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Hepatotoxicity associated with lapatinib in an experimental rat model

Umut Demirci [a,*], *Suleyman Buyukberber* [b], *Guldal Yılmaz* [c], *Mustafa Kerem* [d], *Ugur Coskun* [b], *Aytug Uner* [b], *Meltem Baykara* [b], *Hatice Pasali* [e], *Mustafa Benekli* [b]

[a] *Atatürk Education and Research Hospital, Department of Medical Oncology, Ankara, Turkey*
[b] *Faculty of Medicine, Department of Medical Oncology, Gazi University, Ankara, Turkey*
[c] *Faculty of Medicine, Department of Pathology, Gazi University, Ankara, Turkey*
[d] *Faculty of Medicine, Department of General Surgery, Gazi University, Ankara, Turkey*
[e] *Faculty of Medicine, Department of Biochemistry, Gazi University, Ankara, Turkey*

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ABSTRACT

Background: The current study is the first to evaluate the biochemical and histopathological features of hepatic toxicity of lapatinib.

Methods: Twenty Wistar albino rats were allocated into three groups: experimental toxicity was induced with lapatinib (10 mg/kg) administered for 28 days (Group 1), 42 days (Group 2) orally in a single dose by gavage. Control group received only sterile water. Rats in Group 1 and Group 2 were sacrificed after the collection of blood and tissue samples on the 28th and 42nd days, respectively.

Results: Subjects in Group 1 and Group 2 had significantly higher levels of alanin aminotransferase (ALT), albumin, triglyceride and very low density lipoprotein (VLDL) when compared with the control group. None of the subjects in the two experimental groups showed normal histology. There were parenchymal acinar transformation zones, sinusoidal dilatation, hydropic degeneration of hepatocytes, vacuolisation of hepatocytes around the portal areas, and mild inflammation with dominance of mononuclear cells besides neutrophil and eosinophil leucocytes in portal areas, especially pronounced in Group 2.

Conclusion: This study demonstrated that lapatinib brings about deterioration of lipid profile and triggers hepatic toxicity mainly as sinusoidal injury with elevation in transaminase levels, especially ALT.

1. Introduction

Breast cancer is the most common malignancy, and the second most common cause of cancer-related deaths only after lung cancer in women. Tyrosine kinase receptors (TKR) transduce extracellular signals into the cell, regulating cell proliferation, survival and apoptosis.[1,2] Components of the human epidermal growth factor receptor (HER) oncogene family are over-expressed in the majority of solid tumours.[3] The HER family consists of four receptors: HER1, HER2 (HER2/c-neu, ErbB2), HER3 and HER4.[4,5] Increased expression and activation of HER1 and HER2 has been established in 17–30% of patients with breast cancer.[6] Over-expression of HER2 is related to resistance to hormonal and cytotoxic treatment, increased

* *Corresponding author*. Address: Atatürk Education and Research Hospital, Department of Medical Oncology, Ankara 06800, Turkey. Tel.: +90 3122912525; fax: +90 3122158710.
E-mail address: drumutdemirci@gmail.com (U. Demirci).
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rate of recurrence following primary treatment, and ultimately, poor clinical progression.

HER2-targeted therapy with the monoclonal antibody trastuzumab has yielded significant results in early and advanced stage breast cancer.[7–9] Some patients with HER2-positive breast cancer do not respond to treatment with trastuzumab and chemotherapeutics. Lapatinib ditosylate (Tyverb®/Tykerb®, GlaxoSmithKline, Research Triangle Park, NC) is the first orally active dual inhibitor for both HER1 and HER2. Lapatinib reversibly binds intracellular ATP-binding cytoplasmic domain of TKR, therefore blocking the receptor. This blockage in intracellular signal pathways also leads to the activation of extracellular signal-related kinase and phosphatidylinositol 3-kinase/Akt (PI3K/AKT).[10–12] Lapatinib (1250 mg/day) reaches maximum plasma levels 3–6 h after preprandial oral administration. In the circulation, Lapanitib highly binds to albumin and alpha-1 acid glycoprotein (99%). Lapatinib undergoes extensive hepatic metabolism, primarily by the cytochrome P450 (CYP3A4) system, and is excreted in the faeces.

