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EPIDEMIOLOGY

Risk factors associated with the incidence and time to onset of lapatinib-induced hepatotoxicity

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Abstract

Purpose Although lapatinib-induced hepatotoxicity can cause severe clinical complications in patients, the factors affecting hepatotoxicity have rarely been investigated. The purpose of this study was to investigate risk factors for hepatotoxicity and time to lapatinib-induced hepatotoxicity.

Methods This retrospective study was performed on metastatic breast cancer patients treated with lapatinib. Various factors were evaluated for hepatotoxicity and time to hepatotoxicity, including sex, age, body weight, height, body surface area, underlying disease, smoking history, start dose of lapatinib, status of liver metastasis, and concomitant drugs.

Results Among 159 patients, the percentage of patients with hepatotoxicity after lapatinib initiation was 57.9% ($n=92$). Multivariate analysis showed that concomitant use of H2 blockers increased the incidence of hepatotoxicity by 2.3-fold. Patients who received CYP3A4 inducers had 3.1 times higher risk of hepatotoxicity incidence; the attributable risks of H2 blockers and CYP3A4 inducers were 56.7% and 68.1%, respectively. Use of H2 blockers increased the hazard of time to hepatotoxicity by 1.8-fold compared to non-use of H2 blockers.

Conclusions Our study demonstrated that concomitant use of H2 blockers and CYP3A4 inducers was associated with lapatinib-induced hepatotoxicity. Close liver function monitoring is recommended, especially in patients receiving H2 blockers or CYP3A4 inducers.

Keywords Lapatinib · Hepatotoxicity · H2 blocker · CYP3A4 inducer

Introduction

Breast cancer is one of major causes of cancer mortality among women [1]. It has been reported that approximately 25% of all breast cancer patients show overexpression of epidermal growth factor receptor family members, especially human epidermal growth factor receptor 1 (ErbB1) and ErbB2 (also known as HER-2), which are associated with poor prognosis in breast cancer [2–4].

Lapatinib is a dual small molecule kinase inhibitor used to treat metastatic breast cancer, and was first approved in 2007 [5]. Its proposed mechanism of action includes inhibition of HER-2 and ErbB1, which are signaling proteins known to be involved in the pathogenesis of breast cancer by controlling various cellular processes [6].

The toxic effects of lapatinib include diarrhea, rash, pruritus, nausea, and hepatotoxicity [1]. The prevalence of aspartate aminotransferase (AST)/alanine aminotransferase (ALT) elevation ranges between 37 and 53% and onset of hepatotoxicity varies widely from days to several months after lapatinib administration [7]. Lapatinib-induced hepatotoxicity is generally well tolerated, but life-threatening hepatotoxicity has been reported in clinical trials and post-marketing surveillances even in rare cases [8]. The black box warning for lapatinib-induced hepatotoxicity was released in 2008 based on these clinical experiences [1].

Several mechanisms of action have been suggested for lapatinib-induced hepatotoxicity [9, 10]. Lapatinib is known to form chemically reactive metabolites (RMs) through

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Table 1 Hepatotoxicity induced by lapatinib administration

