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REVIEW

Lapatinib plus chemotherapy or endocrine therapy (CET) versus CET alone in the treatment of HER-2-overexpressing locally advanced or metastatic breast cancer: systematic review and meta-analysis

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Background: This paper reports a systematic review and meta-analysis of all randomized controlled trials comparing the efficacy of lapatinib plus chemotherapy or endocrine therapy (CET) versus CET alone in human epidermal growth factor receptor 2-overexpressing (HER-2+) locally advanced or metastatic breast cancer.

Methods: Several databases were searched, including MEDLINE, EMBASE, LILACS, and CENTRAL. The primary endpoints were progression-free survival and overall survival. The side effects of each treatment were analyzed. The data extracted from the studies were combined by using the hazard ratio or risk ratio with their corresponding 95% confidence interval (CI).

Results: A total of 113 references were identified and screened. The final analysis included four trials comprising 1,073 patients with HER-2+. The overall response rate was higher in patients who received the combination of CET plus lapatinib (risk ratio 0.78; 95% CI 0.71–0.85; $P < 0.00001$) but with significant heterogeneity ($\chi^2 = 15.61$, $df = 3$; $P = 0.001$; $I^2 = 81\%$). This result remained favorable to the use of lapatinib when a random-effects model analysis was performed (risk ratio 0.76; 95% CI 0.62–0.94; $P = 0.01$). Progression-free survival was also higher in patients who received CET plus lapatinib (hazard ratio 0.57; 95% CI 0.49–0.66; $P < 0.00001$) with no heterogeneity detected on this analysis ($\chi^2 = 3.05$; $df = 3$; $P = 0.38$; $I^2 = 1\%$). Overall survival was significantly longer in patients who received CET plus lapatinib (hazard ratio 0.80; 95% CI 0.69–0.92; $P = 0.002$) without heterogeneity on this analysis ($\chi^2 = 1.26$; $df = 3$; $P = 0.74$; $I^2 = 0\%$). Regarding adverse events and severe toxicities (grade ≥ 3), the group receiving CET plus lapatinib had higher rates of neutropenia (risk ratio 2.08; 95% CI 1.64–2.62; $P < 0.00001$), diarrhea (risk ratio 4.82; 95% CI 3.14–7.41; $P < 0.00001$), and rash (risk ratio 8.03; 95% CI 2.46–26.23; $P = 0.0006$).

Conclusion: The combination of CET plus lapatinib increased the overall response rate, progression-free survival, and overall survival in patients with HER-2+ locally advanced or metastatic breast cancer.

Keywords: chemotherapy, lapatinib, breast cancer, meta-analysis

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Outcome measure	Evidence	Implications
Disease-oriented evidence	The combination of CET plus lapatinib showed superiority to CET alone	The overall response rate was higher in patients who received the combination of CET plus lapatinib
Patient-oriented evidence	The combination of CET plus lapatinib showed superiority to CET alone	Progression-free survival and overall survival were higher in patients who received CET plus lapatinib
Economic evidence	Neither a cost effectiveness nor a budgetary impact analysis were performed	Neither a cost effectiveness nor a budgetary impact analysis were performed

Background

Breast cancer is the most common cancer among women worldwide.[1] Each year, about 1.4 million new cases of breast cancer are diagnosed worldwide, and over 450,000 women will die of the disease annually.[1] Women have a one in nine lifetime risk of developing breast cancer.[2] The incidence of breast cancer increases with age, doubling every 10 years until menopause, after which the rate of increase slows down.[2] Advanced or metastatic breast cancer is defined as a clinical stage that corresponds to cancer stage III and IV, based on the tumor itself, on lymph node involvement, and on metastases. Approximately 16%–20% of women with breast cancer have advanced or metastatic breast cancer and 50% of early-stage breast cancers ultimately develop into metastatic breast cancer.[3] The human epidermal growth factor receptor 2 gene (*ErbB2*, usually cited as *HER-2*) appears to be amplified in around 15%–22% of breast cancer patients,[3,4] and this carries a bad prognosis.[4–6]

On March 13, 2007, the US Food and Drug Administration (FDA) approved lapatinib, an oral, small molecule, dual tyrosine kinase inhibitor of ErbB-2 and ErbB-1, for use in combination with chemotherapy (capecitabine) in the treatment of patients with human epidermal growth factor receptor 2-overexpressing (HER-2+) metastatic breast cancer who had received prior therapy including anthracycline, a taxane, and trastuzumab. This approval was based on a randomized Phase III trial published by Geyer et al[7] showing a longer time to progression in favor of the group receiving lapatinib.

On January 29, 2010, the FDA granted accelerated approval to lapatinib for use in combination with endocrine therapy (letrozole) for the treatment of postmenopausal women with HER-2+ metastatic breast cancer and for whom hormonal therapy is indicated. The approval was based on a clinically meaningful increase in progression-free survival observed in a single trial.[8,9] Until then, there was no randomized controlled trial (RCT) demonstrating gains in overall survival.[10] Recently, Guan et al[11] published the first RCT demonstrating benefits in overall survival of patients who used lapatinib with chemotherapy versus chemotherapy alone.

The objective of this research was to analyze all published RCTs comparing the efficacy of lapatinib plus chemotherapy or endocrine therapy (CET) versus CET alone in the treatment of patients with HER-2+ locally advanced (a T4 primary tumor and stage IIIB or IIIC disease) or metastatic breast cancer.