The combination of lapatinib and capecitabine is approved in HER2-positive metastatic breast cancer previously treated with other anticancer regimens including taxanes, anthracyclines and trastuzumab. Adverse effects, usually seen early during treatment, are generally mild. The most commonly reported adverse events with lapatinib are diarrhoea, skin toxicity, nausea, vomiting, fatigue and headache.

Tyrosine kinase inhibitors (TKI) have been associated with hepatotoxicity. Lapatinib-related hepatotoxicity is generally asymptomatic, appears days or months after initiation of treatment, and normalises with discontinuation of lapatinib. After the pivotal study by Geyer et al. that formed the basis for the approval of lapatinib, prescribing information was amended to include mandatory monitoring of hepatic function following post-marketing reports of serious hepatic adverse effects.[13] In this study, we aimed the biochemical and histopathological evaluation of lapatinib-related hepatic toxicity in an experimental rat model.

2. Methods

The study was carried out in the Gazi University Laboratory of Experimental Animal Studies following approval by the Gazi University Faculty of Medicine Animal Studies Ethics Committee (4th June 2010; 125–9368). Biochemical analyses were performed in the biochemistry, and pathological investigation in the pathology departments of the same faculty. The study budget was reimbursed by the Association of Gastrointestinal Oncology (GIOD).

A total of 20 Wistar albino rats weighing 200–350 g were used. Four rats account for control (sham) group that received sterile water as placebo. The rats were retained in the laboratory at 21 °C and sustained on standard rat feed and water for one week before instigation of the study.

3. Study groups

Control group (sham group) received distilled water, ($n = 4$).

Group 1 – Experimental hepatic toxicity induced, treated for 28 days, then sacrificed after collection of blood and tissue samples ($n = 8$).

Group 2 – Experimental hepatic toxicity induced, treated for 42 days, then sacrificed after collection of blood and tissue samples ($n = 8$).

Lapatinib was administered orally by gavage, as a single dose of 10 mg/kg as a study in the literature.[14] On Day 28, the rats in Group 1 and rats number 1 and 2 in the control group, and on Day 42, the rats in Group 2 and rats number 3 and 4 in the control group were sacrificed after proper collection of blood and tissue samples. Liver function was evaluated by levels of aspartate aminotransferase (AST), ALT, total bilirubin, direct bilirubin, albumin and alkaline phosphatase (ALP), lactate dehydrogenase (LDH), gamma glutamyl transferase (GGT). Additionally, kidney function tests (blood urea nitrogen (BUN), creatinine and uric acid), lipid profile; total cholesterol, low-density lipoprotein (LDL), high density lipoprotein (HDL), VLDL, triglyceride were processed. At completion of study groups (days 28 and 42), rats were anaesthetised in sterile conditions with 50 mg/kg ketamine (Ketalar, Eczacıbaşı, Türkiye) and 5 mg/kg xylazine HCl, and laparotomy was performed by median incision. Subjects' abdominal regions were sterilised with 10% polyvinylpyrrolidone-iodine complex (Batticon, Adeka). Following a 3 cm median abdominal incision, intraabdominal organs were pushed aside, thereby revealing all structures (hepatic artery, portal vein and bile duct) entering the left and median lobes. Unprocessed blood and tissue samples were obtained from all groups, and then rats were euthanised by the intracardiac exsanguination method. Liver tissue specimens were fixed in 10% formaldehyde and embedded in paraffin blocks. Sectioned slices were stained with haematoxylin and eosin (H&E), and each section was analysed at 40× and 100× magnification. All study groups were histopathologically examined in terms of hepatic parenchymal acinar transformation, sinusoidal dilatation, hepatocyte shifts, portal inflammation, lobular inflammation (focal necrosis), apoptosis and mitotic activity. Fibrosis was assessed by trichrome staining.

3.1. *Statistical analysis*

Since all groups consisted of eight subjects, data were expressed as median (minimum–maximum) values. Comparisons were between three study groups (control group [received no medicine], Group 1 [received lapatinib for 28 days], and Group 2 [received lapatinib for 42 days]). The "***One-way ANOVA Test for Unrelated (Independent) Samples***" is used in the statistical significant comparison of three or more groups. However, the small number of subjects analysed in our study (under 30 in each study group) did not meet the assumptions of parametric tests. Therefore the Kruskal–Wallis Test, the non-parametric counterpart of the ***One-way ANOVA Test for Unrelated (Independent) Samples*** was used in our analyses. In cases where a P value of <0.05 was obtained, groups were compared with the Mann–Whitney U test in order to discriminate which group was responsible for the difference. Study data were analysed using the SPSS16 package.

