Journal Syifa Sciences and Clinical Research (JSSCR)
Volume 8 Nomor 3, 2026
Journal Homepage: http://ejurnal.ung.ac.id/index.php/jsscr, E-ISSN: 2656-9612 P-ISSN:2656-8187
DOI : https://doi.org/10.37311/jsscr.v8i3.32895

Adverse Effects of Lapatinib as Adjuvant Therapy in Woman with HER-2 Positive Breast Cancer: A Narative Review

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ABSTRACT

HER-2 positive breast cancer is an aggressive subtype associated with a poorer prognosis due to the overexpression of the HER-2 receptor. Lapatinib, a tyrosine kinase inhibitor targeting HER-2 and epidermal growth factor receptor (EGFR), is widely used in therapy; however, it is associated with potential adverse effects. This study aimed to evaluate the adverse effect profile of lapatinib in patients with HER-2 positive breast cancer. This study employed a narrative review approach by conducting a literature search in PubMed over the past 10 years. A total of 20 articles were initially identified, and after applying selection criteria, 12 articles were included and analyzed descriptively. The results indicate that the most commonly reported adverse effects are gastrointestinal toxicities, particularly diarrhea, with an incidence ranging from 70% to 89%. Other adverse effects include nausea and vomiting (30–50%), as well as skin rash. Hematological adverse effects are relatively uncommon and are generally associated with combination therapy, whereas cardiovascular effects such as decreased left ventricular function are reported at a lower incidence (<10%) and are typically reversible. In conclusion, lapatinib demonstrates a predictable and generally manageable adverse effect profile. Regular monitoring of adverse effects, particularly gastrointestinal symptoms and cardiac function, is essential to ensure treatment safety and optimize therapeutic outcomes.

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Keywoard:
Lapatinib; Adverse Effects; HER-2 Positive Breast Cancer; Targeted Therapy

Received:	*Accepted:*	*Online:*
2025-05-21	*2026-08-07*	*2026-10-29*

1. Introduction

Breast cancer is one of the most prevalent cancers among women worldwide and remains a leading cause of cancer-related mortality in the female population. According to the Global Cancer Observatory (GLOBOCAN), breast cancer accounts for more than 2.3 million new cases annually and represents the most frequently diagnosed cancer among women globally [1]. In Indonesia, breast cancer is also the most commonly diagnosed malignancy in women and poses a substantial burden on the healthcare system [1], [3]. Breast cancer is a heterogeneous disease that can be classified into several

molecular subtypes based on hormone receptor expression and Human Epidermal Growth Factor Receptor-2 (HER-2), each of which exhibits distinct biological characteristics and therapeutic responses [2].

HER-2 positive breast cancer is characterized by gene amplification or overexpression of the HER-2 receptor, which occurs in approximately 15–20% of breast cancer cases and is associated with increased tumor cell proliferation, greater disease aggressiveness, and poorer prognosis compared to other subtypes [4], [7]. The HER-2 receptor belongs to the family of tyrosine kinase receptors and plays a crucial role in activating intracellular signaling pathways such as PI3K/AKT and MAPK, which regulate cell proliferation, survival, and tumor metastasis [5], [6]. Understanding the biological role of HER-2 in breast cancer progression has led to the development of targeted therapies aimed at inhibiting these signaling pathways to improve treatment outcomes [7].

One of the targeted therapeutic agents used in HER-2 positive breast cancer is lapatinib, an oral tyrosine kinase inhibitor that acts by inhibiting the intracellular domains of HER-2 and epidermal growth factor receptor (EGFR). By blocking the phosphorylation of these receptors, lapatinib disrupts signal transduction pathways involved in tumor cell proliferation and survival, thereby inhibiting tumor growth [8]. This mechanism of action also explains the occurrence of several commonly reported adverse effects, such as diarrhea resulting from disruption of gastrointestinal epithelial regulation and skin rash associated with EGFR inhibition in epithelial tissues [11], [12]. In addition, some studies have reported more serious adverse effects, including hepatotoxicity and potential cardiotoxicity, which require careful clinical monitoring during lapatinib therapy [13], [14].