Materials and methods

Study selection criteria

RCTs with a parallel design comparing use of CET regimens associated with lapatinib against others without lapatinib were included. Patients with locally advanced or metastatic breast cancer and with HER-2+ (immunohistochemistry 3+/fluorescence in situ hybridization-positive or chromogenic in situ hybridization-positive for HER-2).[12]

Search strategy for identification of studies

A wide search of the main computerized databases of interest was conducted, including EMBASE, LILACS, MEDLINE, SCI, CENTRAL, The National Cancer Institute Clinical Trials service, and The Clinical Trials Register of Trials Central. In addition, abstracts published in the proceedings of the American Society of Clinical Oncology, the European Society for Medical Oncology, and San Antonio Breast Cancer Symposium were also searched.

For MEDLINE, we used the search strategy methodology for RCT[13] recommended by the Cochrane Collaboration.[14] For EMBASE, adaptations of this same strategy were used,[13] and for LILACS, we used the search strategy methodology reported by Castro et al.[15] An additional search of the Science Citation Index (SCI) database was performed, looking for studies cited on the included RCTs. The specific terms pertinent to this review were added to the overall search strategy methodology for each database.

The overall search strategy was as follows: #1, "lapatinib" (Supplementary Concept) OR "lapatinib" (All Fields); #2, "breast neoplasms" (MeSH Terms) OR "breast cancer" (All Fields); #3, "Randomized Controlled Trial" (Publication Type). Searches of electronic databases combined the terms #1 AND #2 AND #3.

Critical evaluation of selected studies

All the references retrieved by the search strategies had their title and abstract evaluated by two of the researchers. Every reference with the least indication of fulfilling the inclusion criteria was listed as preselected. The complete articles of all preselected references were retrieved and analyzed by two different researchers, and later included or excluded according to the criteria reported previously. The excluded trials and the reason for their exclusion are listed in this paper. Data were extracted from all the trials included.

Details regarding the main methodology characteristics empirically linked to bias[16] were extracted, with the methodologic validity of each selected trial assessed by two reviewers (TEAB and OACC). Particular attention was given to some items, including the generation and concealment of the sequence of randomization, blinding, application of intention-to-treat analysis, sample size predefinition, loss of follow-up description, adverse events reports, and whether the trial was multicenter and/or sponsored.

Data extraction

The data were extracted by two independent reviewers. The name of the first author and year of publication were used to identify the study. All data were extracted directly from the text or calculated from the available information when necessary. The data from all trials were based on the intention-to-treat principle, so they compared all patients allocated to one treatment with all those allocated to another.

The primary endpoints were progression-free survival and overall survival. The definition of progression-free survival adopted was time from randomization to either death or disease progression (whichever occurs first). If data on progression-free survival were not available, data on time to progression or event-free survival were assessed.

Other clinical outcomes were evaluated: overall response rate (complete response and partial response) and more frequent adverse hematologic events (anemia and neutropenia) and nonhematologic events (headache, diarrhea, vomiting, rash, nausea, hand-foot syndrome, fatigue, dyspnea, myalgia, and cardiac toxicity). Cardiac events were defined as a symptomatic decline in left ventricular ejection fraction or, if asymptomatic, as a 20% decrease in left ventricular ejection fraction relative to baseline that was less than the institution's lower normal limit.

Analysis and presentation of results

Data were analyzed using the Review Manager 5.0.24 statistical package Cochrane Collaboration Software, Copenhagen, Denmark. Dichotomous clinical outcomes are reported as the risk ratio (RR) and survival data as the hazard ratio (HR).[17] The corresponding 95% confidence interval (CI) was calculated, considering P-values less than 5% ($P < 0.05$). A statistic for measuring heterogeneity was calculated using the I^2 method (25% was considered low-level heterogeneity, 25%–50% moderate-level heterogeneity, and >50% high-level heterogeneity).[18,19]

To estimate the absolute gains in progression-free survival and overall survival, we calculated the meta-analytic survival curves as suggested by Parmar et al.[17] A pooled estimate of the HR was computed using a fixed-effect model according to the inverse-variance method.[20] Thus, for effectiveness or side effects, an HR or RR >1 favors the standard arm (control), whereas an HR or RR <1 favors treatment with lapatinib.

If statistical heterogeneity was found in the meta-analysis, an additional analysis was performed, using the random-effects model described by DerSimonian and Laird,[21] that provides a more conservative analysis.

To assess the possibility of publication bias, a funnel plot test as described by Egger et al[22] was performed. When the pooled results were significant, the number of patients needed to treat or needed to harm (NNT or NNH, respectively) to cause or to prevent one event was calculated by pooling absolute risk differences in the trials that were included in this meta-analysis.[23–25] For all analyses, a forest plot was generated to display the results.

In the analysis of efficacy, a subgroup analysis was planned to evaluate the influence of the use of CET plus lapatinib only in first-line treatment, according to the type of systemic therapy (ie, lapatinib plus chemotherapy or endocrine therapy, or chemotherapy alone).

Results

Figure 1 represents the flow of identification and inclusion of trials, as recommended by the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.[26] Overall, 113 references were identified and screened. Nine studies were selected and retrieved for full-text analysis. Of these, five studies were excluded for various reasons (not randomized, adjuvant treatment, HER-2(–), and lapatinib in both arms).

