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CLINICAL TRIAL

Pooled analysis of diarrhea events in patients with cancer treated with lapatinib

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Abstract *Purpose* To characterize diarrhea events in patients with cancer treated with lapatinib as monotherapy or in combination with capecitabine or taxanes. *Patients and methods* Eleven clinical trials (phase I, II, or III) in patients with metastatic cancer were analyzed. Lapatinib was administered at doses ranging from 1,000 to 1,500 mg/day as monotherapy ($n = 926$) or in combination with capecitabine ($n = 198$) or taxanes ($n = 687$). Diarrhea events were characterized based on severity, time to onset, duration, required interventions, and clinical outcomes. *Results* In the pooled analysis of nine studies, diarrhea occurred in 55% of lapatinib-treated patients and 24% of patients not receiving lapatinib. All grade diarrhea occurred in 51% of patients treated with lapatinib monotherapy and 65% treated with lapatinib plus capecitabine. In a separate analysis, 48% of patients treated with lapatinib plus a taxane experienced diarrhea. Overall, most diarrhea events were grade 1/2. Grade 3 events occurred in <10% of patients and grade 4 events were rare (≤1%). Most diarrhea events resolved with conventional approaches and without dose modification. Approximately 40% of patients treated with lapatinib monotherapy or combination therapy experienced a first diarrhea event within 6 days of treatment initiation, with a median duration of 7–9 days. Lapatinib-containing chemotherapy regimens do not cause severe diarrhea when proactive monitoring and intervention is introduced. *Conclusion* Most diarrhea events in lapatinib-treated patients are low grade, requiring infrequent lapatinib dose modification or interruption. Proactive management of diarrhea is crucial to prevent more serious complications in lapatinib-treated patients.

Keywords Advanced or metastatic breast cancer · Adverse events · Diarrhea · Epidermal growth factor receptor · Gastrointestinal events · Tyrosine kinase inhibitor

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Introduction

Diarrhea is one of the most common side effects of cancer treatment [1]. Approximately 10% of patients with advanced cancer experience acute or persistent chemotherapy-induced diarrhea, ranging from mild to fatal in severity. Certain chemotherapeutic agents, including fluoropyrimidines and irinotecan, are associated with a significantly higher risk for chemotherapy-induced diarrhea. As many as 80% of patients treated with these agents, either alone or in combination, experience diarrhea, and ≥30% of patients experience serious diarrhea, which can be life-threatening [2]. Diarrhea may delay treatment or reduce patient compliance with oral medications, thus reducing the efficacy of anticancer therapy. The management of diarrhea events also increases the cost of cancer treatment [3, 4].

Consequently, early recognition and timely implementation of appropriate intervention strategies are crucial for the successful control of chemotherapy-induced diarrhea in patients with cancer [5, 6].

Lapatinib (Tykerb®/Tyverb®; GlaxoSmithKline, Philadelphia, PA) is an oral, dual tyrosine kinase inhibitor targeting both EGFR (ErbB1) and HER2 (ErbB2) receptors. Lapatinib is approved in the United States, Switzerland, Australia, and several other international markets for the treatment of advanced or metastatic breast cancer in patients with HER2-positive tumors who have progressed on treatment regimens containing an anthracycline, a taxane, and trastuzumab [7]. Lapatinib is clinically active as a single agent or in combination with various chemotherapy agents in patients with HER2-positive breast cancer and other solid tumors [8–11].

Commonly reported side effects of lapatinib in clinical trials include diarrhea, rash, nausea, and vomiting. Diarrhea was the most frequently reported adverse event in phase I studies of lapatinib-treated patients with advanced or metastatic solid tumors [12]. In addition, diarrhea occurred more frequently in patients with breast cancer who were treated with lapatinib in combination with capecitabine compared with capecitabine alone [9]. Gastrointestinal toxicity is a known side effect of EGFR receptor inhibition; hence, diarrhea events are expected in lapatinib-treated patients. Diarrhea may affect patients' well-being, the likelihood of continuing therapy, and treatment outcomes more than other side effects of lapatinib.