Although numerous studies have evaluated the use of lapatinib in HER-2 positive breast cancer, most have primarily focused on therapeutic efficacy and clinical outcomes, while comprehensive synthesis of toxicity profiles and adverse effects remains limited, particularly across different treatment regimens used in clinical practice [8], [9]. This gap highlights the need for a more systematic evaluation of lapatinib-related adverse effects to provide a clearer understanding of its safety profile. Therefore, this narrative review aims to comprehensively examine the adverse effects associated with lapatinib use in patients with HER-2 positive breast cancer based on published studies, in order to support clinical decision-making and optimize therapeutic monitoring in clinical practice.

2. Methods

This study employed a narrative review approach to examine the literature on the adverse effects of lapatinib use in patients with breast cancer. A literature search was conducted using the PubMed database with *Medical Subject Headings* (MeSH) and the following keywords: ("Lapatinib/adverse effects"[Mesh] AND "Breast Neoplasms"[Mesh]), limited to publications from the past 10 years. A total of 20 articles were initially identified, followed by screening based on titles and abstracts. Eight articles were excluded due to unavailability of full-text access or lack of relevance, resulting in 12 articles that met the inclusion criteria and were subsequently analyzed.

The inclusion criteria comprised original research articles involving patients with HER-2 positive breast cancer that reported adverse effects of lapatinib, including studies with randomized controlled trial, cohort, case reports and observational designs, published in English and available in full text. The exclusion criteria included review

articles, non-human studies, and articles with incomplete or irrelevant data. Article selection was performed independently by two reviewers to minimize potential bias, beginning with title and abstract screening followed by full-text assessment. Any disagreements were resolved through discussion until consensus was reached.

Data extraction was conducted independently using a standardized format that included author names, year of publication, study design, patient population, and reported adverse effects. The extracted data were then synthesized descriptively by categorizing adverse effects. Additionally, variations in study characteristics and patient populations were analyzed to identify patterns of adverse effects and differences in findings across studies. The article selection process followed the predefined inclusion and exclusion criteria and is illustrated in a PRISMA flow diagram (**Figure 1**).