4. Results

Distribution of results per study group and dispersion criteria are summarised in Tables 1 and 2. We found significant differences in ALT ($X^2_{(2)} = 8.957$, $p < 0.050$), albumin ($X^2_{(2)} = 7.774$, $p < 0.050$), triglyceride ($X^2_{(2)} = 9.203$, $p < 0.050$) and VLDL ($X^2_{(2)} = 9.100$, $p < 0.050$) values, but none in any other parameter ($p > 0.050$) (Table 3). The pathologies detected during histopathological investigations are demonstrated in Table 4. We experienced no loss due to toxicity. One rat in Group 2 was diagnosed with a mediastinal cyst.

The sham group showed normal histological findings (Fig. 1h), while none of the rats in the other two study groups had normal histology. We observed parenchymal acinar transformation zones, sinusoidal dilatation, hydropic degeneration of hepatocytes, vacuolisation of hepatocytes around the portal areas and mild inflammation with dominance of mononuclear cells besides neutrophil and eosinophil leucocytes in portal areas in both study groups, but more pronounced in Group 2 (Fig. 1a–f). Histochemical evaluation with trichrome staining revealed no cases of fibrosis in any group (Fig. 1g).

Vacuolisation of hepatocytes around portal areas was observed in Group 1 (Fig. 1a), while one rat in Group 2 (42/8) had focal lobular necrosis involving apoptotic cells (Fig. 1f). In Group 1, besides sinusoidal dilatation, hydropic degeneration of hepatocytes and sporadic vacuolisation of hepatocytes around portal areas were observed (Fig. 1b–d). In Group 2, in addition to an increased rate of the same findings, we also observed mild inflammation with dominance of mononuclear cells as well as neutrophil and eosinophil leucocytes in portal areas, and in one rat, apoptotic cells and focal necrosis in the lobular region (Fig. 1d–f).

5. Discussion

There are sufficient data regarding liver toxicity with conventional chemotherapeutic agents. These data have been gathered largely from studies evaluating the hepatotoxicity of pre-operative therapy in colorectal cancer. Steatosis, steatohepatitis and sinusoidal damage are the major pathologies encountered.[15,16] Monoclonal antibodies and orally active small-molecule TKIs, recently introduced in cancer treatment, are molecular agents that have been developed owing to an increased understanding of specific signal pathways. As the patient population being treated with targeted molecular agents expands, the toxicity profile of these therapeutic agents has come under scrutiny. They have various adverse effects, most notably serious gastrointestinal (GI) effects. TKIs have been associated with hepatotoxicity, but existing data are insufficient.[17] The GI and hepatic side-effects of orally active targeted therapies such as lapatinib can compromise patient compliance and lead to discontinuation of treatment or cause diminishment of treatment response. Hepatic side-effects such as asymptomatic elevation of transaminase levels are observed during targeted therapies. Hepatotoxicity is one of the leading causes of discontinuation of treatment with imatinib. The secretion of bile acids into the canaliculi involves pumping and some TKI compounds inhibit the pump of bile acid from the Golgi to the canaliculi. Some TKIs (lapatinib, erlotinib, imatinib) may cause elevation in GGT and bilirubin levels through enzyme induction or bilirubin carriers.[18–20]

We chose treatment duration of 28 and 42 days, approximating the period of clinical follow-up for liver toxicity. Both lapatinib groups (28-day and 42-day) had higher transaminase levels compared to the control group, and ALT values were

Table 1 – Median values of liver function tests in study groups.

Median (minimum–maximum)	Control	Group 1	Group 2
AST (U/L)	93.5 (80–117)	103 (78–129)	106 (90–187)
ALT (U/L)	42.5 (40–48)	62.5 (46–89)	46 (38–49)
Albumin (g/dL)	3.25 (3–3.5)	3.75 (3.2–4)	3.5 (3.3–3.8)
T. bilirubin (mg/dL)	0.1 (0.1–0.1)	0.1 (0.1–0.1)	0.1 (0.1–0.1)
ALP (U/L)	149.5 (118–240)	154.5 (73–338)	104.5 (69–307)
GGT (U/L)	4 (4–17)	4 (4–4)	4 (4–4)
LDH (U/L)	654.5 (542–1093)	734.5 (278–1208)	618 (470–1140)

Table 2 – Median values of other biochemical tests in study groups.