Characteristics of included studies

The final analysis included four trials comprising 1,073 patients with HER-2+.[7,9,11,27–30] All results from these studies were analyzed on an intention-to-treat principle. Lapatinib was associated with chemotherapy in three tri-

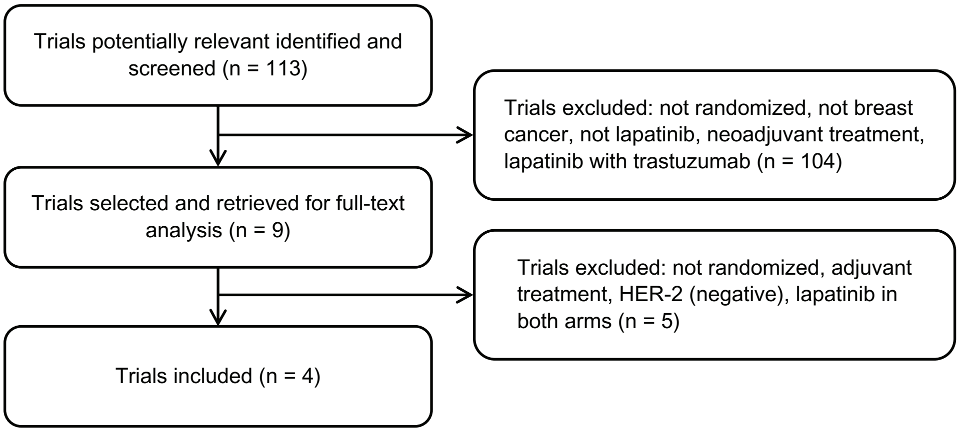

Figure 1 Trial selection flow.
Abbreviation: HER-2, human epidermal growth factor-2.

als,[7,11,27–29] with paclitaxel in two,[11,29] and with capecitabine in one.[7,27,28] One study[9,30] associated lapatinib with endocrine therapy (letrozole; Table 1). The different schemes used for CET and lapatinib are detailed in Table 2.

Overall survival was the primary endpoint of the Guan et al[11] study, whereas progression-free survival was the primary endpoint of the study reported by Johnston et al.[9,30] In another two studies,[7,27,28] the primary endpoint was time to progression, defined as time from randomization to disease progression or death resulting from breast cancer (Table 1).

Two of the eligible studies allowed patients in the "no lapatinib" arm to cross over to lapatinib at disease progression, while the other trials did not permit[9] or did not mention[29] cross over. Data were extracted from updates for some studies, including those reported by Geyer et al and Cameron et al,[7,27,28] and by Johnston et al and Schwartzberg et al.[9,30] With the exception of only one study,[7,27,28] the overall response rate was significantly higher in the groups receiving lapatinib.

Progression-free survival was favorable to the association of CET with lapatinib in all studies singly, while overall survival was significantly superior in favor of lapatinib in only one recently published study[11] (Table 2). The toxicity profile for the HER-2+ subpopulation was described in three trials or in their updates.[7,9,11,27,28,30]

Meta-analyses

The overall response rate was higher in patients who received the combination of CET plus lapatinib (RR 0.78; 95% CI 0.71–0.85; $P < 0.00001$; NNT = 7), but with significant heterogeneity ($\chi^2 = 15.61$; $df = 3$; $P = 0.001$; $I^2 = 81\%$; Figure 2).

As planned, a random-effects model analysis was performed to explore this heterogeneity further. In this analysis, the result remained favorable to the use of CET plus lapatinib (RR 0.76; 95% CI 0.62–0.94; $P = 0.01$, Figure 3).

Progression-free survival was also longer in patients who received CET plus lapatinib (HR 0.57; 95% CI 0.49–0.66;

Table 1 Characteristics of studies that evaluated different schemes of CET in patients with HER-2+ locally advanced or metastatic breast cancer

Study	Design	n HER-2+	Patients	Analysis	Primary end point
Chemotherapy with or without lapatinib					
Guan et al[11]	Randomized, double-blind, placebo-controlled, multicenter	444	Metastatic breast cancer	ITT	OS
Di Leo et al[29]	Randomized, double-blind, placebo-controlled, multicenter	86	Locally advanced or metastatic breast cancer	ITT	PFS
Geyer et al[7] Cameron et al[27,28]	Randomized, nonblinded, open-label, multicenter	324	Locally advanced or metastatic breast cancer	ITT	PFS
Endocrine therapy with or without lapatinib					
Johnston et al[9] Schwartzberg et al[30]	Randomized, double-blind, placebo-controlled, multicenter	219	Locally advanced or metastatic breast cancer	ITT	TTP

Abbreviations: ITT, intention-to-treat; OS, overall survival; PFS, progression free survival; TTP, time to progression; HER-2, human epidermal growth factor receptor-2; CET, chemotherapy or endocrine therapy.

Table 2 Characteristics and results of randomized studies that evaluated different schemes of CET in patients with HER-2+ locally advanced or metastatic breast cancer

Study	Line of treatment	n HER-2+	Interventions	ORR n (%)	PFS HR, 95% CI	OS HR, 95% CI
Chemotherapy with or without lapatinib						
Guan et al[11,*]	First-line	222	Lapatinib + paclitaxel	154 (69%)	9.7 months	27.8 months
		222	Placebo + paclitaxel	110 (50%)	6.5 months	20.5 months
					HR 0.52 (0.42–0.64)	HR 0.74 (0.58–0.94)
Di Leo et al[29,**]	First-line	49	Lapatinib + paclitaxel	31 (63.3%)	8.8 months	26.2 months
		37	Paclitaxel + placebo	14 (37.8%)	5.5 months	20.6 months
					HR 0.52 (0.31–0.86)	HR 0.74 (0.40–1.40)
Geyer et al[7,***]	At least	163	Lapatinib + capecitabine	36 (22%)	8.4 months	18.8 months
Cameron et al [27,28,***]	Second-line	161	Capecitabine	23 (14%)	4.4 months	16.2 months
					HR 0.55 (0.40–0.74)	HR 0.87 (0.71–1.08)
Endocrine therapy with or without lapatinib						
Johnston et al[9,§]	First-line	111	Lapatinib + letrozole	31 (28%)	8.2 months	33.3 months
Schwartzberg et al[30,§]		108	Placebo + letrozole	16 (15%)	3.0 months	32.3 months
					HR 0.71 (0.53–0.96)	HR 0.74 (0.50–1.10)