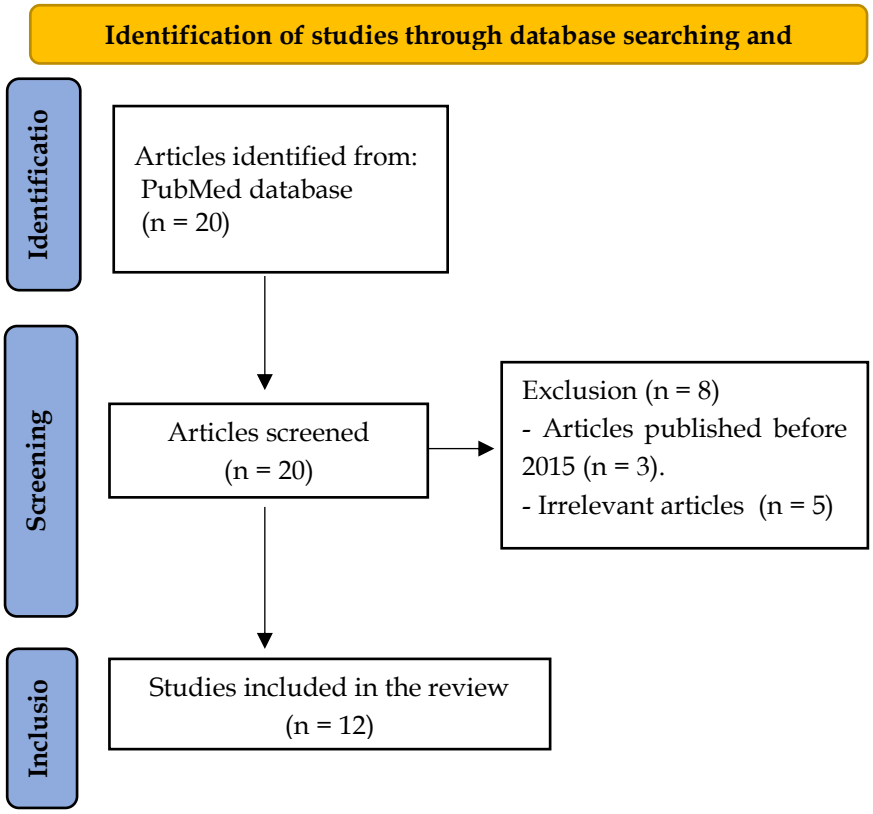


Figure 1. PRISMA Flow Diagram of Literature Search

3. Result and Discussion

Based on the review of several studies evaluating the adverse effects of lapatinib-based combination therapy in HER2-positive breast cancer, it was found that the reported adverse effects varied considerably depending on the treatment combinations, study design, and patient population characteristics. The included studies involved patients with breast cancer ranging from early-stage to metastatic disease, with ages ranging from 25 to 75 years. The detailed findings of each study are summarized in **Table 1**.

Table 1. Studies on Adverse Effects of Lapatinib-Based Combination Therapy as Adjuvant Treatment in Women with Breast Cancer

Reference	Full Journal Title	Study Design	Study Location	Study Population	Sample Size	Age Group	Drug Combination / Treatment	Adverse Effects (category %)
Lim B, Murthy RK, Lee J, Jackson SA, Iwase T, Davis DW, Willey JS, Wu J, Shen Y, Tripathy D, et al. (2019)	A phase Ib study of entinostat plus lapatinib with or without trastuzumab in patients with HER2-positive metastatic breast cancer that progressed during trastuzumab treatment	Phase Ib, dose escalation, single-centre, open-label, single-arm	USA	Adult patients with HER2-positive metastatic breast cancer who progressed during trastuzumab therapy	35	Median age 52 years (range: 26–72)	Entinostat + lapatinib with or without trastuzumab	Diarrhea (high: 89%), neutropenia (high: 31%), thrombocytopenia (high: 23%)
Moon JY, Han JM, Seo I, Gwak HS. (2019)	Risk factors associated with the incidence and time to onset of lapatinib-induced hepatotoxicity	Retrospektive Study	Korea	Pasien kanker payudara metastatik wanita yang menerima lapatinib	159	>18 years (majority >50 years)	Lapatinib, with or without H2 blocker, CYP3A4 inducer, PPI, capecitabine, and other anticancer agents	Hepatotoxicity (elevated AST/ALT) (moderate: 10–15%), with higher risk in patients receiving H2 blockers and CYP3A4 inducers
Patel et al. Breast Cancer Research (2019)	A randomized, controlled phase II trial of neoadjuvant ado-trastuzumab emtansine, lapatinib, and nab-paclitaxel versus trastuzumab, pertuzumab, and paclitaxel in HER2-positive breast cancer (TEAL study)	Randomized controlled, open-label, phase II clinical trial	USA	Patients with early-stage HER2-positive breast cancer	30 patients (14 in experimental arm, 16 in standard arm)	>18 years (median 55 years, range 28–75 years)	Experimental arm: T-DM1 + lapatinib + nab-paclitaxel; Standard arm: trastuzumab + pertuzumab + paclitaxel	Elevated liver function (moderate: 28.1%), diarrhea (moderate: 21.9%), fatigue (moderate: 25.0%), neuropathy (low: 10%)