Characteristics	No. (%) ($n=159$)	Hepatotoxicity, no. (%)		*P*
		Presence ($n=92$)	Absence ($n=67$)	
Age, years				0.591
< 50	68 (42.8)	41 (44.6)	27 (40.3)	
≥ 50	91 (57.2)	51 (55.4)	40 (59.7)	
BW, kg				0.106
< 57	83 (52.2)	43 (46.7)	40 (59.7)	
≥ 57	76 (47.8)	49 (53.3)	27 (40.3)	
Height, cm				0.275
< 157	75 (47.2)	40 (43.5)	35 (52.2)	
≥ 157	84 (52.8)	52 (56.5)	32 (47.8)	
BSA, m^2				0.120
< 1.6	98 (61.6)	52 (56.5)	46 (68.7)	
≥ 1.6	61 (38.4)	40 (43.5)	21 (31.3)	
Smoking history[a]				0.948
Yes	5 (3.2)	3 (3.3)	2 (3.1)	
No	152 (96.8)	89 (96.7)	63 (96.9)	
HTN or DM				0.919
Yes	41 (25.8)	24 (26.1)	17 (25.4)	
No	118 (74.8)	68 (73.9)	50 (74.6)	
Liver metastasis				0.631
Yes	58 (36.5)	35 (38.0)	23 (34.3)	
No	101 (63.5)	57 (62.0)	44 (65.7)	
Start dose, mg				0.291
≤ 1000	22 (13.8)	15 (16.3)	7 (10.4)	
> 1000	137 (86.2)	77 (83.7)	60 (89.4)	
CYP3A4 inducer				0.002
Yes	41 (25.8)	32 (34.8)	9 (13.4)	
No	118 (74.2)	60 (65.2)	58 (86.6)	
CYP3A4 inhibitor				0.282
Yes	14 (8.8)	10 (10.9)	4 (6.0)	
No	145 (91.2)	82 (89.1)	63 (94.0)	
PPI				0.091
Yes	73 (45.9)	37 (40.2)	36 (53.7)	
No	86 (54.1)	55 (59.8)	31 (46.3)	
H2 blocker				0.005
Yes	94 (59.1)	63 (68.5)	31 (46.3)	
No	65 (40.9)	29 (31.5)	36 (53.7)	
Anticancer drug				0.336
Alone	2 (1.3)	1 (1.1)	1 (1.5)	
With capecitabine	147 (92.5)	83 (90.2)	64 (95.5)	
With others	10 (6.3)	8 (8.7)	2 (3.0)	

BSA body surface area, *BW* body weight, *HTN* hypertension, *DM* diabetes mellitus, *HBV* hepatitis B virus, *PPI* proton pump inhibitor

[a]Smoking history data for 2 patients were missing

the drug metabolism process [9]. Since RMs cause direct or indirect toxicity to cellular proteins or DNA, lapatinib metabolism can lead to hepatotoxicity though formation of RMs. Human leukocyte antigen (HLA) polymorphism may also be a potential cause based on the result of a pharmacogenetic study, which suggested as strong association between HLA-DQA1*02:01 and ALT elevation [10]. However, the molecular mechanism underlying lapatinib-induced hepatotoxicity remains unclear.

Table 2 Univariate and multivariate analyses to identify predictors for lapatinib-induced hepatotoxicity

Characteristics	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Attributable risk (%)
Age ≥ 50 years	0.840 (0.444–1.590)		
BW ≥ 57 kg	1.688 (0.893–3.193)		
CYP3A4 inducer	3.437 (1.509–7.826)**	3.138 (1.359–7.247)**	68.1
H2 blocker	2.523 (1.315–4.838)**	2.307 (1.183–4.499)*	56.7
PPI	0.579 (0.307–1.094)		

BW body weight, *PPI* proton pump inhibitor

*$P < 0.05$, **$P < 0.01$

Although hepatotoxicity induced by lapatinib can cause severe clinical complications in patients, the factors affecting hepatotoxicity have rarely been investigated. The purpose of this study was to investigate risk factors for hepatotoxicity and time to lapatinib-induced hepatotoxicity.

Methods and materials

Patients

This retrospective study was performed from October 2008 to December 2018 using medical records at the National Cancer Center, Korea. Eligible patients included females (older than 18 years of age) who received lapatinib treatment for metastatic breast cancer. The exclusion criteria were as follows: patients who were not diagnosed with metastatic breast cancer, patients with elevated AST or ALT level before lapatinib administration, and patients with underlying liver disease or hepatitis B virus (HBV).

The following demographic and clinical data were collected: sex, age, body weight, height, body surface area (BSA), underlying disease, smoking history, start dose of lapatinib, status of liver metastasis, and concomitant drugs. Concomitant drugs included CYP3A4 inducers, CYP3A4 inhibitors, anticancer drugs, H2 blockers, and proton pump inhibitors (PPIs). CYP3A4 inducers included carbamazepine, phenytoin, dexamethasone, and prednisolone. CYP3A4 inhibitors included aprepitant, cimetidine, ciprofloxacin, and fluconazole. Anticancer drugs included capecitabine, vinorelbine, letrozole, tamoxifen, trastuzumab, cyclophosphamide, 5-fluorouracil, methotrexate, gemcitabine, paclitaxel, docetaxel, and cisplatin. H2 blockers included famotidine. PPIs included pantoprazole.