Notes: *Experimental group received paclitaxel (80 mg/m^2 intravenously once per week for 3 weeks every 4 weeks) and lapatinib (1,500 mg once per day), and control group received paclitaxel (80 mg/m^2 intravenously once per week for 3 weeks every 4 weeks) and placebo (once per day); **experimental group received paclitaxel (175 mg/m^2 intravenously over 3 hours on day 1, every 3 weeks) with lapatinib (1,500 mg per day once daily) and control group received paclitaxel (175 mg/m^2 intravenously over 3 hours on day 1, every 3 weeks) plus placebo once daily; ***experimental group received capecitabine at a dose of 2,000 mm/m^2 in two divided doses on days 1 through 14 of a 21-day cycle plus lapatinib at a dose of 1,250 mg daily and the control group received capecitabine at a dose of 2,000 mm/m^2 in two divided doses on days 1 through 14 of a 21-day cycle; §experimental group received letrozole 2.5 mg orally daily plus lapatinib 1,500 mg orally, and the control group received letrozole 2.5 mg daily with matching lapatinib placebo pill.

Abbreviations: ORR, overall response rate; OS, overall survival; PFS, progression free survival; HR, hazard ratio; CET, chemotherapy or endocrine therapy; HER-2, human epiderman growth factor-2.

$P < 0.00001$; NNT = 2), with no heterogeneity detected in this analysis ($\chi^2 = 3.05$; $df = 3$, $P = 0.38$; $I^2 = 1\%$, Figure 4). Overall survival was significantly longer in patients who received CET plus lapatinib (HR 0.80; 95% CI 0.69–0.92; $P = 0.002$; NNT = 5), without heterogeneity in this analysis ($\chi^2 = 1.26$; $df = 3$; $P = 0.74$; $I^2 = 0\%$, Figure 5).

Regarding overall adverse events (toxicities of any grade), patients receiving CET plus lapatinib had higher rates of neutropenia (RR 1.63; 95% CI 1.39–1.91; $P < 0.00001$; NNH = 12), and anemia (RR 1.55; 95% CI 1.2–1.99; $P = 0.0007$; NNH = 17, Figure 6), and diarrhea (RR 2.44; 95% CI 2.15–2.78; $P < 0.00001$; NNH = 2), nausea (RR 1.23; 95% CI 1.06–1.43; $P = 0.006$; NNH = 14), vomiting (RR 1.50; 95% CI 1.22–1.85; $P = 0.0001$; NNH = 12), and rash (RR 2.4; 95% CI 2.03–2.83; $P < 0.00001$; NNH = 4, Figure 7). The proportion of patients with cardiac events

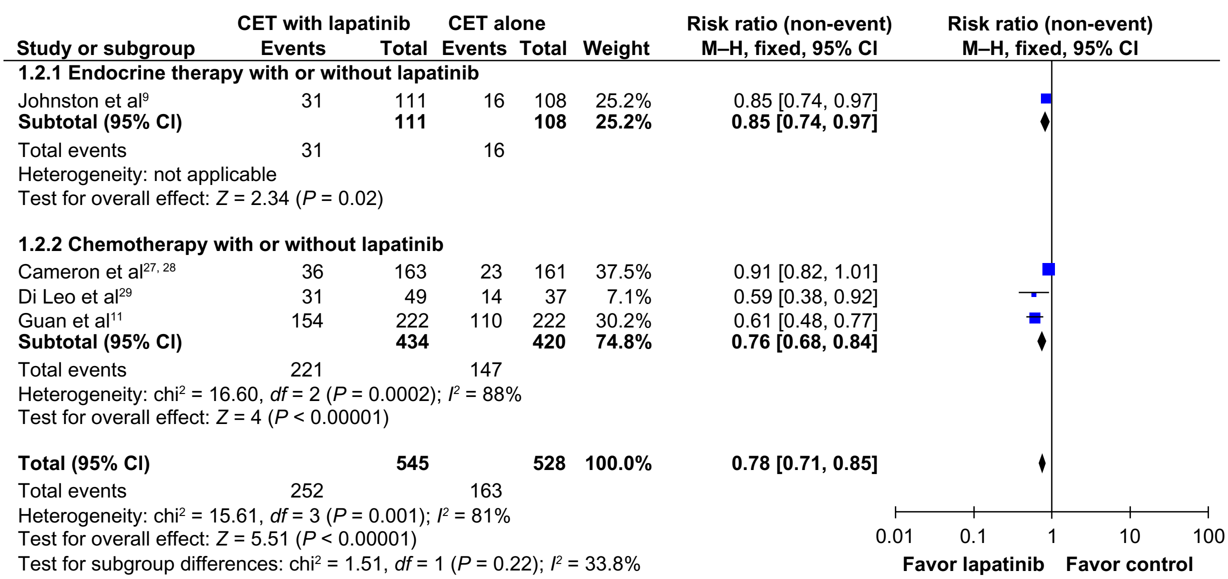

Figure 2 Comparison of objective response rates on CET with lapatinib versus CET alone.

Abbreviations: CET, chemotherapy or endocrine therapy; CI, confidence interval; M–H, Mantel–Haenszel.