	Median (minimum–maximum)							
	T. kol. (mg/dL)	Trig. (mg/dL)	LDL (mg/dL)	VLDL (mg/dL)	HDL (mg/dL)	BUN (mg/dL)	Crea (mg/dL)	Uricacid (mg/dL)
Control ($n = 4$)	35.5 (29–47)	40 (34–46)	13.5 (9–18)	8 (7–9)	14.5 (12–20)	25 (23–29)	0.52 (0.49–0.55)	1 (0.6–1.2)
Group 1 (28 days) ($n = 8$)	46 (40–57)	87 (38–120)	9 (5–24)	17.5 (8–24)	19 (14–23)	28.5 (25–40)	0.50 (0.47–0.63)	1.15 (0.9–8.3)
Group 2 (42 days) ($n = 8$)	45.5 (34–51)	55 (30–84)	13.5 (7–22)	11 (6–17)	18 (15–20)	26 (23–31)	0.52 (0.49–0.54)	1.1 (0.8–1.4)

Table 3 – Comparation of biochemical tests in study groups (Kruskal–Wallis Test).

Biochemical tests	Groups	N	mean rank	X^2	Sd	P	Significant difference
T. bilirubin	1. Control	4	10.50	0.000	2	1.000	
	2. Group 1	8	10.50				
	3. Group 2	8	10.50				
D. bilirubin	1. Control	4	10.50	0.000	2	1.000	
	2. Group 1	8	10.50				
	3. Group 2	8	10.50				
Albumin	1. Control	4	3.62	7.747	2	0.021	1–2, 1–3
	2. Group 1	8	13.56				
	3. Group 2	8	10.88				
AST	1. Control	4	7.88	1.668	2	0.434	
	2. Group 1	8	9.94				
	3. Group 2	8	12.8				
ALT	1. Control	4	6.50	8.957	2	0.011	1–2, 2–3
	2. Group 1	8	15.31				
	3. Group 2	8	7.69				
GGT	1. Control	4	12.50	4.000	2	0.135	
	2. Group 1	8	10.00				
	3. Group 2	8	10.00				
ALP	1. Control	4	12.50	1.971	2	0.373	
	2. Group 1	8	11.75				
	3. Group 2	8	8.25				
LDH	1. Control	4	10.75	1.125	2	0.570	
	2. Group 1	8	12.00				
	3. Group 2	8	8.88				
Uric acid	1. Control	4	8.12	2.344	2	0.310	
	2. Group 1	8	12.88				
	3. Group 2	8	9.31				
T. cholesterol	1. Control	4	5.50	4.103	2	0.129	
	2. Group 1	8	12.81				
	3. Group 2	8	10.69				
VLDL	1. Control	4	4.75	9.100	2	0.011	1–2, 2–3
	2. Group 1	8	15.00				
	3. Group 2	8	8.88				
HDL	1. Control	4	6.50	3.428	2	0.180	
	2. Group 1	8	13.00				
	3. Group 2	8	10.00				
LDL	1. Control	4	12.38	3.773	2	0.152	
	2. Group 1	8	7.38				
	3. Group 2	8	12.69				
Triglyceride	1. Control	4	4.75	9.201	2	0.010	1–2, 2–3
	2. Group 1	8	15.06				
	3. Group 2	8	8.81				
BUN	1. Control	4	6.88	5.196	2	0.074	
	2. Group 1	8	14.06				
	3. Group 2	8	8.75				
Creatinin	1. Control	4	12.00	1.964	2	0.375	
	2. Group 1	8	8.00				
	3. Group 2	8	12.00				

statistically significant. The elevation in albumin levels could not be justified. Bilirubin levels in the lapatinib groups were similar to the control group, and the cholestase enzymes GGT and ALP were unchanged. Toxicity of the hepatobiliary system has not been specified in lapatinib phase I and II studies.[21–23] In a Japanese phase II study evaluating lapatinib monotherapy, 17.2% of total 122 patients (22 patients) had elevated ALT levels, and three patients had grade 3–4 ALT elevations. AST levels were elevated in 23% (28 patients), grade 3–4 in five patients. ALP elevation was observed in 16.4% (20

Table 4 – Histopathological features of study groups.

