Assessment of physician compliance to liver function test monitoring guidance for patients treated with lapatinib

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Background and objective A cumulative review of hepatobiliary abnormalities in the lapatinib clinical program resulted in inclusion of detailed instructions for liver function test (LFT) monitoring in the US prescribing information (label). We sought to determine whether or not physicians adhere to these recommended guidelines.

Methods A retrospective observational cohort study comprising 396 women with HER2+ metastatic breast cancer who initiated lapatinib between March 1, 2007 and June 30, 2010. Data were captured from electronic medical records (EMR) of community-based oncology practices. Patients were categorized by whether they initiated lapatinib before or after the label change; LFT monitoring was evaluated using a pre- versus post-label study design. We measured the proportion of patients who had LFTs within 30 days before lapatinib initiation, LFTs during each 6-week period of treatment, and lapatinib permanently withdrawn after experiencing an extreme LFT elevation.

Results Among 396 patients, 128 (32%) initiated lapatinib pre-label change, and 268 (68%) initiated post-label change. LFTs were conducted 30 days prior to lapatinib start in 82% post-label versus 63% pre-label change patients ($P < .001$). Testing during each 6-week treatment interval was higher in post-label change patients: 81% versus 68% pre-label change patients during the first 6 weeks of therapy ($P = .004$), and 83% versus 62%, respectively, during weeks 18-24 ($P = .0103$). Four patients experienced a severe LFT elevation: 2 pre-label patients who resumed treatment, and 2 post-label change patients with complete discontinuation.

Conclusions We demonstrated that LFT monitoring increased after the addition of detailed LFT guidance to the lapatinib label.

Metastatic breast cancer is an incurable disease and a leading cause of death from cancer among women worldwide.[1] Patients are at a greater risk for disease progression and death when their tumors overexpress human epidermal growth factor receptor type 2 (ErbB2, also referred to as HER2) compared with patients with tumors that do not overexpress HER2.[2] In the United States, lapatinib is indicated for use in patients with advanced or metastatic HER2-postive breast cancer, in combination with capecitabine for patients who have been previously treated with an anthracycline, a taxane, and trastuzumab, or in combination with letrozole for postmenopausal women with hormone-receptor positive metastatic breast cancer for whom hormonal therapy is indicated.[3] This oral tyrosine kinase inhibitor (TKI), inhibiting both HER2 and epidermal growth factor receptor (EGFR), has an acceptable safety profile during treatment of breast cancer.[4] However, grade 3 alanine transaminase (ALT) elevations (defined as ALT > 5 times upper limit of normal (ULN) up to 20 times ULN) and serious liver injury with hyperbilirubinemia have been reported in the clinical development of lapatinib.[3,5] GlaxoSmithKline,

Manuscript received June 5, 2013; accepted June 28, 2013.
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Disclosures This work was fully funded by a contract from GlaxoSmithKline to McKesson/US Oncology. GSK manufactures lapatinib. Julie Byrne, Sarah Landis, and Jeanenne Nelson are paid employees of GSK and hold stock in the company. Clara Chen, Rahul Dhanda, and Stephen Jones are paid employees of McKesson Specialty/US Oncology. The authors report no conflicts of interest.

Commun Oncol 2013;10:258-265
DOI: 10.12788/j.cmonc.0057

which manufactures lapatinib as *Tykerb* in the United States, conducted a cumulative review of hepatobiliary events as well as hepatobiliary laboratory abnormalities in the lapatinib clinical program in March 2008. The review identified an association between lapatinib and hepatobiliary disorders (specifically transaminase elevations) with evidence of improvement with treatment discontinuation and a small number of positive rechallenges when lapatinib was reintroduced. The lapatinib US prescribing information (label) was therefore updated on July 9, 2008, to include a boxed warning related to hepatoxicity and detailed instructions for monitoring liver function before and during lapatinib exposure. These instructions stipulated the following:[3] Hepatoxicity (ALT or asparate transaminase (AST) > 3 times the upper limit of normal and total bilirubin > 1.5 times the upper limit of normal has been observed in clinical trials (< 1% of patients) and postmarketing experience; the hepatoxicity may be severe and deaths have been reported; causality of the deaths is uncertain; the hepatoxicity may occur days to several months after initiation of treatment; liver function tests (transaminases, bilirubin, and alkaline phosphatase) should be monitored before initiation of treatment, every 4 to 6 weeks during treatment, and as clinically indicated; and if changes in liver function are severe, therapy with lapatinib should be discontinued and patients should not be re-treated with lapatinib.