Study or subgroup	CET with lapatinib Events	CET with lapatinib Total	CET alone Events	CET alone Total	Weight	Risk ratio (non-event) M–H, random, 95% CI
1.2.1 Endocrine therapy with or without lapatinib						
Johnston et al[9]	31	111	16	108	30.1%	0.85 [0.74, 0.97]
Subtotal (95% CI)		**111**		**108**	**30.1%**	**0.85 [0.74, 0.97]**
Total events	31		16			
Heterogeneity: not applicable						
Test for overall effect: $Z = 2.34$ ($P = 0.02$)						
1.2.2 Chemotherapy with or without lapatinib						
Cameron et al[27,28]	36	163	23	161	32.0%	0.91 [0.82, 1.01]
Di Leo et al[29]	31	49	14	37	13.7%	0.59 [0.38, 0.92]
Guan et al[11]	154	222	110	222	24.2%	0.61 [0.48, 0.77]
Subtotal (95% CI)		**434**		**420**	**69.9%**	**0.71 [0.48, 1.04]**
Total events	221		147			
Heterogeneity: $tau^2 = 0.10$; $chi^2 = 16.60$, $df = 2$ ($P = 0.0002$); $I^2 = 88\%$						
Test for overall effect: $Z = 1.75$ ($P = 0.08$)						
Total (95% CI)		**545**		**528**	**100.0%**	**0.76 [0.62, 0.94]**
Total events	252		163			
Heterogeneity: $tau^2 = 0.03$; $chi^2 = 15.61$, $df = 3$ ($P = 0.001$); $I^2 = 81\%$						
Test for overall effect: $Z = 2.53$ ($P = 0.01$)						
Test for subgroup differences: $chi^2 = 0.74$, $df = 1$ ($P = 0.39$); $I^2 = 0\%$						

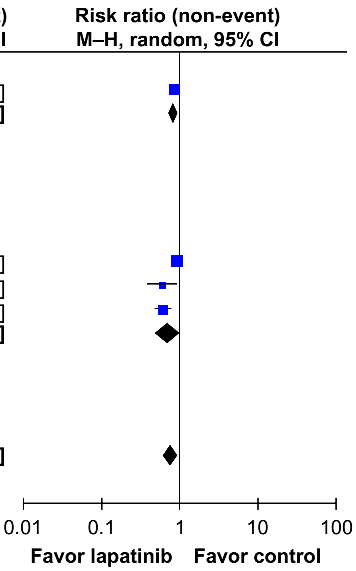

Figure 3 Comparison of objective response rates on CET with lapatinib versus CET alone (random-effects model analysis).
Abbreviations: CET, chemotherapy or endocrine therapy; CI, confidence interval; M–H, Mantel–Haenszel.

was similar in both groups (RR 1.6; 95% CI 0.92–2.80; $P = 0.10$, Figure 7).

Concerning severe toxicities (of grade ≥3), patients receiving CET plus lapatinib had higher rates of neutropenia (RR 2.08; 95% CI 1.64–2.62; $P < 0.00001$; NNH = 9), diarrhea (RR 4.82; 95% CI 3.14–7.41; $P < 0.00001$; NNH = 8), and rash (RR 8.03; 95% CI 2.46–26.23; $P = 0.0006$; NNH = 33).

Because there was significant heterogeneity in adverse events, we undertook an analysis with and without inclusion of the study reported by Di Leo et al,[29] given that this study reported toxicity in patients with HER-2+ and HER-2− disease. There was no difference in the results. As planned, we also performed a random-effects model analysis to explore this heterogeneity further and the result remained favorable to the control group. According to funnel plot[22] analysis, the possibility of publication bias was low for all endpoints.

Subgroup analysis

According to the type of systemic therapy (CET), lapatinib associated only with chemotherapy was more effective than the use of CET alone, showing a better overall response rate (RR 0.76; 95% CI 0.68–0.84; $P < 0.00001$; NNT = 6), longer progression-free survival (HR 0.53; 95% CI 0.45–0.62; $P < 0.00001$; NNT = 2), and longer overall

Study or subgroup	Log[hazard ratio]	SE	Weight	Hazard ratio IV, fixed, 95% CI
1.1.1 Endocrine therapy with or without lapatinib				
Johnston et al[9]	−0.34249031	0.14918027	24.8%	0.71 [0.53, 0.95]
Subtotal (95% CI)			**24.8%**	**0.71 [0.53, 0.95]**
Heterogeneity: not applicable				
Test for overall effect: $Z = 2.30$ ($P = 0.02$)				
1.1.2 Chemotherapy with or without lapatinib				
Cameron et al[27,28]	−0.597837	0.16247938	20.9%	0.55 [0.40, 0.76]
Di Leo et al[29]	−0.65392647	0.26391123	7.9%	0.52 [0.31, 0.87]
Guan al[11]	−0.65392647	0.10896838	46.4%	0.52 [0.42, 0.64]
Subtotal (95% CI)			**75.2%**	**0.53 [0.45, 0.62]**
Heterogeneity: $chi^2 = 0.09$, $df = 2$ ($P = 0.96$); $I^2 = 0\%$				
Test for overall effect: $Z = 7.46$ ($P < 0.00001$)				
Total (95% CI)			**100.0%**	**0.57 [0.49, 0.66]**
Heterogeneity: $chi^2 = 3.05$, $df = 3$ ($P = 0.38$); $I^2 = 1\%$				
Test for overall effect: $Z = 7.61$ ($P < 0.00001$)				
Test for subgroup differences: $chi^2 = 2.96$, $df = 1$ ($P = 0.09$); $I^2 = 66.2\%$				

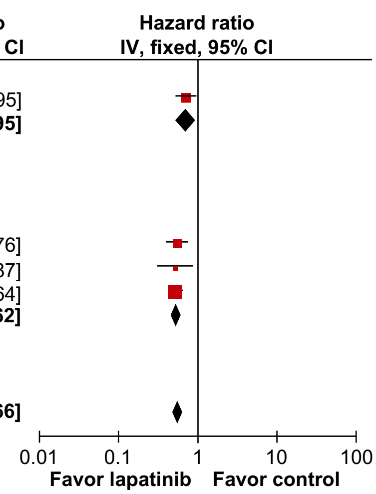

Figure 4 Comparison of progression-free survival on CET with lapatinib versus CET alone.
Abbreviations: CET, chemotherapy or endocrine therapy; CI, confidence interval; SE, standard error; IV, inverse variance.