	VH	HD	SD	AT	PAI	FN	AH	M
28.control 1								
28.control 2								
28.1				+ (f)				
28.2		+	+					
28.3	+							
28.4		+	+					
28.5	+	+	+					+
28.6			+					
28.7			+					
28.8	+				+			
42.control 1								
42.control 2								
42.1			+	+ (f)				
42.2		+	+					
42.3		+	+					
42.4		+	+	+ (f)				
42.5		+	+	+ (f)	+			
42.6			+++		+			
42.7		+	+					
42.8		+	+	+ (d)	+	+	+	

VH: vacuolised hepatocytes around the portal area, HD: hydropic degeneration in hepatocytes, SD: sinusoidal dilatation, AT: aciner transformation in parenchyma (f: focal) (d: diffuse), PAI: mild inflammation with neutrophile and eosinophile in portal area, FN: focal necrosis in lobular area, AH: apoptotic cell, M: mitosis.

patients), grade 3–4 in four patients.[23] After the pivotal study by Geyer et al., real-life incidence of serious hepatic adverse effects led to mandatory monitoring for toxicity and the amendment of the prescribing information to include the routine monitoring of liver function.[13,24] A recent study reported a correlation between the risk of liver toxicity with lapatinib and Class II MHC HLA DQA1*201 carrier status in women. 70% of ALT elevations were observed in HLA DQA1*201 carriers.[25]

Congruently, histopathological evaluations demonstrated hydropic degeneration, vacuolated hepatocytes, and in Group 2 (42-day lapatinib exposure), portal inflammation and additionally apoptotic cells and lobular focal necrosis with extended exposure. We observed lapatinib-related injury to be prominently on sinusoids.

We did not observe hepatic failure with lapatinib, but serious hepatitis cases have been reported with imatinib and gemtuzumab ozogamicin.[26,27] The histopathology of imatinib-induced hepatotoxicity shows, along with necrosis, intermediate cholestasis accompanied by cytolytic hepatitis and occasionally portal and lobular inflammation.[28] As in viral hepatitis, lymphocytic infiltration has been observed in the perimeter of necrotic lesions.[29] Similar cytolytic hepatitis has been reported with gefitinib.[30] Clinical studies with CP-724714, a selective oral HER2 TKI, have been terminated due to serious liver failure with jaundice. It caused hepatocyte necrosis, Kupffer cell hyperplasia, and elevations in serum transaminase and total bilirubin levels in rats.[31] We observed vacuolated hepatocytes, hydropic degeneration and sinusoidal dilatation in the short term in relation to lapatinib-induced toxicity. Long-term (Group 2) findings included marked sinusoidal dilatation and parenchymal acinar transformation, mild portal inflammation produced by neutrophil and eosinophil leucocytes and lobular focal necrosis.

The short-term sinusoidal injury with lapatinib which we observed as sinusoidal dilatation is a well-defined pathology in relation to cytotoxic chemotherapeutics. While the prevalence of sinusoidal injury is lower with chemotherapeutic agents such as irinotecan and 5-fluorourocil (5-FU), the primary liver toxicity of oxaliplatin is sinusoidal dilatation.[32–36] Sinusoidal obstruction syndrome (SOS) is another toxicity that has been described in relation to chemotherapeutic agents (oxaliplatin, gemtuzumab ozogamicin).[37] We did not observe SOS-related pathological changes. Further studies are needed to evaluate the correlation with this syndrome.

Although we observed portal inflammation, none of the study subjects demonstrated fibrosis with trichrome staining. However, the relatively short duration of our study (42 days) might be responsible for the absence of fibrosis. We observed deterioration of the lipid profile in both lapatinib groups. We found significantly high levels of triglyceride and VLDL. However due to a lack of difference in bilirubin and the cholestase enzymes ALP and GGT in comparison to the control group and the absence of steatosis during histopathological evaluations led us to conclude that lapatinib does not cause cholestatic type hepatic toxicity. Unexplained high albumin levels of study groups were the lack of study.

In conclusion, this study is the first that reports the biochemical and histopathological evaluation of lapatinib-related hepatic toxicity. We observed that lapatinib causes primarily sinusoidal damage in the liver, and significant elevation in transaminase levels, especially ALT.