Administration and laboratory assessment

Patients were administered lapatinib (dose range: 750–1250 mg/day) orally. Serum AST and ALT levels were measured before initiation of therapy and every month thereafter. The hepatotoxicity grade was determined using Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. The CTCAE defines grade I, grade II, grade III, and grade IV toxicity levels of AST and ALT as 1 to 3 times, 3 to 5 times, 5 to 20 times, and more than 20 times the upper limit of normal, respectively. In this study, hepatotoxicity was defined as grade I or higher.

Statistical analysis

The Chi-squared or Fisher's exact test was used to compare categorical variables between patients with and without hepatotoxicity. Multivariate logistic regression analysis was used to identify independent risk factors for hepatotoxicity. Factors having a P value < 0.2 from the univariate analysis along with the strong confounding factors (age) were included in the multivariate analysis. Odds ratio (OR) and adjusted OR were estimated by univariate and multivariate analyses, respectively. Attributable risk was estimated by 1-1/OR.

The time to reach hepatotoxicity was analyzed using Kaplan–Meier survival analysis and the log-rank test. The Cox proportional-hazards model was used for multivariate analysis. Factors having a P value < 0.2 from the univariate analysis along with the strong confounders (age) were included in the multivariate analysis. Hazard ratio (HR) and adjusted HR were calculated using univariate and multivariate analyses, respectively.

P values less than 0.05 were considered statistically significant. All statistical analyses were performed with the Statistical Package for Social Sciences version 20.0 for Windows (SPSS Inc., Chicago, Illinois, USA).

Results

A total of 273 patients treated from October 2008 and December 2018 were eligible for participation in this study. The following patients were excluded: patients not diagnosed with metastatic breast cancer ($n = 10$), patients with

Table 3 Time to lapatinib-induced hepatotoxicity

Characteristics	No. (%) ($n=159$)	Time to hepatotoxicity median (95% CI)	*P*
Age, years			0.398
< 50	68 (42.8)	139.0 (104.6–173.4)	
≥ 50	91 (57.2)	162.0 (36.3–287.7)	
BW, kg			0.564
< 57	83 (52.2)	161.0 (0.0–322.8)	
≥ 57	76 (47.8)	140.0 (85.9–194.1)	
Height, cm			0.169
< 157	75 (47.2)	259.0 (6.1–511.9)	
≥ 157	84 (52.8)	139.0 (124.8–153.2)	
BSA, m^2			0.062
< 1.6	98 (61.6)	233.0 (51.8–414.2)	
≥ 1.6	61 (38.4)	129.0 (88.0–176.2)	
Smoking history[a]			0.316
Yes	5 (3.2)	97.0 (37.3–156.7)	
No	152 (96.8)	140.0 (103.6–176.4)	
HTN or DM			0.693
Yes	41 (25.8)	139.0 (100.3–179.7)	
No	118 (74.8)	140.0 (100.3–179.7)	
Liver metastasis			0.936
Yes	58 (36.5)	129.0 (85.4–172.6)	
No	101 (63.5)	161.0 (129.1–192.9)	
Start dose, mg			0.367
≤ 1000	22 (13.8)	139.0 (88.1–189.9)	
> 1000	137 (86.2)	161.0 (87.5–234.5)	
CYP3A4 inducer			0.205
Yes	41 (25.8)	139.0 (124.2–153.8)	
No	118 (74.2)	161.0 (39.5–282.5)	
CYP3A4 inhibitor			0.309
Yes	14 (8.8)	140.0 (88.0–192.0)	
No	145 (91.2)	140.0 (92.8–187.2)	
PPI			0.016
Yes	73 (45.9)	254.0 (176.9–331.1)	
No	86 (54.1)	108.0 (58.1–157.9)	
H2 blocker			0.005
Yes	94 (59.1)	112.0 (61.0–163.0)	
No	65 (40.9)	259.0 (107.6–410.4)	
Anticancer drug			0.310
Alone	2 (1.3)	18.0 (NA)	
With capecitabine	147 (92.5)	139.0 (105.3–172.7)	
With others	10 (6.3)	343.0 (295.9–390.1)	

BSA body surface area, *BW* body weight, *HTN* hypertension, *DM* diabetes mellitus, *HBV* hepatitis B virus, *PPI* proton pump inhibitor

[a]Smoking history data for 2 patients were missing

elevated AST/ALT levels on the 1st day of lapatinib administration ($n=78$), patients with an underlying disease or HBV ($n=26$). Consequently, data from 159 patients treated with lapatinib were analyzed.

