Risk Of Cardiotoxicity With Lapatinib Treatment In Patients With Or Without Previous Cardiotoxicity Induced By Trastuzumab With Cardiac Disorder Who Were Treated With Lapatinib: A Single Institutional Retrospective Study.

Yumiko Shimanuki
National Center for Global Health and Medicine
Akihiko Shimomura (akshimomura@hosp.ncgm.go.jp)
National Center for Global Health and Medicine
Shuji Kubota
National Center for Global Health and Medicine
Masato Komuro
National Center for Global Health and Medicine
Yukino Kawamura
National Center for Global Health and Medicine
Tomoko Taniyama
National Center for Global Health and Medicine
Hiroyuki Terakado
National Center for Global Health and Medicine
Chikako Shimizu
National Center for Global Health and Medicine

Research Article

Keywords: Human epidermal growth factor receptor 2, Breast Cancer, Lapatinib, Cardiotoxicity, Cardiac Disorder, Left ventricular ejection fraction

Posted Date: March 18th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1437692/v1

Abstract

Background: Cardiotoxicity is a significant adverse event of trastuzumab, which is used in human epidermal growth factor receptor 2 (HER2)-positive breast cancer patients. Lapatinib (Lap) is a small molecule tyrosine kinase inhibitor of HER1 and HER2, serving as an anti-HER2 treatment. Lap reportedly causes lesser cardiotoxicity than does trastuzumab. In clinical practice, Lap is often administered to patients with cardiac disorder (CD) induced by trastuzumab. However, there are only a few reports on the safety of Lap administration and subsequent evaluation of CDs in such patients. We evaluated whether there was a difference in cardiac toxicity due to Lap administration based on the presence or absence of previous cardiotoxicity induced by trastuzumab.

Methods: Ten patients who received Lap for the treatment of metastatic or recurrent and HER2-positive breast cancer at the National Center for Global Health and Medicine, Tokyo, Japan, between April 1, 2016 and August 31, 2020, were included in this study. All patients had a history of trastuzumab administration, and two had developed CD after trastuzumab administration. Lap was carefully administered to these two patients after consultation with a cardiologist. Left ventricular ejection fraction (LVEF) and other clinical information before and after Lap treatment were retrieved from electronic medical records.

Results: All patients other than the two with CD after trastuzumab treatment had a baseline LVEF of >55%, and there was no clinically relevant decrease in LVEF after the initiation of Lap. The two patients with CD after trastuzumab treatment exhibited LVEF of 38% and 51% after Lap treatment, respectively.

Conclusion: Our data indicate that Lap can be administered without causing further deterioration of cardiac function in patients with CD induced by anti-HER2 monoclonal antibodies. The number of cases must be expanded for further investigation.

Background

Lapatinib (Lap) is an HER1- and HER2-receptor small molecule tyrosine kinase inhibitor approved for use as anti-HER2 therapy. It is used in combination with chemotherapy after treatment with the monoclonal antibody trastuzumab for metastatic or recurrent breast cancer or in combination with an aromatase inhibitor or exemestane as first-line therapy for HER2-positive breast cancer. Lap reportedly has lesser cardiotoxicity than does trastuzumab[1)]. In clinical practice, Lap is usually administered under appropriate safety management, including consultation with cardiologists for patients with cardiac disorder (CD) or cardiotoxicity due to the use of trastuzumab. However, there are only a few reports[1)] on the safety of Lap administration in patients with previous CD and the subsequent evaluation of cardiotoxicity in these patients.

In this case series, we evaluated whether there was a difference in cardiotoxicity after Lap administration based on the presence or absence of previous cardiotoxicity, such as cardiac disease or trastuzumab-induced CD.