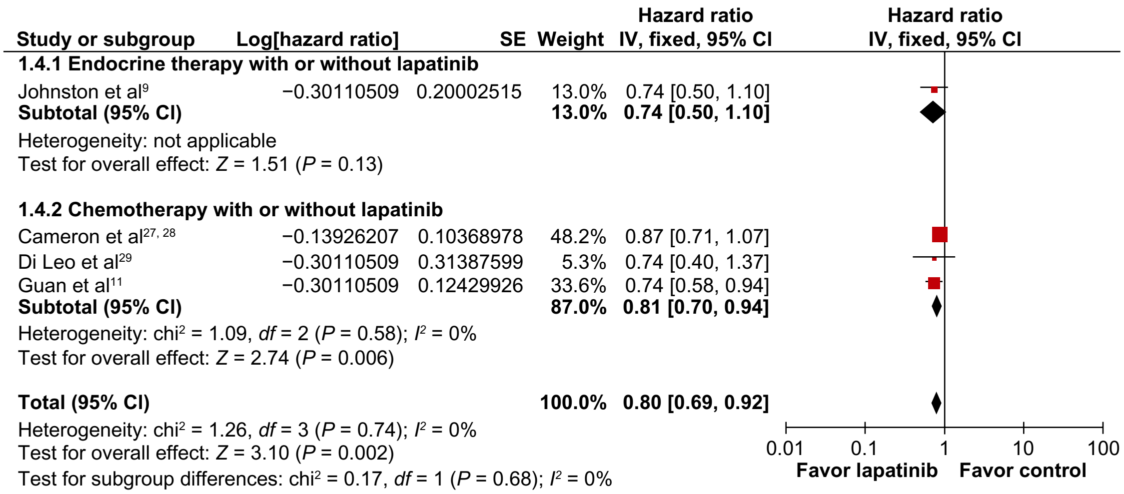

Figure 5 Comparison of overall survival on CET with lapatinib versus CET alone.
Abbreviations: CET, chemotherapy or endocrine therapy; CI, confidence interval; SE, standard error; IV, inverse variance.

survival (HR 0.81; 95% CI 0.70–0.94; $P = 0.006$; NNT = 5). However, no statistically significant interaction was found between type of lapatinib combination (endocrine or chemotherapy) and the endpoints analyzed.

In accordance with the line of treatment, use of lapatinib plus CET only as first-line treatment also remained superior to the control group in relation to the overall response rate (RR 0.70; 95% CI 0.61–0.80; $P < 0.00001$; NNT = 6), progression-free survival (HR 0.57; 95% CI 0.49–0.68; $P < 0.00001$; NNT = 2), and overall survival (HR 0.74; 95% CI 0.61–0.90; $P = 0.003$; NNT = 3).

Discussion

Anti-HER-2 agents have been widely investigated as a strategy for improving survival in advanced or metastatic breast cancer. Trastuzumab, a recombinant humanized monoclonal antibody, was the first molecular targeted agent, and was approved by the FDA for treatment of HER-2+ breast cancer in 1998.[31]

It is known that not all metastatic breast cancer and HER-2+ patients respond to treatment with trastuzumab, and even in those who do respond, the response is transient and rarely exceeds one year.[31,32] The benefit of continued

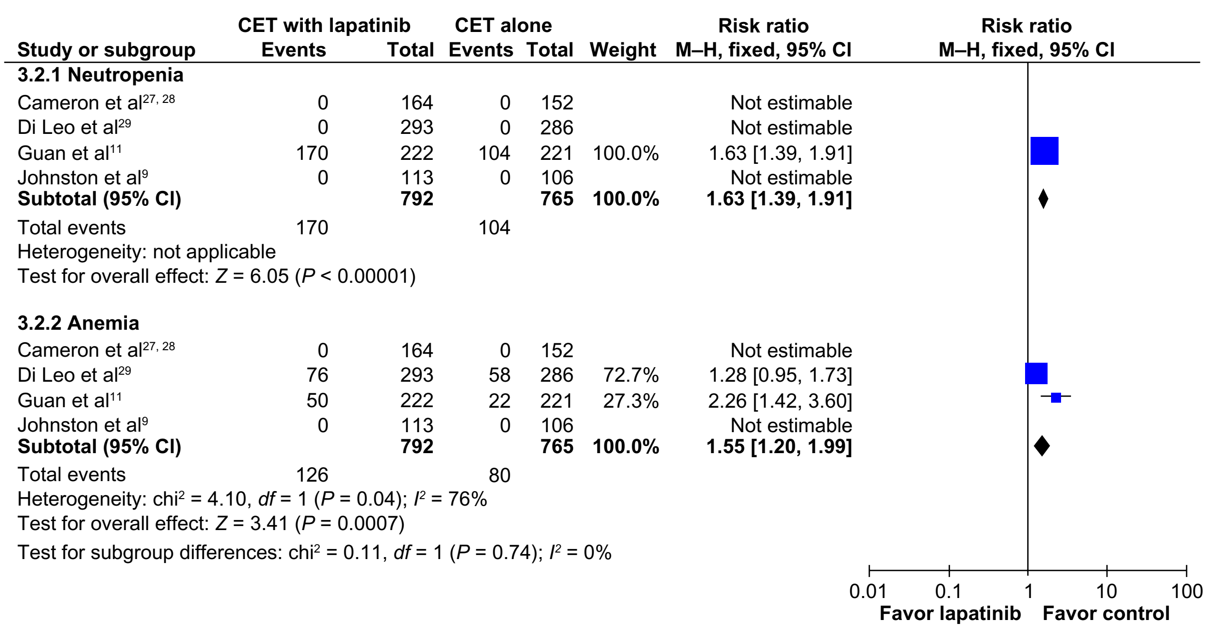

Figure 6 Comparison of hematologic toxicity (any grade) on CET with lapatinib versus CET alone.
Abbreviations: CET, chemotherapy or endocrine therapy; CI, confidence interval; M–H, Mantel–Haenszel.