This article reviews only diarrhea-related safety and tolerability data from 11 clinical studies; patients with breast cancers or other solid tumors were administered lapatinib either as monotherapy (seven studies) or in combination with paclitaxel, docetaxel, or capecitabine (four studies).

Patients and methods

Lapatinib clinical studies

To characterize diarrhea events, two analyses were performed on 11 completed lapatinib clinical studies in patients with locally advanced or metastatic cancer (Table 1). Five studies enrolled patients with breast cancer, and six studies enrolled patients with other solid tumors. Lapatinib was administered as monotherapy in seven studies and as combination therapy with paclitaxel in two studies, docetaxel in one study, and capecitabine in one study. Lapatinib was administered as a once-daily oral medication at doses ranging from 1,000 to 1,500 mg/day. Paclitaxel was administered intravenously at doses ranging from 80 mg/m^2 every week to 135 to 225 mg/m^2 every

Table 1 Lapatinib clinical studies

Study number	Indication	Phase	Randomized population (*N*)	Safety population (*N*)	Lapatinib (mg/day)	Combination treatment	Control arm
EGF20001	RCC	III	512	404	1,250 mg/QD	–	Hormone therapy
EGF20002	MBC	II	78	78	1,250–1,500 mg/QD	–	–
EGF20003	Bladder	II	83	59	1,250 mg/QD	–	–
EGF20004	Colorectal	II	86	86	1,250 mg/QD	–	–
EGF20008	MBC	II	229	229	1,500 mg/QD	–	–
EGF20009	MBC	II	138	138	1,500 mg/QD or 500 mg/BID	–	–
EGF20014	NSCLC	II	131	131	1,500 mg/QD or 500 mg/BID	–	–
EGF100151	MBC	III	402	389	1,250 mg/QD	C 2,000 mg/m^2	C 2,500 mg/m^2
EGF10009[a]	Refractory tumors	I	56	44	1,250–1,500 mg/QD	P 135–225 mg/m^2 Q3W	
				12	1,500 mg/QD	P 80 mg/m^2 QW	P 80 mg/m^2 QW
EGF30001	MBC	III	580	579	1,500 mg/QD	P 175 mg/m^2 Q3W	Plac + P175 mg/m^2 Q3W
EGF10021[a]	Refractory tumors	I	52	52	1,000–1,500 mg/QD	D 50–75 mg/m^2 Q3W	

C, Capecitabine; D, Docetaxel; LEAP, Lapatinib Expanded Access Program; MBC, Metastatic breast cancer; NSCLC, Non-small cell lung cancer; P, Paclitaxel; Plac, Placebo; QD, Once-daily; QW, Every week; Q3W, Every 3 weeks; RCC, Renal cell carcinoma

[a] EGF10009 and EGF10021 were not included in the pooled analysis of the nine studies. EGF10009, EGF10021, and EGF30001 were pooled for analysis of lapatinib–taxane combination therapy

Table 2 NCI common toxicity criteria for grading diarrhea [2]

Toxicity grade	Diarrhea[a]
1	Increase of <4 stools/day over baseline
	Mild increase in ostomy output compared with baseline
2	Increase of 4–6 stools/day over baseline
	Intravenous fluids >24 h
	Moderate increase in ostomy output compared with baseline
	Not interfering with daily living
3	Increase of >7 stools/day over baseline
	Incontinence
	Intravenous fluids
	Severe increase in ostomy output compared with baseline
	Interfering with daily living activities
4	Life-threatening consequences (e.g., hemodynamic collapse)
5	Death

[a] Includes diarrhea of small bowel or colonic origin and/or ostomy diarrhea

3 weeks. Docetaxel was administered intravenously at a dose of 50–75 mg/m^2 every 3 weeks. Capecitabine was administered as an oral medication at a dose of 2,000–2,500 mg/m^2 from day 1 to 14 of a 21-day cycle.