As shown in Table 1, the number of patients with hepatotoxicity after lapatinib initiation was 92 (57.9%). More than half of the patients (57.2%) were older than 50 years. Drugs concurrently administered with lapatinib included a CYP3A4 inducer ($n=41$), CYP3A4 inhibitor ($n=14$), PPI ($n=73$), H2 blocker ($n=94$), and anticancer drug ($n=157$). Concurrent use of CYP3A4 inducers and H2 blockers significantly increased the incidence of hepatotoxicity.

Multivariate analysis demonstrated that patients who took H2 blockers with lapatinib had a 2.3-fold increased incidence of hepatotoxicity than those not using H2 blockers (Table 2). Also, concurrent use of CYP3A4 inducers increased the incidence of hepatotoxicity by 3.1 times. The attributable risks of H2 blockers and CYP3A4 inducers were 56.7% and 68.1%, respectively.

The median time to reach hepatotoxicity was 91 days. H2 blockers and PPIs were significant factors that influenced time to hepatotoxicity (Table 3). Because BSA and height are co-related, two models were established for multivariate analysis. Model I included height, H2 blocker, and PPI addition to the strong confounder age; model II included BSA instead of height. In both models, the use of H2 blockers increased the hazard of time to hepatotoxicity by 1.8-fold compared to non-use of H2 blockers (Table 4, Fig. 1).

Discussion

The results of this study showed that H2 blockers and CYP3A4 inducers were significant factors influencing lapatinib-induced hepatotoxicity. Use of H2 blockers increased the incidence of hepatotoxicity by 2.3-fold. Patients who received CYP3A4 inducers had 3.1 times higher risk of hepatotoxicity; the attributable risks of H2 blockers and CYP3A4 inducers were 56.7% and 68.1%, respectively. Use of H2 blockers increased the hazard of time to hepatotoxicity by 1.8-fold compared to non-use of H2 blockers.

Use of H2 blockers, a class of acid-reducing agents, significantly increased the risk of hepatotoxicity. H2 blockers and lapatinib are substrates of adenosine triphosphate-binding cassette subfamily B member 1 (ABCB1), which is located in the gastrointestinal tract and liver and acts as a drug efflux transporter [11]. When these two ABCB1 substrates are administered concurrently, H2 blockers are released from the liver by ABCB1, but lapatinib may remain in the liver, leading to increased lapatinib concentrations, and thus hepatotoxicity.

By contrast, it has been known that lapatinib has a pH-dependent solubility [12]. H2 blockers can decrease lapatinib accumulation by elevating gastric pH, which reduces the solubility of lapatinib. Increased risk of hepatotoxicity by concomitant use of H2 blockers was unpredictable in our

Table 4 Univariate and multivariate analyses to identify predictors for time to lapatinib-induced hepatotoxicity

Characteristics	Unadjusted HR (95% CI)	Model I Adjusted HR (95% CI)	Model II Adjusted HR (95% CI)
Age ≥ 50 years	0.838 (0.553–1.269)		
Height ≥ 157 cm	1.338 (0.879–2.037)		
BSA ≥ 1.6 m^2	1.478 (0.973–2.245)		
H2 blocker	1.855 (1.190–2.892)**	1.855 (1.190–2.892)**	1.842 (1.181–2.872)**
PPI	0.602 (0.394–0.919)*		

For model I construction, age, height, H2 blocker, and PPI were included. For model II construction, age, BSA, H2 blocker, and PPI were included