Methods

All patients who received Lap for the treatment of metastatic or recurrent and HER2-positive breast cancer at the National Center for Global Health and Medicine, Tokyo, Japan, between April 1, 2016 and August 31, 2020, were included in this study. All patients received anti-HER2 agents (trastuzumab with/without pertuzumab and trastuzumab emtansine) prior to Lap, and two developed drug-induced cardiotoxicity due to chemotherapy, prior to Lap administration. Data were retrieved from electronic medical records. We evaluated the duration of the Lap treatment, age, comorbidities, presence of cardiotoxicity (history of cardiac disease, presence of cardiotoxicity after anthracycline/trastuzumab treatment)

before Lap treatment, changes in the left ventricular ejection fraction (LVEF) before and after Lap treatment, and history of anthracycline administration.

This study was approved by the Ethical Review Committee of our hospital (project number: NCGM-G-003652-00) and complied with the ethical guidelines for medical and health research involving human subjects.

Results

A total of 13 patients were treated with Lap during the study period, and three patients with missing data were excluded. Eventually, 10 patients were included in the study. The background characteristics of the patients are shown in Table 1. The changes in LVEF before and after Lap treatment are shown in Fig. 1. Two patients had cardiotoxicity after trastuzumab administration; they had no significant decrease in LVEF after lapatinib administration.

Table 1 Background characteristics of patients who received lapatinib treatment

(Case 1 represents patient number 4, while case 2 represents patient number 5.)

Patient number	Age	Duration of lapatinib treatment (days)	Presence of cardiotoxicity	Comorbidities*	Presence of cardiotoxicity after chemotherapy	History of trastuzumab administration	History of anthracycline administration
1	50s	458	No	No	No	Yes	Yes
2	60s	596	No	No	No	Yes	Yes
3	70s	196	No	No	No	Yes	No
4	50s	245	No	No	Yes	Yes	Yes
5	70s	104	Yes	Yes	Yes	Yes	Yes
6	50s	224	No	Yes	No	Yes	No
7	50s	887	No	No	No	Yes	No
8	50s	919	No	No	No	Yes	No
9	60s	588	No	No	No	Yes	No
10	70s	2562	No	No	No	Yes	No

*presence or absence of risk factors for cardiotoxicity with the use of trastuzumab (other than cardiac disease such as hypertension).

Case 1

A woman in her late 50s received four courses of AC (doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2) every 3 weeks and 18 courses of trastuzumab (8 mg/kg during the first administration and 6 mg/kg after the second administration) every 3 weeks as adjuvant chemotherapy for hormone-positive and HER2-positive right breast cancer. The patient relapsed approximately 1 year and 7 months later.

After her relapse, she received PHD (pertuzumab 840 mg/body during the first administration, 420 mg/body after the second administration; trastuzumab 8 mg/kg during the first administration, 6 mg/kg after the second administration; and docetaxel 75 mg/m^2) every 3 weeks. After 10 courses, PH (pertuzumab and trastuzumab alone) was continued.

The LVEF was 62% before the initiation of PHD therapy and decreased to 54% after 5 courses of PH, which was then continued with caution. After 11 courses of PH, her LVEF decreased to 25%, and she was diagnosed with drug-induced CD. She was withdrawn from PH therapy and treated with 2.5 mg carvedilol, 2.5 mg enalapril maleic acid, and 25 mg spironolactone. Approximately 3 months after PH withdrawal, the LVEF recovered to 33%. Two months later, after consultation with a cardiologist, she received Lap and capecitabine (Lap 1250 mg/day daily, capecitabine 1250 mg/ m^2 twice daily on days 1–14, every 3 weeks). At the end of the Lap and capecitabine therapy, the LVEF was at 51%.

Case 2

A woman in her late 70s had a baseline LVEF of approximately 45%, and she was taking a β-blocker and angiotensin-converting enzyme inhibitor. She received four courses of FEC (fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, cyclophosphamide 500 mg/m^2) every 3 weeks and four courses of trastuzumab (8 mg/kg during the first administration, 6 mg/kg after the second administration) and nab-paclitaxel (260 mg/m^2) as neoadjuvant chemotherapy for hormone receptor-positive and HER2-positive left breast cancer. In the FEC, fluorouracil and cyclophosphamide were reduced to 70%, epirubicin to 60%, and nab-paclitaxel to 75% from the first course.