Diarrhea events were characterized in a pooled analysis of nine studies (seven monotherapy studies: EGF20001, EGF20002, EGF20003, EGF20004, EGF20008, EGF20009, and EGF20014; a lapatinib plus paclitaxel study: EGF30001; and a lapatinib plus capecitabine study: EGF100151). An additional analysis of study EGF30001 combined with two additional phase I taxane studies (EGF10009 and EGF10021) was conducted to further assess diarrhea events in patients treated with lapatinib–taxane combination therapy.

Monitoring of diarrhea events

Diarrhea events included the following MedDRA terms: diarrhea, diarrhea hemorrhagic, frequent bowel movements, and loose stools. Diarrhea severity was graded on a scale from 1 to 5 using the National Cancer Institute Common Toxicity Criteria (CTC, versions 2.0 and 3.0; Table 2) [13, 14]. Diarrhea events were assigned possible causality to the study medication by the investigators and were characterized based on severity, time to onset, duration, required interventions (lapatinib dose adjustment, interruption, or discontinuation), and clinical outcomes. Patients' ages and events associated with diarrhea, including nausea, vomiting, and dehydration, were also reviewed. Patients who were not treated with lapatinib but received paclitaxel, docetaxel, capecitabine, or hormonal therapy in the same studies served as comparators.

Results

Patient population

The pooled analysis of nine completed phase II and III studies included 2,093 patients with locally advanced or metastatic cancer—1,413 patients with breast cancer and 680 with other solid tumors. An additional analysis of patients treated with a combination of lapatinib and taxanes included 687 patients from three studies—two phase I studies, EGF10009 (56 patients) and EGF10021 (52 patients), and a phase III study, EGF30001 (579 patients; Table 1). Patients were treated with lapatinib 1,000–1,500 mg once daily (QD) either as monotherapy ($n = 926$) or in combination with capecitabine ($n = 198$), paclitaxel (EGF30001, $n = 293$; EGF10009, $n = 56$), or docetaxel (EGF10021; $n = 52$). Patients who were not exposed to lapatinib but received paclitaxel, docetaxel, capecitabine, hormones, or placebo in the same studies served as comparators ($n = 676$).

Patient disposition

In the pooled analysis of nine studies, the median age of patients was 55 years (range from 19 to 87 years; Table 3). Elderly (≥70 years) patients accounted for 13% of lapatinib-treated patients and 11% of patients not treated with lapatinib. All patients in the breast cancer studies were female, whereas only 35% of patients in the non-breast cancer studies were female. About 78% of patients were white. A higher percentage of non-white patients participated in breast cancer (2–13%) versus non-breast cancer studies (<3%). Most (96%) patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, and 63% of patients had a Karnofsky performance status score of 90–100 at study entry. In the analysis of lapatinib–taxane combination therapy, the median age of patients was 52 years (range, 19–88 years), 91% of patients were female, and 68% of patients were white.

Diarrhea events

In the pooled analysis ($n = 2,093$), all grade diarrhea events occurred more frequently in lapatinib-treated patients compared with patients treated with comparator agents (all grades, 55% vs. 24%, respectively; Table 4). Diarrhea events in both the lapatinib and comparator groups were predominantly grade 1/2 in severity. Grade 3