For patient safety, it is important to know the extent to which physicians are adherent with these guidelines for hepatic monitoring of lapatinib users. Thus, the aim of our study is to determine if physicians conduct LFT prior to prescribing lapatinib, at regular intervals during treatment exposure, and if they permanently withdraw lapatinib for patients who demonstrate severe liver enzyme elevations while being treated.

Materials and methods

Study design

We conducted a retrospective observational cohort study (NCT01462552) using medical records from the McKesson Specialty Health/US Oncology Network's electronic medical record (EMR) database, iKnowMed (iKM). Outpatient encounter history for patients under the care of US Oncology-affiliated physicians are captured in this database, including, but not limited to, laboratory test results, diagnoses, therapy administration, line of therapy, staging, comorbidities, toxicities, and performance status information. We identified the study period of interest as March 1, 2007 through June 30, 2010. At the time of our study, the US Oncology network accounted for more than 850,000 patients or 12% of the US cancer population across 39 states.

Patients

From the iKM database, we identified women breast cancer patients, aged ≥ 19 years old with documented HER2+ metastatic disease, at least 1 documented LFT (to ensure that laboratory tests were captured), and at least 1 documented prescription for lapatinib between March 1, 2007 and December 31, 2009. We excluded patients who had participated in a clinical trial or received care for another cancer during the time periods covered by the study. Patients who received lapatinib as adjuvant or neoadjuvant therapy during the study period were also excluded.

We categorized eligible patients by whether they initiated lapatinib before or after the July 9, 2008 label change. We placed patients into the pre-label change group if lapatinib was initiated between March 1, 2007 and December 31, 2007. Patients were categorized into the post-label change group if lapatinib was initiated between July 9, 2008, and December 31, 2009. We required patients in each group to have at least 6 months of follow-up time; pre-label change patients were followed through June 30, 2008 and post-label change patients were followed through June 30, 2010. We excluded patients that initiated lapatinib between January 1, 2008 and July 8, 2008 since it was impossible for them to complete 6 months of follow-up before the label change went into effect.

Exposure definitions

We based exposure on the duration of lapatinib treatment during the follow-up period, defined as the date of first prescription for lapatinib (index date) through to the end of the study period for each cohort group, specifically June 30, 2008 for the pre-label change group or June 30, 2010, for the post-label change group.

We calculated treatment duration of each individual prescription as the standardized dispensed unit quantity divided by the standardized unit dose as captured in the iKM database. Using this duration data, a first administration date and a last administration date for each prescription was identified. The gap(s) between consecutive prescriptions was calculated, where the gap was defined as the difference between the first administration of the current prescription and the last administration date of the previous prescription.

Using a gap width of 60 days or more, we identified distinct periods of lapatinib exposure for each patient. Patient exposure was described in 3 levels:

TABLE 1 Patient demographics, clinical characteristics, and treatment attributes

Characteristics	Overall (N = 396)	Lapatinib initiation period		*P* value[a]
		Pre-label change (n = 128)	Post-label change (n = 268)	
Age				
Mean (SD), y	56.4 (11.8)	55.5 (11.7)	56.8 (11.8)	.32
Stage at diagnosis, no. (%)				.02
I	23 (6)	14 (11)	9 (3)	
II	101 (26)	29 (23)	72 (27)	
III	108 (27)	37 (29)	71 (26)	
IV	141 (36)	39 (30)	102 (38)	
Missing/Unknown	23 (6)	9 (7)	14 (5)	
ER status, no. (%)				.13
Positive	230 (58)	82 (64)	148 (55)	
Negative	142 (36)	37 (29)	105 (39)	
Missing/Unknown	24 (6)	9 (7)	15 (6)	
PR status, no. (%)				.77
Positive	159 (40)	54 (42)	105 (39)	
Negative	199 (50)	61 (48)	138 (51)	
Missing/unknown	38 (10)	13 (10)	25 (9)	
HER2 status, no. (%)				.12
Positive	303 (77)	90 (70)	213 (79)	
Negative	37 (9)	14 (11)	23 (9)	
Missing/unknown	56 (14)	24 (19)	32 (12)	
ECOG status, no. (%)				.79
0	54 (14)	17 (13)	37 (14)	
1	197 (50)	65 (51)	132 (49)	
2	48 (12)	17 (13)	31 (12)	
3	6 (2)	3 (2)	3 (1)	
Missing/Unknown	91 (23)	26 (20)	65 (24)	
Liver metastases at initiation, no. (%)				.85
Yes	117 (30)	37 (29)	80 (30)	
No	279 (70)	91 (71)	188 (70)	
Total lapatinib exposure time during first exposure (d)				
Median (range)	57 (10-531)	73 (10-451)	53 (21-531)	.01
< 6 wk	137 (35)	36 (28)	101 (38)	.13
6 to < 12 wk	93 (23)	29 (23)	64 (24)	
12 to < 18 wk	52 (13)	21 (16)	31 (12)	
18 to < 24 wk	42 (11)	12 (9)	30 (11)	
≥ 24 wk	72 (18)	30 (23)	42 (16)	
Pattern of lapatinib use, no. (%)				< .0001
Consistently used throughout study period	15 (4)	15 (12)	0 (0)	
Discontinued and not restarted	266 (67)	73 (57)	193 (72)	
Discontinued and restarted	115 (29)	40 (31)	75 (28)	
Patient status at end of study period, no. (%)				.85
Lost to follow-up	18 (5)	6 (5)	12 (5)	
Alive	234 (59)	78 (61)	156 (58)	
Dead	144 (36)	44 (34)	100 (37)	

[a] Continuous variables were analyzed with t-tests or Kruskal-Wallis tests; chi-square tests were conducted for categorical variables.
Abbreviations: ER, estrogen receptor; PR, progestin receptor; HER2, human epidermal growth factor receptor type 2; ECOG, Eastern Cooperative Oncology Group.

TABLE 2 Proportion of patients tested within 30 days prior to lapatinib initiation

LFT lab	Overall (N = 396)		Pre-label change (n = 128)		Post-label change (n = 268)		*P* value[a]
	No. (%)	95% CI	No. (%)	95% CI	No. (%)	95% CI	
Any LFT	302 (76)	72-80	82 (64)	55-72	220 (82)	77-86	< .001
ALT (U/L)	299 (76)	71-80	81 (63)	54-72	218 (81)	76-86	< .001
AST (U/L)	301 (76)	71-80	82 (64)	55-72	219 (82)	77-86	.001
ALP (U/L)	301 (76)	71-80	81 (63)	54-72	220 (82)	77-86	< .001
BILI (mg/dL)	300 (76)	71-80	81 (63)	54-72	219 (82)	77-86	< .001

[a] Comparing pre- to post-label change group.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, asparate transaminase; BILI, total bilirubin; LFT, liver function test.

- Continually took the medication throughout the follow-up period with no interruptions;
- Appeared to have a complete discontinuation of lapatinib where the patient had an interruption and never restarted the drug during the remainder of the follow-up period; or
- Appeared to have 1 or more temporary discontinuations of lapatinib where the patient had an interruption and later restarted the drug at some point during the follow-up period.

For patients with a complete discontinuation, we used the last administration date of the prescription that preceded the interruption plus 21 days as the prescription discontinuation date.