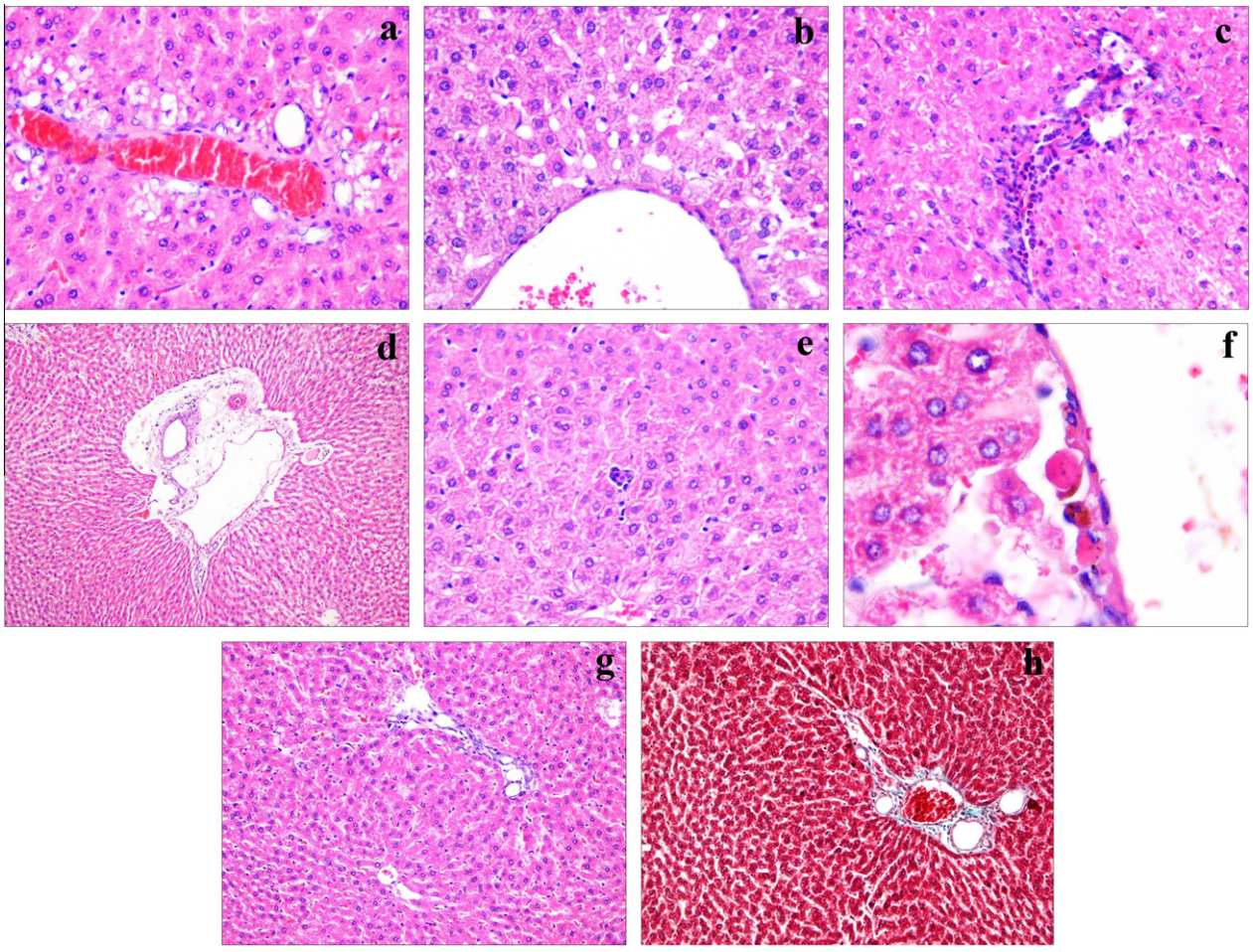

Fig. 1 – (a) Vacuolised hepatocytes around portal area, Group 1–3 (H&E, 400×). (b) Sinusoidal dilatation and hepatocytes with hydropic changes around the central vein, Group 1–5 (H&E, 400×). (c) Inflammation with neutrophil and rare eosinophil in portal area, Group 1–8 (H&E, 100×). (d) Mild inflammation with neutrophil and eosinophil in portal area, Group 2–8 (H&E, 100×). (e) Focal necrosis in lobular area, Group 2–8 (H&E, 400×). (f) Apoptotic body in periportal area, Group 2–8 (H&E, 1000×). (g) Normal liver parenchyma, 28 day control-1, (H&E, 200×). (h) Normal liver parenchyma, Group 2–7 (Trichrome, 200×).