Table 3 Patient demographics

	Age (range) (years)	Sex		Race	
		Female	Male	White	Non-white
Pooled analysis					
All ($N = 2,093$)					
Lapatinib ($n = 1,417$)	56 (20–87)	1,123 (79)	294 (21)	1,077 (76)	340 (24)
No lapatinib ($n = 676$)	54 (19–83)	527 (78)	149 (22)	549 (81)	127 (19)
Breast ($n = 1,413$)					
Lapatinib ($n = 936$)	53 (20–87)	936 (100)	(0)	633 (68)	303 (32)
No lapatinib ($n = 477$)	51 (25–83)	477 (100)	(0)	353 (74)	124 (26)
Nonbreast ($n = 680$)					
Lapatinib ($n = 481$)	62 (22–86)	187 (39)	294 (61)	444 (92)	37 (8)
No lapatinib ($n = 199$)	62 (19–81)	50 (25)	149 (75)	196 (98)	3 (2)
Lapatinib					
Lapatinib monotherapy ($n = 926$)	58 (20–86)	632 (68)	294 (32)	705 (76)	221 (24)
Lapatinib + capecitabine ($n = 198$)[a]	54 (26–80)	198 (100)	(0)	181 (91)	17 (9)
Capecitabine ($n = 191$)	51 (28–83)	191 (100)	(0)	172 (90)	19 (10)
Taxane analysis					
Lapatinib + taxanes ($n = 687$)[b]	52 (19–88)	626 (91)	61 (9)	470 (68)	217 (32)
Taxane alone ($n = 286$)	51 (25–78)	286 (100)	(0)	181 (63)	105 (37)

[a] EGF100151

[b] EGF10009, EGF10021, and EGF30001

events occurred in 9% of lapatinib-treated patients versus 4% of no lapatinib-treated patients. Grade 4 events occurred in <1% of patients in both treatment groups, and the mean number of diarrhea events per patient was similar in both groups (two events). Almost half (42%) of lapatinib-treated patients had a first diarrhea event within 6 days of treatment initiation, whereas the largest proportion of patients not treated with lapatinib (36%) had a first event after 28 days. Forty-one patients in the lapatinib group and four patients in the comparator group had grade 3/4 diarrhea at first presentation. Diarrhea rarely worsened from grade 1/2 to 3/4 in the lapatinib (13 patients) or comparator (three patients) groups. The median duration in patients treated with lapatinib was 5 days compared to 4 days in patients not treated with lapatinib (Table 5).

The majority of diarrhea events resolved (lapatinib 92%; no lapatinib 96%). Outcomes were similar in breast and

Table 4 Maximum toxicity of diarrhea events

	CTC grade (%)									
	Patients (*N*)		Lapatinib				No lapatinib			
	L	No L	All	G1/2	G3	G4	All	G1/2	G3	G4
Pooled analysis										
All studies	1417	676	54	45	9	<1	24	20	4	0
Breast	936	477	58	46	111	<1	31	26	5	0
Other solid tumors	481	199	48	44	4	<1	6	5	1	0
Lapatinib monotherapy	926	N/A	51	45	6	<1	N/A	N/A	N/A	N/A
Lapatinib + capecitabine[a]	198	191	65	51	13	1	40	30	10	0
Taxane analysis										
Lapatinib + taxanes[b]	401	286	48	39	9	<1	26	24	1	0

No lapatinib is monotherapy with either hormones ($n = 197$), capecitabine ($n = 191$), or paclitaxel ($n = 286$)

CTC, Common toxicity criteria

[a] EGF100151

[b] EGF10009, EGF10021, and EGF30001

non-breast cancer studies. Diarrhea events rarely led to treatment discontinuation (2%), and most diarrhea events did not require dose reductions or interruptions in study drug (lapatinib 85%; no lapatinib 78%). Patients who required intervention responded to standard antidiarrheal medications (e.g., loperamide and diphenoxylate hydrochloride/atropine sulfate) and, in more severe cases, to hydration, octreotide, and antibiotics.

Four percent of patients treated with lapatinib experienced diarrhea as a serious adverse event (SAE; lapatinib 4%; no lapatinib 2%). Most diarrhea SAEs were considered treatment-related (lapatinib, 82%; no lapatinib, 81%). However, most diarrhea SAEs resolved (lapatinib, 97%; no lapatinib, 94%), and there were no fatal lapatinib-related diarrhea SAEs.