After treatment with neoadjuvant chemotherapy, the LVEF decreased to 32%, and she was diagnosed with suspected drug-induced CD. New York Heart Association functional classification remained class I, and brain natriuretic peptide (BNP) levels ranged from 70 to 120 pg/mL. Trastuzumab was not administered as neoadjuvant chemotherapy owing to the decreased LVEF. The patient then received 50 Gy of radiation postoperatively.

One year after surgery, LVEF had improved to 40%, but the breast cancer recurred at 1 year and 2 months. She was initially treated with fulvestrant but developed intolerance after the second month. Since drug-induced CD was strongly suspected during the initial treatment, administration of trastuzumab was deemed to be high-risk, and Lap and capecitabine therapy was only initiated after a consultation with the cardiologist. After four courses of Lap and capecitabine, the LVEF was found to be approximately 38%. Although there was a very mild decrease in cardiac function, there was no significant increase in BNP or the development of symptomatic cardiac disorders.

Other patients did not have clinically relevant values during the treatment period, which is indicated by < 50% or > 20% LVEF reduction from baseline[2)].

Discussion

The results of this study showed no marked decrease in LVEF after Lap treatment, regardless of the presence or absence of cardiotoxicity prior to Lap administration.

The difference in the incidence of cardiotoxicity between trastuzumab and Lap is unknown, but various factors have been considered. One of these is mitochondrial dysfunction caused by trastuzumab[3)]. Destabilization of the mitochondrial membrane is thought to impair the contractile function of cardiomyocytes due to ATP depletion. AMP-activated protein kinase (AMPK) contributes to mitochondrial activity. It has been reported that trastuzumab inhibits AMPK, causing ATP depletion, while Lap increases ATP production by promoting AMPK activity[4)]. It has been theorized that this difference in the mechanisms of trastuzumab and Lap may contribute to the difference in the incidence of cardiotoxicity.

One of the risk factors for cardiotoxicity of trastuzumab is the history of anthracycline therapy. Both cases 1 and 2 received anthracyclines prior to trastuzumab administration. It has been reported that drug-induced CD is mainly irreversible in anthracyclines and reversible in trastuzumab[5)]. In case 1, recovery of LVEF was observed after trastuzumab withdrawal, suggesting that the decrease in LVEF was due to trastuzumab use. In addition, trastuzumab

emtansine was administered under the careful guidance of a cardiologist, wherein LVEF recovery was observed after Lap administration. No decrease in LVEF was observed after the administration of trastuzumab emtansine. When trastuzumab-induced cardiotoxicity appears, it may still be possible to safely administer the drug by discontinuing the administration first and waiting for the LVEF to recover. Even in this case, careful monitoring of cardiac function in collaboration with an onco-cardiologist with expertise in drug-induced CD is necessary. Since only case 2 had cardiac disease in this study, we were unable to determine the extent to which trastuzumab treatment affects the reduction of LVEF in patients with a low baseline LVEF. However, it is possible that Lap can be administered without worsening cardiotoxicity in patients with an already low baseline LVEF.

In addition, adverse effects in oncology are often assessed by Common Terminology Criteria for Adverse Events (CTCAE). CTCAE is assessed as changes of LVEF, systolic dysfunction, and heart failure, with each category classified by its own severity. However, the cardiac guidelines recommend the use of more subdivided indices for evaluation[6]. Therefore, collaboration with cardiologists may be essential[7].

This study has several limitations. First, the first incidence of cardiotoxicity observed in case 2 could not be attributed to trastuzumab. The patient received anthracyclines and radiation to the breast during the initial treatment. Both of these have been reported to cause cardiotoxicity, but the timing of the occurrence is variable. Therefore, we were unable to declare that the present case was affected by the previous treatments. In addition, we cannot oppose the possibility that the decrease in LVEF in the present case may be due to worsening of the initial cardiac disease.