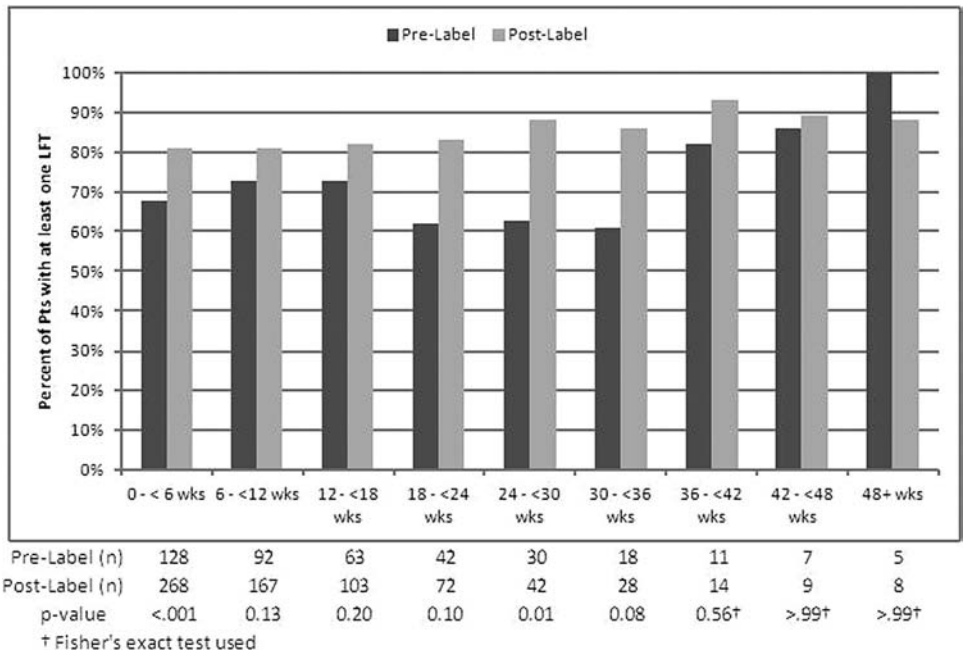

FIGURE 1 Proportion of patients with at least 1 liver function test during each 6-week interval after lapatinib initiation.

Outcome assessments

We obtained LFT laboratory results from the laboratory information stored within the iKM database, including their documented lower limit of normal and ULN values. On the infrequent occasion (about 4%) where no ULN was given, the average ULN of all laboratory results for that test was calculated and used as the reference. We considered the following LFTs: ALT (also known as serum glutamic pyruvate transaminase), AST (also known as serum glutamic oxaloacetic transfaminase), alkaline phosphatase (ALP), and total bilirubin (BILI).

We assessed physician compliance with the recommended LFT monitoring guidelines relative to the initiation of lapatinib treatment (index date) and during treatment exposure. All of these analyses were calculated for the full population and for the pre- and post-label change groups separately. First, we measured LFT testing compliance prior to initiation of lapatinib as the proportion of patients that had LFTs completed within 30 days prior to (and including) the index date. Second, the frequency and proportion of patients that were tested at least once during treatment exposure was determined. We also calculated the frequency and proportion of patients that had at least 1 LFT completed within each 6-week interval that they were exposed to lapatinib based on the total number of individuals that contributed at least 1 exposure day within that specific 6-week interval.