Eiger D, Pondé NF, Agbor-Tarh D, et al. (2020)	Long-term cardiac outcomes of patients with HER2-positive breast cancer treated in the adjuvant lapatinib and/or trastuzumab Treatment Optimization Trial	Sub-analysis of a randomized, open-label, multicenter phase III trial (ALTTO trial)	International, multicenter	Patients with early-stage HER2-positive breast cancer	4,190 (2,097 receiving trastuzumab [T], 2,093 receiving trastuzumab + lapatinib [T+L])	Majority <65 years (90%); ≥65 years (10%)	Trastuzumab (T) saja vs. kombinasi Trastuzumab + Lapatinib (T+L)	Cardiotoxicity: penurunan LVEF asimtomatik (rendah : 6,3%), CE simtomatik (rendah : 2,2%), kematian jantung (<0,1%) (efek samping lebih sering selama terapi anti-HER2 (6,4%) dibandingkan follow-up (2,2%)
Tsuda M, Ishiguro H, Toriguchi N, et al. Cancer Medicine. (2020)	Overnight fasting before lapatinib administration to breast cancer patients leads to reduced toxicity compared with nighttime dosing: a retrospective cohort study from a randomized clinical trial	Retrospective cohort study derived from randomized phase II clinical trial data	Japan	Patients with HER2-positive breast cancer receiving lapatinib	140 patients (from a total of 213 clinical trial participants)	Mean age 53.5 ± 10.3 years (range: 26–69 years)	Lapatinib (1000 mg/day or 750 mg/day) + trastuzumab ± paclitaxel ± endocrine therapy, with administration timing before breakfast, between meals, or before bedtime	Diarrhea (high: 94.3%), skin rash (high: 80.0%), hepatotoxicity (low: 25.7%); lower risk of diarrhea and rash observed in patients taking lapatinib before breakfast compared to before bedtime.
Wang et al. (2021)	The Effectiveness of Lapatinib in HER2-Positive Metastatic Breast Cancer Patients Pretreated With Multiline Anti-HER2 Treatment: A Retrospective Study in China	Retrospective study	China	Patients with HER2-positive metastatic breast cancer receiving lapatinib	115	Median age 45 years (range: 27–77 years)	Lapatinib (monotherapy or in combination with trastuzumab and/or chemotherapy)	Gastrointestinal disorders (all grades: 55.9%), skin disorders (all grades) (moderate: 23.5%), hematologic disorders (low: 2.6%), neutropenia (low: 3.5%), hand-foot syndrome (low: 1.7%); most adverse effects were manageable with appropriate medical treatment

Hu et al. (2025)	ACE-Breast-02: a randomized phase III trial of ARX788 versus lapatinib plus capecitabine for HER2-positive advanced breast cancer	Randomized, open-label, controlled phase III trial	China	Patients with advanced HER2-positive breast cancer who had progressed after at least one trastuzumab-based regimen	441 (ARX788: 221; LC: 220)	18–75 years, median 52 years	ARX788 (1.5 mg/kg IV Q3W) vs. lapatinib (1250 mg QD) + capecitabine (1000 mg/m² BID, days 1–14, Q3W)	Lapatinib + capecitabine: grade ≥3 adverse events including hand-foot syndrome (moderate: 18.1%) and hypokalemia (low: 5.1%)
Damayanti Sulistianingrum, N., Indrastuti, N., & Widodo Wirohadidjojo, Y. (2023)	Cutaneous Manifestations of Breast Cancer Patients In Combination With Capecitabine and Lapatinib Chemotherapy	Case Report	Indonesia	Patients with HER2-positive breast cancer	1	38 years	Combination chemotherapy: lapatinib + capecitabine	Higher incidence of adverse effects when lapatinib and capecitabine are combined, including acneiform eruption (acne-like rash), palmar–plantar erythrodysesthesia (PPE/hand–foot syndrome), and paronychia (infection/inflammation around the nail)
Xie Y, Ge R, Sang D, et al. (2020)	Real-world data of lapatinib and treatment after lapatinib in patients with previously treated HER2-positive metastatic breast cancer: A multicenter, retrospective study	Multicenter, retrospektif	China	Patients with HER2-positive metastatic breast cancer previously treated with trastuzumab and taxanes	242	Median age 52 years (range: 26–86 for LX; 28–75 for HLC)	Lapatinib + capecitabine (LX) (n=164) and lapatinib + trastuzumab + chemotherapy (HLC) (n=78)	Lapatinib + capecitabine: grade ≥3 adverse events including diarrhea (moderate: 5.5%), neutropenia (moderate: 6.7%), and leukopenia (moderate: 6.1%). Lapatinib + trastuzumab + chemotherapy showed similar adverse effects, with higher incidence rates of diarrhea (moderate: 7.7%), neutropenia (high: 11.5%), and leukopenia (high: 11.5%). No mortality related to adverse effects was reported.