Second, the variability in the timing of LVEF measurements during the Lap treatment period is another limitation. Since all patients in this study had received trastuzumab, LVEF was measured in all patients prior to Lap administration. However, cardiac function was re-evaluated immediately before Lap administration (within 1 month) in only two patients, and the timing of follow-up during treatment was also varied. This study found that cardiac function monitoring was sparse during Lap treatment, contrary to that during trastuzumab treatment, which was measured every 3 to 6 months. One of the reasons for this is the lack of intervention by pharmacists.

At our hospital, confirmation by a pharmacist is mandatory for use of injectable anticancer drugs before administration. If cardiac function has not been assessed in an appropriate period of time in patients receiving trastuzumab, we seek help from doctors who assess cardiac function. However, since Lap is an oral drug, its administration was not checked by pharmacists, which might have led to the lower measurement rate. Prior reports[7] have pointed out that without baseline LVEF, accurate assessment of cardiotoxicity is not possible, so measurement of LVEF before the starting therapy is essential. Although previous studies have reported a low incidence of cardiotoxicity with Lap[1], cardiotoxicity as a late adverse event of drug therapy can be a prognostic factor. As LVEF decline is asymptomatic it may not be replaced by monitoring biomarkers such as BNP. Prior reports[8–11] showed that LVEF decline can affect continuation of cancer therapy and prognosis. Regular cardiac follow-up every 3–6 months may be necessary. Further investigation is needed to find additional evaluation methods that provide a more sensitive alternative to LVEF. Global longitudinal strain (GLS) has been reported[12] to be more effective than LVEF as a method of detecting subtle changes. Furthermore, there is a report[13] that GLS helps to predict the development of cardiotoxicity in breast cancer patients treated with anthracyclines and trastuzumab.

Third, there was an error in the LVEF measurement method. In the present study, most cases were measured using the Teichholz method; measurement using the Simpson method, which is said to be more accurate, was performed only in cases with drug-induced CD. The method used to measure the results at other hospitals was also unclear in this retrospective study.

Conclusions

Lap has been reported to be effective in patients with brain metastases[14,15)], and its failure to be used at the appropriate time may limit patients' treatment options and affect their ability to control their disease. From the results of this study, we hypothesize that Lap can be administered without causing further cardiotoxicity in patients with trastuzumab-induced CD; however, prospective observational studies are needed for further investigation.

Abbreviations

human epidermal growth factor receptor 2 (HER2)

lapatinib (Lap)

cardiac disorder (CD)

left ventricular ejection fraction (LVEF)

AC (doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2)

PHD (pertuzumab 840 mg/body during the first administration, 420 mg/body after the second administration; trastuzumab 8 mg/kg during the first administration, 6 mg/kg after the second administration; and docetaxel 75 mg/m^2)

PH (pertuzumab and trastuzumab alone)

angiotensin-converting enzyme

brain natriuretic peptide (BNP)

AMP-activated protein kinase (AMPK)

Declarations

Ethics approval and consent to participate

This study was approved by the Ethical Review Committee of our hospital (project number: NCGM-G-003652-00) and complied with the ethical guidelines for medical and health research involving human subjects. The need for informed consent was waived because of the retrospective nature of this study.

Consent for publication

Not applicable

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

Funding

Not applicable

Authors' contributions

Y.S. and A.S. conceived and designed the study. Y.S. interpreted data and wrote the manuscript. A.S, S.K, M.K, Y.K, T.T, H.T, C.S have read and approved the submission of the manuscript.

Acknowledgements

We would like to thank Masayo Kawamura, Department of Breast and Medical Oncology, National Center for Global Health and Medicine, for her helpful with the procedures.