Conflict of interest statement

None declared.

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REFERENCES

1. Atalay G, Cardoso F, Awada A, Piccart MJ. Novel therapeutic strategies targeting the epidermal growth factor receptor (EGFR) family and its downstream effectors in breast cancer. *Ann Onc* 2003;**14**:1346–63.
2. Stern DF. Tyrosine kinase signalling in breast cancer: ErbB family receptor tyrosine kinases. *Breast Cancer Res* 2000;**2**:176–83.
3. Demonty G, Bernard-Marty C, Puglisi F, Mancini I, Piccart M. Progress and new standards of care in the management of HER-2 positive breast cancer. *Eur J Cancer* 2007;**43**:497–509.
4. Citri A, Yarden Y. EGF-ERBB signalling: towards the systems level. *Nat Rev Mol Cell Biol* 2006;**7**:505–16.
5. Ross JS, Slodkowska EA, Symmans WF, et al. The HER-2 receptor and breast cancer: ten years of targeted anti-HER-2 therapy and personalized medicine. *Oncologist* 2009;**14**:320–68.
6. Klijn JGM, Berns PMJJ, Schmits PLM, Foekens JA. The clinical significance of epidermal growth factor receptor (EGF-R) in human breast cancer: a review on 5232 patients. *Endocr Rev* 1992;**13**:3–17.
7. Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med* 2005;**353**:1673–84.
8. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Herceptin Adjuvant (HERA) Trial Study Team. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med* 2005;**353**:1659–72.
9. Joensuu H, Kellokumpu-Lehtinen PL, Bono P, et al. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. *N Engl J Med* 2006;**354**:809–20.