Lastly, we assessed physician behavior with regard to withdrawing lapatinib when patients experienced severe LFT elevations. For this analysis, we defined a severe elevation as an occurrence of ALT > 8 times ULN or a

TABLE 3 Cumulative incidence and incidence rates of LFT elevations during lapatinib treatment

		Overall				
		Cumulative incidence			Incidence rate/1000 PM	
LFT lab	Elevated LFT	n	%	95% CI	IR	95% CI
ALT (U/L)	≥ 3x ULN	12	3.8	2.0-6.6	10.95	5.66-19.13
	≥ 5x ULN	6	1.9	0.7-4.1	5.42	1.99-11.79
	≥ 10x ULN	0	0	0	–	–
	Grade 2[a]	19	6.0	3.7-9.3	17.59	10.59-27.47
	Grade 3[b]	6	1.9	0.7-4.1	5.42	1.99-11.79
	Grade 4[c]	0	0	0	–	–
AST (U/L)	≥ 3x ULN	29	9.2	6.3-13.0	27.13	18.16-39.95
	≥ 5x ULN	16	5.1	2.9-8.1	14.38	8.22-23.35
	≥ 10x ULN	1	0.3	0.0-1.8	0.90	0.02-5.00
	Grade 2[a]	27	8.6	5.7-12.2	25.56	16.84-37.18
	Grade 3[b]	16	5.1	2.9-8.1	14.38	8.22-23.35
	Grade 4[c]	0	0	0	–	–
ALP (U/L)	≥ 3x ULN	20	6.3	3.9-9.6	18.28	11.17-28.24
	≥ 5x ULN	12	3.8	2.0-6.6	10.86	5.61-18.96
	≥ 10x ULN	1	0.3	0.0-1.8	0.90	0.02-5.03
	Grade 2[a]	28	8.9	6.0-12.6	25.73	17.10-37.18
	Grade 3[b]	12	3.8	2.0-6.6	10.85	5.61-18.96
	Grade 4[c]	0	0	0	–	–
BILI (mg/dL)	≥ 1.5x ULN	44	14.0	10.4-18.4	42.95	31.21-57.66
	≥ 3x ULN	15	4.8	2.7-7.8	13.66	7.65-22.53
	≥ 5x ULN	13	4.1	2.2-7.0	11.76	6.26-20.10
	≥ 10x ULN	9	2.9	1.3-5.4	8.15	3.73-15.47
	Grade 2[d]	34	10.8	7.6-14.8	32.77	22.69-45.79
	Grade 3[e]	12	3.8	2.0-6.6	10.92	5.64-19.07
	Grade 4[f]	8	2.5	1.1-5.0	7.24	3.13-14.27
Thresholds used to define severe elevations in this study						
ALT > 8		1	0.3	0.0-1.8	0.90	0.02-5.03
ALT or AST > 3x ULN, ALP < 2x ULN, BILI > 2x ULN		3	0.9	0.2-2.8	2.68	0.55-7.84

[a] > 2.5x to 5x ULN; [b] > 5x to 20x ULN; [c] > 20x ULN; [d] > 1.5x to 3x ULN; [e] 3x to 10x ULN; [f] > 10x ULN.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, asparate transaminase; BILI, total bilirubin; CI, confidence interval; IR, incidence rate; PM, person months; ULN, upper limit of normal.

combination of elevations defined as ALT or AST ≥ 3x ULN, with ALP < 2x ULN, and with BILI ≥ 2x ULN, corresponding to the adverse event reporting criteria used in the lapatinib clinical program. We calculated the rate of permanent drug discontinuation for those that had a severe elevation as defined above.

For the first 2 outcomes described above, we used only the first lapatinib exposure period for each patient, whereas in the evaluation of drug withdrawal, we used information about all lapatinib exposure periods to understand if any observed discontinuations were complete or temporary.

Our study defined a population-based cohort of patients with detailed lapatinib exposure information, allowing us to determine the prevalence and incidence of new LFT elevations that arise during lapatinib exposure. We believe that these data from patients treated in "real-life" medical practice can provide valuable information about the hepatic safety of the drug and can serve as a benchmark for elevations observed in randomized clinical trials. We explored multiple ULN thresholds including ULN ranges that correspond to grades 2, 3, or 4 liver enzyme elevations as defined by the Cancer Therapy

TABLE 3 (*continued*)