Ye X, Luo X, Du Q, Li H, Liu HY, Yu B, Zhai Q. Ann Transl Med 2020	Efficacy and safety of lapatinib in Chinese breast cancer patients: a real-world study	Prospective, non-interventional, real-world long-term study	China	Patients with HER2-positive breast cancer receiving lapatinib	112	Median age 52 years (range: 29–72 years)	Lapatinib (commonly combined with capecitabine, paclitaxel, or vinorelbine)	Real-world use of lapatinib reported several adverse effects, including diarrhea (high: 50.9%), skin rash (high: 40.2%), hand-foot syndrome (moderate: 28.6%), hepatobiliary events (moderate: 17.0%), paronychia (moderate: 15.2%), and stomatitis (moderate: 10.7%).
Park, Y., Kim, H., Kim, E. *et al*, (2016).	Effective Treatment of Solitary Pituitary Metastasis with Panhypopituitarism in HER2-Positive Breast Cancer by Lapatinib	Case Report	Korea	Patient with HER2-positive breast cancer with solitary pituitary metastasis	1	43 years (adult)	Lapatinib monotherapy, followed by lapatinib + capecitabine combination	Pemberian lapatinib secara tunggal sebelum kombinasi melaporkan kejadian efek samping berupa diare dan hand-foot syndrome pada grade 3-4. Sedangkan pada pemberian lapatinib kombinasi bersama capecitabine, efek samping berat yang dilaporkan adalah toksisitas gastrointestinal yang menyebabkan shock septic, gangguan natrium hingga perubahan kesadaran.
Kuc-Rajca, M., & Walaszkowska-Czyż, A. (2017).	Lapatinib in the treatment of advanced HER2-positive breast cancer	Case Report	Not specified	Patients with advanced/metastatic HER2-positive breast cancer after failure of anthracycline, taxane, and trastuzumab therapy	2	48 and 56 years	Lapatinib 1250 mg/day + capecitabine 2000 mg/m²/day (14 days, 21-day cycle)	Combination therapy with lapatinib and capecitabine was associated with severe skin toxicity, including grade 3 palmar–plantar erythrodysesthesia (hand–foot syndrome). In monotherapy, adverse effects included decreased cardiac function (ejection fraction, EF).

A total of 12 articles that met the inclusion criteria were analyzed in this review, comprising various study designs, including randomized controlled trials, cohort studies, observational studies, and real-world studies. Overall, all included studies reported that the use of lapatinib in patients with HER-2 positive breast cancer is associated with a range of adverse effects with varying degrees of severity [5],[8]. The most frequently reported adverse effects include gastrointestinal toxicity, dermatologic reactions, hepatotoxicity, and cardiovascular effects [11],[12],[15],[16]. Variations in findings across studies may be attributed to differences in study design, patient population characteristics, and treatment regimens [7],[9],[17].

Gastrointestinal Adverse Effects

Gastrointestinal toxicity is one of the most commonly reported adverse effects associated with lapatinib use, particularly in the form of diarrhea, nausea, and vomiting [5],[8],[18]. Several studies have demonstrated that diarrhea is the most frequently observed adverse effect in patients receiving lapatinib therapy, especially among those with metastatic breast cancer [5],[8]. This is closely related to the mechanism of action of lapatinib, which inhibits the EGFR receptor involved in maintaining the integrity of the gastrointestinal epithelium [11],[12]. However, variations in the severity of gastrointestinal adverse effects have been observed across studies. For instance, most cases of diarrhea are reported as mild to moderate and can be managed conservatively [7], whereas other studies have documented more severe cases requiring dose adjustment or treatment discontinuation [9]. These differences may be attributed to variations in study design and treatment regimens, which can influence the overall toxicity profile [7], [9].