References

1. Perez EA, Koehler M, Byrne J, Preston AJ, Rappold E, Ewer MS. Cardiac safety of Lapatinib: pooled analysis of 3689 patients enrolled in clinical trials. Mayo Clin Proc. 2008;83:679 – 86.
2. Cameron D, Casey M, Oliva C, Newstat B, Imwalle B, Geyer CE. Lapatinib plus capecitabine in women with HER-2-positive advanced breast cancer: final survival analysis of a phase III randomized trial. Oncologist. 2010;15:924–34.
3. Albini A, Cesana E, Donatelli F, Cammarota R, Bucci EO, Baravelli M, et al. Cardio-oncology in targeting the HER receptor family: the puzzle of different cardiotoxicities of HER2 inhibitors. Future Cardiol. 2011;7:693–704.
4. Spector NL, Yarden Y, Smith B, Lyass L, Trusk P, Pry K, et al. Activation of AMP-activated protein kinase by human EGF receptor 2/EGF receptor tyrosine kinase inhibitor protects cardiac cells. Proc Natl Acad Sci U S A. 2007;104:10607–12.
5. Ewer MS, Lippman SM. Type II chemotherapy-related cardiac dysfunction: time to recognize a new entity. J Clin Oncol. 2005;23:2900–2.
6. Tsutsui H, Ide T, Ito H, Kihara Y, Kinugawa K, Kinugawa S, et al. JCS/JHFS 2021 Guideline Focused Update on Diagnosis and Treatment of Acute and Chronic Heart Failure. J Card Fail. 2021;27:1404–44.
7. Herrmann J, Lenihan D, Armenian S, Barac A, Blaes A, Cardinale D, et al. Defining cardiovascular toxicities of cancer therapies: an International Cardio-Oncology Society (IC-OS) consensus statement. Eur Heart J. 2022;43:280–99.
8. Cardinale D, Colombo A, Lamantia G, Colombo N, Civelli M, De Giacomi G, et al. Anthracycline-induced cardiomyopathy: clinical relevance and response to pharmacologic therapy. J Am Coll Cardiol. 2010;55:213–20.
9. Cardinale D, Colombo A, Bacchiani G, Tedeschi I, Meroni CA, Veglia F, et al. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. Circulation. 2015;131:1981–8.
10. Rushton M, Lima I, Tuna M, Johnson C, Ivars J, Pritchard K, et al. Impact of stopping trastuzumab in early breast cancer: a population-based study in Ontario, Canada. J Natl Cancer Inst. 2020;112:1222–30.
11. Copeland-Halperin RS, Al-Sadawi M, Patil S, Liu JE, Steingart RM, Dang CT, et al. Early trastuzumab interruption and recurrence-free survival in ERBB2-positive breast cancer. JAMA Oncol. 2020;6:1971–2.
12. Patel J, Rikhi R, Hussain M, Ayoub C, Klein A, Collier P, et al. Global longitudinal strain is a better metric than left ventricular ejection fraction: lessons learned from cancer therapeutic-related cardiac dysfunction: Curr Opin Cardiol. 2020;35:170–177.
13. Sawaya H, Sebag IA, Plana JC, Januzzi JL, Ky B, Tan TC, et al. Assessment of echocardiography and biomarkers for the extended prediction of cardiotoxicity in patients treated with anthracyclines, taxanes, and trastuzumab. Circ Cardiovasc Imaging. 2012;5:596–603.
14. Lin NU, Diéras V, Paul D, Lossignol D, Christodoulou C, Stemmler HJ, et al. Multicenter phase II study of Lapatinib in patients with brain metastases from HER2-positive breast cancer. Clin Cancer Res. 2009;15:1452–9.
15. Bachelot T, Romieu G, Campone M, Diéras V, Cropet C, Dalenc F, et al. Lapatinib plus capecitabine in patients with previously untreated brain metastases from HER2-positive metastatic breast cancer (LANDSCAPE): a single-group

phase 2 study. Lancet Oncol. 2013;14:64–71.