BSA body surface area, *PPI* proton pump inhibitor

*$P < 0.05$, **$P < 0.01$

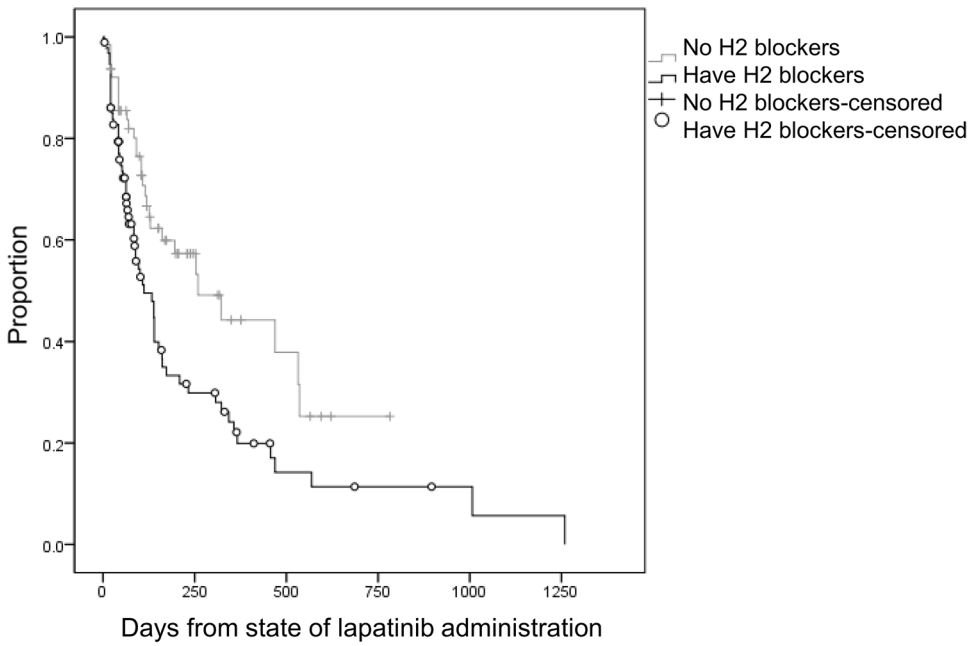

Fig. 1 Kaplan–Meier survival curves of time to lapatinib-induced hepatotoxicity with or without the use of H2 blockers

study; however, it is probably because drug concentration in the liver, not blood, is an important factor for hepatotoxicity.

Several studies have demonstrated that tyrosine kinase inhibitor (TKI)-induced hepatotoxicity is associated with RM formation [5, 13]. Certain TKIs are usually transformed into a more hydrophilic metabolite for excretion through the drug metabolism process, and also form RMs [9]. RMs covalently bind to cellular proteins or DNA, disrupting cell function and resulting in organ failure [14]. RMs affect various organs, the liver being the most frequently affected organ [15]. It has been reported that certain TKIs, including lapatinib, gefitinib, erlotinib, and dasatinib, can form RMs [16].

Since lapatinib is metabolized by CYP3A4, concomitant use of CYP3A4 inducers with lapatinib is generally predicted to reduce the plasma as well as liver concentration of lapatinib [17]. In contrast, our study showed that use of CYP3A4 inducers significantly increased the incidence of lapatinib-induced hepatotoxicity. This may be because co-administration of CYP3A4 inducer accelerated the metabolism of lapatinib and increased the formation of RMs, which results in hepatotoxicity. In a previous clinical study, patients who received a combination of lapatinib and dexamethasone, a CYP3A4 inducer, showed increased risk of hepatotoxicity, which is consistent with the findings of our study [18].

A pharmacokinetic study demonstrated that co-administration of ketoconazole, a strong CYP3A4 inhibitor, with lapatinib induced an increase in C_{max} and area under the curve (AUC) of lapatinib by 114% and 257%, respectively [19]. However, in our study, concomitant use of CYP3A4 inhibitors was not a significant factor for hepatotoxicity. This was possibly because CYP3A4 inhibitors decrease the formation of RMs, which are associated with hepatotoxicity.

There are certain limitations in this study. Firstly, this was a retrospective study and was performed at one center. Secondly, since all the study participants were female patients

with metastatic breast cancer, it was impossible to investigate sex differences. Hence, further prospective studies using a large number of patients are required to increase validity.

Conclusions

Our study demonstrated that concomitant use of H2 blockers and CYP3A4 inducers was an important factor in increasing the incidence of hepatotoxicity. In addition, H2 blockers significantly increased the hazard of time to lapatinib-induced hepatotoxicity. Since this was a retrospective single-center study, it needs to be further validated through a larger, prospective multi-center study.

Author contribution JYM, JMH, and HSG contributed to the study conception and design. Material preparation and data collection were performed by JYM, JMH, and IS. Data analysis and interpretation were performed by JYM, JMH, and IS. The manuscript was written by JYM and JMH. The manuscript was revised by HSG. All authors reviewed and approved the final manuscript.

Data availability The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent This study was approved by the Institutional Review Board of National Cancer Center, Korea (IRB number: NCC 2019-0091), and the requirement for obtaining informed consent was waived due to the retrospective nature of this study.

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