Pre-label change group					Post-label change group				
Cumulative incidence			Incidence rate/1000 PM		Cumulative incidence			Incidence rate/1000 PM	
n	%	95% CI	IR	95% CI	n	%	95% CI	IR	95% CI
3	3.2	0.7-9.0	7.95	0.16-2.32	9	4.1	1.9-7.6	12.53	5.73-23.78
2	2.1	0.3-7.4	5.27	0.06-1.90	4	1.8	0.5-4.6	5.49	1.50-14.07
0	0	0	–	–	0	0	0	–	–
5	5.3	1.7-11.9	13.77	0.45-3.21	14	6.4	3.5-10.5	19.52	10.67-32.75
2	2.1	0.3-7.4	5.27	0.06-1.90	4	1.8	0.5-4.6	5.49	1.50-14.07
0	0	0	–	–	0	0	0	–	–
10	10.4	5.1-18.3	27.30	1.31-5.02	19	8.7	5.3-13.2	27.03	16.28-42.22
3	3.1	0.7-8.9	7.80	0.16-2.28	13	5.9	3.2-9.9	17.85	9.51-30.53
0	0	0	–	–	1	0.5	0.0-2.5	1.37	0.03-7.66
10	10.4	5.1-18.3	27.24	1.31-5.01	17	7.8	4.6-12.1	24.66	14.36-39.48
3	3.1	0.7-8.9	7.80	0.16-2.28	13	5.9	3.2-9.9	17.85	9.51-30.53
0	0	0	–	–	0	0	0	–	–
6	6.3	2.3-13.1	15.74	0.58-3.43	14	6.4	3.5-10.5	19.64	10.74-32.95
4	4.2	1.2-10.3	10.43	0.28-2.67	8	3.7	1.6-7.1	11.08	4.78-21.84
0	0	0	–	–	1	0.5	0.0-2.5	1.38	0.03-7.71
8	8.3	3.7-15.8	21.00	0.91-4.14	20	9.1	5.7-13.8	28.27	17.27-43.67
4	4.2	1.2-10.3	10.43	0.28-2.67	8	3.7	1.6-7.1	11.07	4.78-21.82
0	0	0	–	–	0	0	0	–	–
16	16.8	9.9-25.9	46.68	26.68-75.81	28	12.8	8.7-18.0	41.08	27.29-59.37
6	6.3	2.4-13.2	16.16	5.93-35.16	9	4.1	1.9-7.7	12.38	5.66-23.51
4	4.2	1.2-10.4	10.58	2.88-27.10	9	4.1	1.9-7.7	12.36	5.65-23.47
3	3.2	0.7-9.0	7.94	1.64-23.22	6	2.7	1.0-5.9	8.25	3.03-17.97
15	15.8	9.1-24.7	43.22	24.19-71.28	19	8.7	5.3-13.2	27.52	16.57-42.98
6	6.3	2.4-13.2	16.16	5.93-35.16	6	2.7	1.0-5.9	8.25	3.03-17.95
3	3.2	0.7-9.0	7.94	1.64-23.22	5	2.3	0.8-5.3	6.88	2.23-16.05
0	0	0	–	–	1	0.5	0.0-2.5	1.37	0.03-7.65
2	2.1	0.3-7.3	5.13	0.62-18.54	1	0.5	0.0-2.5	1.37	0.03-7.65

Evaluation Program, Common Terminology Criteria for Adverse Events.[5]

We defined the prevalence of LFT elevations at baseline as the number of patients that experienced an elevation greater than or equal to a defined ULN threshold in the 30-day period prior to (and including) the date lapatinib was initiated divided by the number of patients tested within this time period. We defined cumulative incidence as the number of patients who experienced an elevation greater than or equal to a defined ULN threshold divided by the total number of patients with at least 1 follow-up LFT. The incidence rate was defined similarly but used a denominator of all lapatinib exposed person months among patients with at least 1 follow-up LFT.

Statistical methods

We generated descriptive statistics for patient demographics, clinical and treatment characteristics overall and by pre-label or post-label change status. We compared pre/post changes in each of the groups of variables using t-tests, Kruskal-Wallis tests, and/or chi-square tests, as appropriate.