Figures

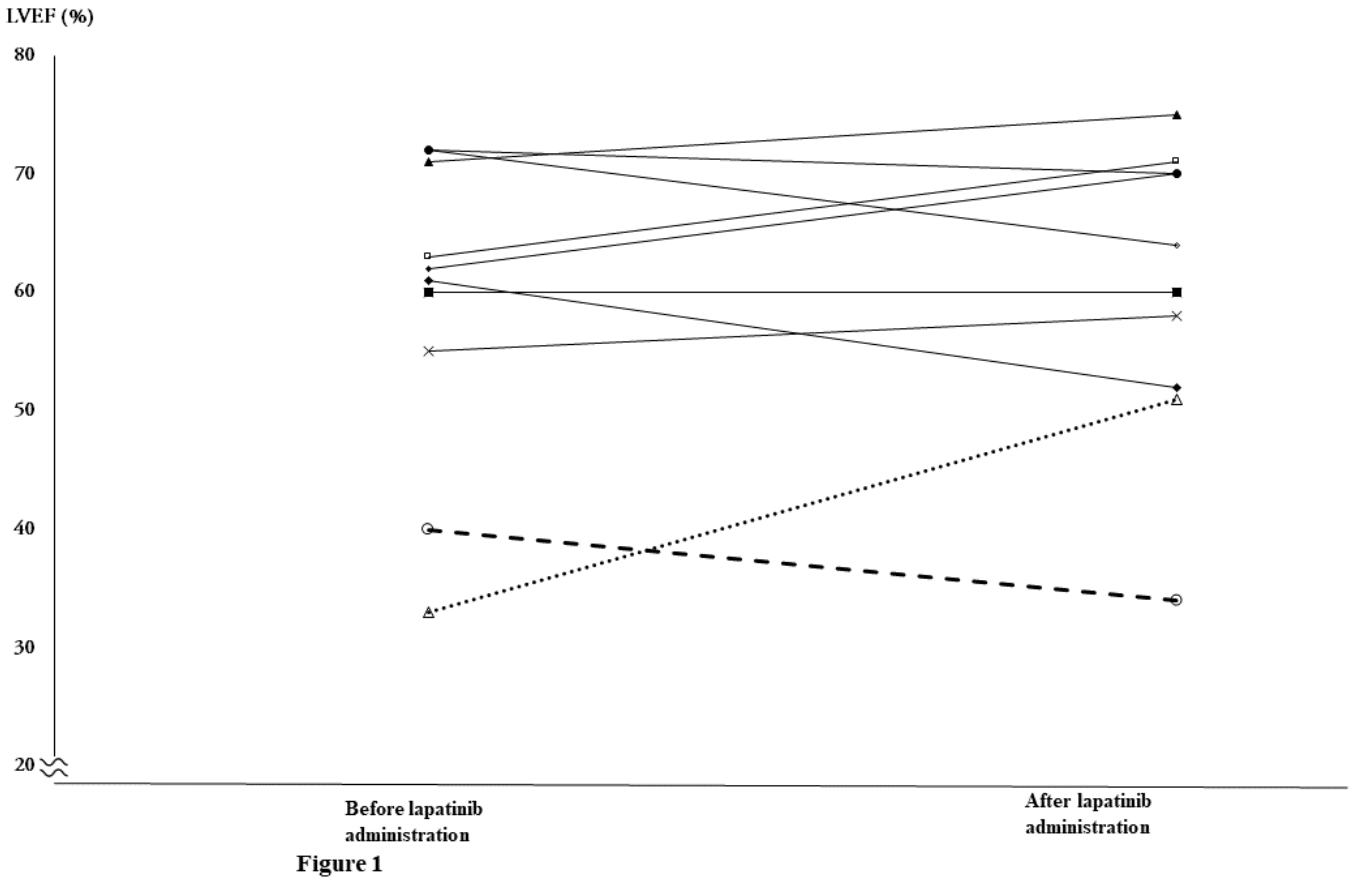

Figure 1

Change in LVEF before and after lapatinib administration (n=10)

The dashed line represents case 1, while the dotted line represents case 2.

LVEF: left ventricular ejection fraction