Hematological Adverse Effects

Hematological adverse effects associated with lapatinib use are relatively less common compared to gastrointestinal toxicity, although they have been reported in several studies [9]. Events such as neutropenia are primarily observed in patients receiving combination therapy, suggesting that hematological toxicity is more likely attributable to concomitant chemotherapeutic agents rather than lapatinib itself [9]. In contrast, some studies have reported no significant hematological adverse effects with lapatinib used as monotherapy [2], [4]. These discrepancies indicate that factors such as treatment type, patient clinical condition, and study design play important roles in determining the hematological safety profile [2], [4]. Therefore, the evaluation of hematological adverse effects should consider the clinical context in which lapatinib is administered, particularly across different therapeutic regimens [9].

Cardiovascular Adverse Effects

Cardiovascular adverse effects represent an important consideration in the use of HER-2–targeted therapies. Several studies have reported that lapatinib is associated with a risk of cardiotoxicity, although this risk is relatively lower compared to other anti-HER-2 agents [6]. The reported manifestations include a decrease in left ventricular function, which is generally reversible [6].

However, these findings are not entirely consistent across studies. Some studies have reported no significant increase in the incidence of cardiotoxicity [11], which may be influenced by differences in patient population characteristics and duration of follow-up [11], [6]. In addition, risk factors such as a history of cardiovascular disease and prior therapies may contribute to the development of these adverse effects [6]. Therefore,

regular monitoring of cardiac function remains recommended during lapatinib therapy [6],[19],[20].

Overall, the findings of this review indicate that lapatinib has a relatively predictable adverse effect profile and is generally manageable in clinical practice [5], [8]. Gastrointestinal toxicity represents the most consistently reported adverse effect across studies [5], [8], whereas hematological and cardiovascular adverse effects demonstrate greater variability [6], [9]. These variations are likely attributable to differences in study design, patient characteristics, and treatment regimens [7], [9].

Comparative analysis across studies suggests that external factors, such as treatment combinations and patients' clinical conditions, play a significant role in determining the adverse effect profile. For example, differences in the severity of diarrhea observed between studies indicate that treatment regimens may influence the level of toxicity [7], [9]. This finding highlights the importance of an individualized approach to lapatinib therapy in order to minimize adverse effects and improve treatment outcomes [8].

This study has several limitations that should be considered. First, the narrative review design is inherently subject to selection bias and lacks the methodological rigor of a systematic review in data synthesis. Second, limited access to certain full-text articles may have affected the completeness of the analyzed data. Third, heterogeneity in study design, patient populations, and treatment regimens among the included studies may limit the generalizability of the findings [7], [9].

4. Conclusion

Based on the findings from the review of 12 studies, the use of lapatinib in patients with HER-2 positive breast cancer demonstrates a consistent adverse effect profile, with gastrointestinal toxicity being the most predominant, followed by hematological and cardiovascular adverse effects at lower frequencies. Variations in the incidence and severity of adverse effects across studies suggest that factors such as patient characteristics and study design may influence the safety profile of lapatinib. Nevertheless, most adverse effects are manageable and do not lead to permanent treatment discontinuation in the majority of patients. The clinical implications of these findings emphasize the importance of regular monitoring of adverse effects, particularly gastrointestinal symptoms, liver function, and cardiac function, to ensure treatment safety and continuity. In addition, healthcare professionals should adopt an individualized approach in patient management to minimize the risk of adverse effects and enhance treatment adherence and effectiveness. Therefore, a comprehensive understanding of the adverse effect profile of lapatinib may support more informed clinical decision-making in the management of HER-2 positive breast cancer.

Acknowledgments

The authors would like to express their sincere gratitude to all parties who have provided support throughout the preparation of this narrative review. Special appreciation is extended to the supervising lecturers for their guidance, valuable insights, and constructive feedback during the research process and manuscript preparation. It is hoped that this study will contribute meaningfully to the advancement of medical knowledge, particularly in the field of medical oncology.

Conflicts of Interest:

The authors declare no conflict of interest regarding the publication of this paper.

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