The proportion of patients tested, prevalence proportions, and cumulative incidence proportions were expressed

as percentages with corresponding 95% confidence intervals (CIs) estimated using the Clopper Pearson method.[6] We calculated the incidence rate (IR) as per 1,000 person months (PM) of follow-up with corresponding 95% CIs estimated using the Poisson method.[7] All data analyses were performed using SAS version 9.1.

Results

Patients

We identified a total of 396 female patients with HER2+ metastatic breast cancer who had lapatinib therapy initiated in the defined study period: 128 (32%) patients pre-label change and 268 (68%) post-label change (Table 1, p. 260). The mean age at diagnosis in the full study population was 56.4 years. Fifty-eight percent were estrogen receptor positive and 40% progesterone receptor positive. Approximately 9% of patients were recorded as being HER2-negative at diagnosis even though they received lapatinib in the metastatic setting. This may reflect the tendency for some tumors to switch HER2 expression status between the primary tumor and metastatic disease (HER2 status of metastases was not available for this study).[8,9] The percentage of patients initially diagnosed with stage IV breast cancer was higher in the post-label change group (38%) compared with the pre-label patients (30%, $P = .02$). All other patient characteristics were similar between the 2 groups.

Table 1 displays treatment attributes. Pre-label change patients had significantly longer median lapatinib exposure (73 days) compared with post-label change patients (53 days, $P = .01$), which is also reflected in the pattern of lapatinib use, with fewer pre-label change patients permanently discontinuing lapatinib (57%) versus the post-label change group (72%). Approximately 28% and 38% of the pre-label and post-label change cohorts, respectively, were treated for less than 6 weeks.

Primary measurements

A statistically significant difference in LFT testing within the 30 days prior to the initiation of lapatinib existed between groups, with 82% of patients in the post-label change group having at least 1 LFT compared with 64% in the pre-label change group ($P < .001$; Table 2, p. 261). Findings were similar across the four individual LFTs.

In the pre-label change group, approximately 74% had at least 1 LFT measured during follow-up compared with approximately 82% in the post-label change group. The majority of those not tested in both the pre- and post-label change cohorts had less than 6 weeks of lapatinib exposure. Figure 1 (p. 261) presents the proportion of patients tested at least once every 6 weeks throughout the follow-up period. Uniformly, the proportion tested was higher among patients who initiated lapatinib after the label change compared with before the change. Comparing the post-label change group with the pre-label change group, percentages of patients tested were 81%-83% compared with 62%-68% during each 6-week interval, up to 24 weeks. The proportion of patients tested every 6 weeks in the post-label group remained relatively consistent across all 6-week intervals. In contrast, the proportion declined between weeks 18-36 and then increased thereafter for patients in the pre-label change group.

Four patients met the criteria for a severe elevation: 2 each in the pre- and post-label change periods. The 2 pre-label change patients had lapatinib withdrawn within 30 days of the severe elevation but later were rechallenged. In contrast, the 2 post-label change patients had a permanent withdrawal of lapatinib after experiencing the severe elevation.

We examined the prevalence of LFT elevations within 30 days prior to the initiation of lapatinib (data not shown). There were no grade 4 elevations. One prevalent grade 3 elevation (1.2% of patients tested for ALP) occurred in the pre-label change group. Two (0.9%) grade 3 ALT elevations and 4 (1.8%) grade 3 AST elevations occurred in the post-label change group.

Table 3 (p. 262) presents the cumulative incidence and incidence rate per 1,000 PM of LFT elevations that occurred while exposed to lapatinib. Overall, grade 3 elevations in any of the four LFTs occurred in approximately 5% or fewer patients. Elevations of Grade 4 were observed for BILI (2.5%, IR = 7.24 per 1,000 PM of exposure). Cases meeting the severe elevation thresholds in this study were uncommon (0.3%, IR = 0.9 per 1,000 PM for ALT > 8; and 0.9%, IR = 2.68 per 1,000 PM for combination threshold). The cumulative incidence and the IRs across all thresholds were generally similar between the pre- and post-label change groups.