Study or subgroup	CET with lapatinib Events	Total	CET alone Events	Total	Weight	Risk ratio M–H, fixed, 95% CI
3.1.1 Headache						
Cameron et al[27,28]	15	164	20	152	62.6%	0.70 [0.37, 1.31]
Di Leo et al[29]	0	293	0	286		Not estimable
Guan et al[11]	0	222	221	0		Not estimable
Johnston et al[9]	16	113	12	106	37.4%	1.25 [0.62, 2.52]
Subtotal (95% CI)		**792**		**544**	**100.0%**	**0.90 [0.57, 1.44]**
Total events	31		253			
Heterogeneity: chi² = 1.49, *df* = 1 (*P* = 0.22); *I*² = 33%						
Test for overall effect: *Z* = 0.43 (*P* = 0.67)						
3.1.2 Diarrhea						
Cameron et al[27,28]	98	164	60	152	29.9%	1.51 [1.20, 1.91]
Di Leo et al[29]	171	293	73	286	35.4%	2.29 [1.83, 2.85]
Guan et al[11]	172	222	64	221	30.8%	2.68 [2.15, 3.33]
Johnston et al[9]	77	113	8	106	4.0%	9.03 [4.58, 17.79]
Subtotal (95% CI)		**792**		**765**	**100.0%**	**2.44 [2.15, 2.78]**
Total events	518		205			
Heterogeneity: chi² = 31.41, *df* = 3 (*P* < 0.00001); *I*² = 90%						
Test for overall effect: Z = 13.70 (*P* < 0.00001)						
3.1.3 Vomiting						
Cameron et al[27,28]	43	164	37	152	31.9%	1.08 [0.74, 1.58]
Di Leo et al[29]	74	293	48	286	40.4%	1.50 [1.09, 2.08]
Guan et al[11]	48	222	26	221	21.7%	1.84 [1.18, 2.85]
Johnston et al[9]	19	113	7	106	6.0%	2.55 [1.12, 5.81]
Subtotal (95% CI)		**792**		**765**	**100.0%**	**1.50 [1.22, 1.85]**
Total events	184		118			
Heterogeneity: chi² = 5.32, *df* = 3 (*P* = 0.15); *I*² = 44%						
Test for overall effect: *Z* = 3.85 (*P* = 0.0001)						
3.1.4 Rash						
Cameron et al[27,28]	45	164	23	152	16.5%	1.81 [1.15, 2.85]
Di Leo et al[29]	126	293	60	286	41.9%	2.05 [1.58, 2.66]
Guan et al[11]	130	222	52	221	35.9%	2.49 [1.91, 3.23]
Johnston et al[9]	52	113	8	106	5.7%	6.10 [3.04, 12.22]
Subtotal (95% CI)		**792**		**765**	**100.0%**	**2.40 [2.03, 2.83]**
3.1.5 Nausea						
Cameron et al[27,28]	72	164	64	152	31.2%	1.04 [0.81, 1.34]
Di Leo et al[29]	100	293	85	286	40.4%	1.15 [0.90, 1.46]
Guan et al[11]	66	222	41	221	19.3%	1.60 [1.14, 2.26]
Johnston et al[9]	30	113	19	106	9.2%	1.48 [0.89, 2.47]
Subtotal (95% CI)		**792**		**765**	**100.0%**	**1.23 [1.06, 1.43]**
Total events	268		209			
Heterogeneity: chi² = 4.76, *df* = 3 (*P* = 0.19); *I*² = 37%						
Test for overall effect: *Z* = 2.76 (*P* = 0.006)						
3.1.6 Hand-foot syndrome						
Cameron et al[27,28]	80	164	74	152	100.0%	1.00 [0.80, 1.26]
Di Leo et al[29]	0	293	0	286		Not estimable
Guan et al[11]	0	222	0	221		Not estimable
Johnston et al[9]	0	113	0	106		Not estimable
Subtotal (95% CI)		**792**		**765**	**100.0%**	**1.00 [0.80, 1.26]**
Total events	80		74			
Heterogeneity: not applicable						
Test for overall effect: *Z* = 0.02 (*P* = 0.99)						
3.1.7 Fatigue						
Cameron et al[27,28]	29	164	41	152	45.7%	0.66 [0.43, 1.00]
Di Leo et al[29]	0	293	0	286		Not estimable
Guan et al[11]	48	222	35	221	37.7%	1.37 [0.92, 2.02]
Johnston et al[9]	25	113	15	106	16.6%	1.56 [0.87, 2.80]
Subtotal (95% CI)		**792**		**765**	**100.0%**	**1.07 [0.83, 1.38]**
Total events	102		91			
Heterogeneity: chi² = 8.30, *df* = 2 (*P* = 0.02); *I*² = 76%						
Test for overall effect: *Z* = 0.55 (*P* = 0.58)						
3.1.8 Dyspnea						
Cameron et al[27,28]	18	164	10	152	47.8%	1.67 [0.80, 3.50]
Di Leo et al[29]	0	293	0	286		Not estimable
Guan et al[11]	0	222	0	221		Not estimable
Johnston et al[9]	10	113	11	106	52.2%	0.85 [0.38, 1.93]
Subtotal (95% CI)		**792**		**765**	**100.0%**	**1.24 [0.72, 2.13]**
Total events	28		21			
Heterogeneity: chi² = 1.43, *df* = 1 (*P* = 0.23); *I*² = 30%						
Test for overall effect: *Z* = 0.79 (*P* = 0.43)						
3.1.9 Myalgia						
Cameron et al[27,28]	0	164	0	152		Not estimable
Di Leo et al[29]	94	293	74	286	93.6%	1.24 [0.96, 1.60]
Guan et al[11]	0	222	0	221		Not estimable
Johnston et al[9]	11	113	5	106	6.4%	2.06 [0.74, 5.74]
Subtotal (95% CI)		**792**		**765**	**100.0%**	**1.29 [1.01, 1.66]**
Total events	105		79			
Heterogeneity: chi² = 0.90, *df* = 1 (*P* = 0.34); *I*² = 0%						
Test for overall effect: *Z* = 2.01 (*P* = 0.04)						
3.1.10 Cardiac event						
Cameron et al[27,28]	4	164	1	152	5.4%	3.71 [0.42, 32.80]
Di Leo et al[29]	6	293	6	286	31.7%	0.98 [0.32, 2.99]
Guan et al[11]	20	222	11	221	57.5%	1.81 [0.89, 3.69]
Johnston et al[9]	1	113	1	106	5.4%	0.94 [0.06, 14.81]
Subtotal (95% CI)		**792**		**765**	**100.0%**	**1.60 [0.92, 2.80]**
Total events	31		19			
Heterogeneity: chi² = 1.58, *df* = 3 (*P* = 0.66); *I*² = 0%						
Test for overall effect: *Z* = 1.65 (*P* = 0.10)						
Test for subgroup differences: chi² = 111.93, *df* = 9 (*P* < 0.00001); *I*² = 92.0%						

