype might be subject to the development of drug resistance resulting from bidirectional cross-talk between receptors. In principle, the dual tyrosine kinase inhibitor, lapatinib, might potentiate the therapeutic effect of endocrine therapy and vice versa. Unfortunately, patient data for the luminal B subpopulation was unavailable for this review.

Third, there is increasing evidence showing the effectiveness of lapatinib use for HER2-positive breast cancer patients with brain metastases [37,38]. A subgroup analysis of patients with brain metastases might generate important information on the use of lapatinib for brain metastases, which are associated with high disease burden and poor prognosis. However, individual patient data was unavailable to further explore its therapeutic effect. A prospective investigation on the site of metastases after treatment with lapatinib in early-stage HER2-overexpressing breast cancer is suggested.

Finally, the review lacks a head-to-head trial comparing lapatinib with trastuzumab, which might influence the clinical practice on the schedule and sequence of using anti-HER agents. An ongoing Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization Trial, which will recruit 8000 patients with early-stage HER2-positive breast cancer from 1218 study sites will have significant impact on the use of lapatinib for early breast cancer and provide a prospective cardiac safety data for lapatinib [39]. Another ongoing Neoadjuvant Lapatinib and/or Trastuzumab Treatment Optimization Trial estimated to recruit 450 patients will also give additional data on the use of lapatinib for early HER2-overexpressing breast cancer [40]. The two large-scale studies will contribute significantly on the whole picture of survival benefits for HER2-overexpressing breast cancer patients in the future review.

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