10. Rusnak DW, Lackey K, Affleck K, et al. The effects of the novel, reversible epidermal growth factor receptor/ErbB-2 tyrosine kinase inhibitor, GW572016, on the growth of human normal and tumor-derived cell lines in vitro and in vivo. *Mol Cancer Ther* 2001;**1**:85–94.
11. Riese 2nd DJ, Stern DF. Specificity within the EGF family/ErbB receptor family signaling network. *Bioessays* 1998;**20**:41–8.
12. Okano J, Gaslightwala I, Birnbaum MJ, Rustgi AK, Nakagawa H. Akt/protein kinase B isoforms are differentially regulated by epidermal growth factor stimulation. *J Biol Chem* 2000;**275**:30934–42.
13. Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med* 2006;**55**:2733–43.
14. Polli JW, Humphreys JE, Harmon KA, et al. The role of efflux and uptake transporters in N-{3-chloro-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2(methylsulfonyl) ethyl] amino}methyl)-2-furyl]-4quinazolinamine(GW572016, lapatinib) disposition and drug interactions. *Drug Metab Dispos* 2008;**36**:695–701.
15. Zorzi D, Laurent A, Pawlik TM, et al. Chemotherapy-associated hepatotoxicity and surgery for colorectal liver metastases. *Br J Surg* 2007;**94**:274–86.
16. Schouten van der Velden AP, Punt CJ, Van Krieken JH, Derleyn VA, Ruers TJ. Hepatic veno-occlusive disease after neoadjuvant treatment of colorectal liver metastases with oxaliplatin: a lesson of the month. *Eur J Surg Oncol* 2008;**34**:353–5.
17. Loriot Y, Perlemuter G, Malka D, et al. Drug insight: gastrointestinal and hepatic adverse effects of molecular-targeted agents in cancer therapy. *Nat Clin Pract Oncol* 2008;**5**:268–78.
18. Burger H, van Tol H, Brok M, et al. Chronic imatinib mesylate exposure leads to reduced intracellular drug accumulation by induction of the ABCG2 (BCRP) and ABCB1 (MDR1) drug transport pumps. *Cancer Biol Ther* 2005;**4**:747–52.
19. Ribero D, Wang H, Donadon M, et al. Bevacizumab improves pathologic response and protects against hepatic injury in patients treated with oxaliplatin-based chemotherapy for colorectal liver metastases. *Cancer* 2007;**110**:2761–7.
20. Klinger M, Eipeldauer S, Hacker S, et al. Bevacizumab protects against sinusoidal obstruction syndrome and does not increase response rate in neoadjuvant XELOX/FOLFOX therapy of colorectal cancer liver metastases. *Eur J Surg Oncol* 2009;**35**:515–20.
21. Medina PJ, Goodin S. Lapatinib: a dual inhibitor of human epidermal growth factor receptor tyrosine kinases. *Clin Ther* 2008;**30**:1426–47.
22. Burris 3rd HA, Hurwitz HI, Dees EC, et al. Phase I safety, pharmacokinetics, and clinical activity study of lapatinib (GW572016), a reversible dual inhibitor of epidermal growth factor receptor tyrosine kinases, in heavily pretreated patients with metastatic carcinomas. *J Clin Oncol* 2005;**23**:5305–13.
23. Toi M, Iwata H, Fujiwara Y, et al. Lapatinib monotherapy in patients with relapsed, advanced, or metastatic breast cancer: efficacy, safety, and biomarker results from Japanese patients phase II studies. *Br J Cancer* 2009;**10**:1676–82.
24. Moy B, Rappold E, Williams L, et al. Hepatobiliary abnormalities in patients with metastatic cancer treated with lapatinib. *J Clin Oncol* 2009;**27**:1043 [abstr.].
25. Spraggs CF, Budde LR, Briley LP, et al. HLA-DQA1*02:01 is a major risk factor for lapatinib-induced hepatotoxicity in women with advanced breast cancer. *J Clin Oncol* 2011;**29**:667–73.
26. Pariente A, Etcharry F, Cales V, et al. Imatinib mesylate-induced acute hepatitis in a patient treated for gastrointestinal stromal tumour. *Eur J Gastroenterol Hepatol* 2006;**18**:785–7.
27. Rajvanshi P, Shulman HM, Sievers EL, McDonald GB. Hepatic sinusoidal obstruction after gemtuzumab ozogamicin (Mylotarg) therapy. *Blood* 2002;**99**:2310–4.
28. Lin NU, Sarantopoulos S, Stone JR, et al. Fatal hepatic necrosis following imatinib mesylate therapy. *Blood* 2003;**102**:3455–6.
29. Ohyashiki K, Kuriyama Y, Nakajima A, et al. Imatinib mesylate-induced hepato-toxicity in chronic myeloid leukemia demonstrated focal necrosis resembling acute viral hepatitis. *Leukemia* 2002;**16**:2160–1.
30. Ho C, Davis J, Anderson F, Bebb G, Murray N. Side effects related to cancer treatment: CASE 1. Hepatitis following treatment with gefitinib. *J Clin Oncol* 2005;**23**:8531–3.
31. Jani JP, Finn RS, Campbell M, et al. Discovery and pharmacologic characterization of CP-724,714, a selective ErbB2 tyrosine kinase inhibitor. *Cancer Res* 2007;**67**:9887–93.
32. Jager W, Gehring E, Hagenauer B, et al. Biliary excretion of flavopiridol and its glucuronides in the isolated perfused rat liver: role of the multidrug resistance protein 2 (Mrp2). *Life Sci* 2003;**73**:2841–54.
33. Nordlinger B, Benoist S. Benefits and risks of neoadjuvant therapy for liver metastases. *J Clin Oncol* 2006;**24**:4954–5.
34. Aloia T, Sebagh M, Plasse M, et al. Liver histology and surgical outcomes after preoperative chemotherapy with fluorouracil plus oxaliplatin in colorectal cancer liver metastases. *J Clin Oncol* 2006;**24**:4983–90.
35. Mehta NN, Ravikumar R, Coldham CA, et al. Effect of preoperative chemotherapy on liver resection for colorectal liver metastases. *Eur J Surg Oncol* 2008;**34**:782–6.
36. Nakano H, Oussoultzoglou E, Rosso E, et al. Sinusoidal injury increases morbidity after major hepatectomy in patients with colorectal liver metastases receiving preoperative chemotherapy. *Ann Surg* 2008;**247**:118–24.
37. McKoy JM, Angelotta C, Bennett CL, et al. Gemtuzumab ozogamicin associated sinusoidal obstructive syndrome (SOS): an overview from the research on adverse drug events and reports (RADAR) project. *Leuk Res* 2007;**31**:599–604.