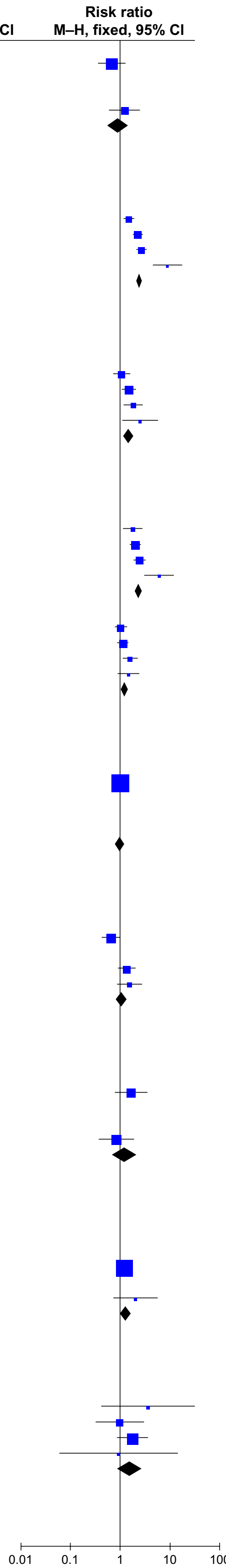

Figure 7 Comparative effect non-hematologic toxicities (any grade) of chemo- or endocrine therapy (CET) with Lapatinib versus CET alone.
Abbreviations: CET, chemotherapy or endocrine therapy; CI, confidence interval; M–H, Mantel–Haenszel.

use of trastuzumab beyond disease progression remains controversial.[33] Geyer et al[7] published the first study demonstrating the benefits of another anti-HER-2 agent, ie, lapatinib, for patients with trastuzumab-refractory metastatic breast cancer.

As has been shown, studies with this drug in first-line treatment were published subsequently. Based on studies showing a gain in progression-free survival, international guidelines[10,34] recommend use of the CET plus lapatinib combination in patients with stage IIIB, inoperable stage IIIC, stage IV, recurrent, or metastatic breast cancer. So far, there are no studies directly comparing the two drugs.

Two other previously published meta-analyses have indicated the benefits of using lapatinib plus CET for metastatic and HER-2+ breast cancer.[31,35] The present meta-analysis incorporated the results of another published RCT[11] and confirmed the benefits of lapatinib plus CET regardless of the treatment line and the efficacy endpoints evaluated, including overall survival. The fact that benefits in overall survival were observed even while some trials allowed cross over from "no lapatinib" to "lapatinib" arms reinforces the activity and effectiveness of this drug. Although no survival benefit was observed in lapatinib combined with endocrine therapy in the only trial that analyzed this combination, it is important to note that the absence of a statistically significant interaction between the lapatinib combination therapy subgroups (CET) and overall survival suggests that other factors, such as cross over, may have accounted for this result.

There was heterogeneity in the overall response rate. This heterogeneity can be attributed to different somatic tumor characteristics. Genomic variants in patients may influence the response to drug treatment. As reported in the following two references, alterations in the estrogen receptor, PI3K-PTEN-Akt signaling cascade, and downstream FOXO3a and FOXM1 are poor prognostic predictors of clinical response.[36,37] In addition to HER-2 expression and amplification, other genomic variants should be considered in patients to be treated with lapatinib plus CET.

The group receiving CET plus lapatinib had higher rates of adverse hematologic events (neutropenia and anemia), adverse gastrointestinal events (diarrhea, nausea, and vomiting), and rash. The proportions of headache, hand-foot syndrome, fatigue, dyspnea, and myalgia were similar. The proportions of cardiac events were also similar. The majority of these cardiac events were grade 1 or 2, asymptomatic, transient, and reversible.[7,9,11,29]

Conclusion

The combination of CET plus lapatinib increased the overall response, progression-free survival, and overall survival rates in patients with HER-2+ locally advanced or metastatic breast cancer. Side effects resulting from the combination were mild and transient.

Author contributions

All the authors of this research paper participated directly in its planning, execution, or analysis. All authors read and approved the final version submitted.

Disclosure

The authors report no conflicts of interest in this work.

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