Conclusions

Our study evaluated physician adherence to LFT monitoring guidelines based on a group of 396 female patients diagnosed with HER2+ metastatic breast cancer and treated with lapatinib in a usual care setting. This was accomplished through the separation of these patients into 2 cohorts defined relative to the change in lapatinib's Prescribing Information in mid-2008. Overall, the findings of the study suggest that physicians were more likely to order LFT after the implementation of detailed guidance was added to the product's Prescribing Information.

Patients in the post-label change period were statistically more likely to be tested immediately prior to initiating a new prescription for lapatinib than were patients in the pre-label period (82% vs 64%, respectively). This increase was ob-

served despite the fairly high rate of pre-guideline testing (> 60%). The pre-existing high rate of testing may be expected since LFT testing is standard practice for clinical evaluation of metastatic breast cancer patients.[10] Frequency of baseline LFT testing is substantially higher when compared with other agents and other populations with LFT monitoring recommendations and/or clinical guidelines, such as amiodarone, an antiarrhythmic medication. In one study, only 20% of patients receiving amiodarone were tested prior to initiation, regardless of concomitant use of a statin, which also has LFT monitoring guidelines.[11]

LFT at least once after the initiation of lapatinib was slightly more common in the post-label change group (82% across all four LFTs) than the pre-label change group (approximately 75%); however, this increase was not statistically significant. Moreover, the percentage increase in testing frequency for LFT for lapatinib over the 2 time periods is not as great as the improvement seen in compliance with the introduction of LFT monitoring recommendations for troglitazone, as an example. In the troglitazone example, compliance improved by 30%.[12] It is noteworthy that compliance was much lower to begin with, at 15%. The level of improvement seen in our study may be limited by an already high testing rate in this metastatic breast cancer setting. Physician tendency to test at regular intervals was apparent even among patients that were exposed to lapatinib for more than 36 weeks.

Only four patients met the pre-defined definition of severe elevation during their initial lapatinib exposure. Physicians appeared to withdraw lapatinib slightly more in post-label patients, with both patients having a complete discontinuation. However, due to the small sample size, we cannot draw definitive conclusions. In addition, it is possible that subsequent discontinuation may not have been solely due to the LFT elevation, given the lack of detailed information about the reasons for discontinuation in our study.

One possible alternative explanation for the higher frequency of LFT monitoring in the post-label change period is more familiarity with TKIs over calendar time. Increased knowledge of the product and related side effects could have been driven by increased use due to lapatinib's approval for first-line therapy in 2009 and increased communication by the manufacturer to physicians regarding the label change. Another limitation is the accuracy of defined lapatinib exposure, which may be overestimated for those non-compliant with their medications or underestimated if the prescription information was not documented within the EMR database. The lack of documentation of any LFTs conducted outside of the US Oncology practices may also underestimate the number of tests conducted.

Our study has several strengths. It is population-based and has high generalizability of results. The clinically-rich data from EMRs allowed categorization of patients by stage of breast cancer, molecular subtype, and treatment dates. The level of follow-up of patients was comprehensive, allowing us to sufficiently capture outcomes.

This study demonstrated a high level of LFT monitoring overall in metastatic breast cancer patients. It showed higher frequency of testing in advance of prescribing lapatinib, and routinely during lapatinib exposure, after the addition of detailed guidance on LFT to the product's Prescribing Information. Both the high LFT testing baseline rate and high rate during treatment demonstrates that clinical evaluation of patients with advanced breast cancer and ongoing monitoring of key laboratory parameters are cornerstones of effective patient management.

Acknowledgment

The authors thank Susan Weidner, MS, with Medical Outcomes & Innovations Consulting, who was a paid medical writer. Ms. Weidner reports no conflict of interest.

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