Seven percent of elderly patients (≥70 years) treated with lapatinib experienced diarrhea events. Diarrhea events in elderly patients had similar severity, onset, and resolution compared with diarrhea events in patients <70 years, although some minor differences existed. Elderly patients with breast cancer experienced more grade 3 events (33% vs. 19% in patients <70 years), and the median duration of diarrhea events was longer in elderly patients with other solid tumors, including colon and renal cancer (28 days), compared with patients <70-year-old (10 days).

Nausea (12%), vomiting (8%), or nausea and vomiting (4%) occurred within 3 days of onset of diarrhea in lapatinib-treated patients. Nausea and vomiting occurred more frequently in patients treated with lapatinib in combination with paclitaxel or capecitabine. Mucositis was associated with diarrhea in <1% of patients.

Lapatinib monotherapy (n = 926)

Fifty-one percent of patients treated with lapatinib monotherapy experienced diarrhea events (Table 4). Forty-five percent of patients reported grade 1/2 events, 6% of patients reported grade 3 events, and <1% of patients reported grade 4 events. Forty-five percent of patients who received lapatinib monotherapy had a first diarrhea event within 6 days of treatment initiation. The median duration of diarrhea events was similar by grade in lapatinib monotherapy studies (5–6 days; Table 5). Two percent of patients treated with lapatinib monotherapy experienced diarrhea as an SAE. Most (87%) diarrhea events did not require changes to lapatinib treatment. The lapatinib dose was adjusted in 3% of events, treatment was interrupted in 8% of events, and treatment was discontinued in 2% of events. Most diarrhea events resolved with conventional approaches in patients receiving lapatinib monotherapy (89%).

Lapatinib in combination with capecitabine (n = 198)

Diarrhea events were reported in 65% of patients treated with lapatinib in combination with capecitabine (EGF100151; Table 4). Most (89%) diarrhea events were deemed to be treatment-related. The majority of patients experienced grade 1/2 events, grade 3 events occurred in 13% of patients, and grade 4 events occurred in 1% of patients. Forty-one percent of patients had a first diarrhea event within 6 days of treatment initiation, and the median duration of diarrhea events was longer in patients with severe events (8.5 days vs. 4–5 days for mild to moderate events; Table 5). There were no fatal diarrhea events, and diarrhea was reported as an SAE in 7% of patients. Ninety-one percent of events resolved, and 2% of events led to discontinuation of treatment.

In contrast, diarrhea events were reported in 40% of patients treated with capecitabine monotherapy. Grade 1/2 events occurred in 30% of patients, and grade 3 events occurred in 10% of patients. There were no grade 4 events. Diarrhea events in patients treated with capecitabine monotherapy had a median onset of 16 days and a median duration of 6 days. Diarrhea as an SAE was reported in 6% of patients. Most (94%) diarrhea events resolved, and only 3% of events resulted in withdrawal.

Table 5 Median duration of diarrhea events

	Time (days)			
	Grade 1	Grade 2	Grade 3	Grade 4
Pooled analysis (N = 2,093)				
Lapatinib (n = 1,417)	5	5	5	3
No lapatinib (n = 676)	3	5	7	0
Lapatinib monotherapy (n = 926)	6	5	5	5
Lapatinib + capecitabine (n = 198)[a]	4	5	8.5	3
Capecitabine alone (n = 191)	3	5	12	N/A
Taxane analysis				
Lapatinib + taxanes (N = 687)[b]	4	4	4	3
Taxane alone (n = 286)	3	3	3	N/A

[a] EGF100151

[b] EGF10009, EGF10021, and EGF30001

Table 6 Action taken with lapatinib

	Diarrhea events (%)			
	No action	Treatment interruption	Dose adjustment	Treatment discontinuation
Pooled analysis ($N = 2{,}093$)				
Lapatinib ($n = 1{,}417$)	85	9	3	2
No lapatinib ($n = 676$)	78	13	7	2
Lapatinib monotherapy ($n = 926$)	87	8	3	2
Lapatinib + capecitabine ($n = 198$)[a]	81	11	5	3
Capecitabine alone ($n = 191$)	70	12	12	3
Taxane analysis				
Lapatinib + taxanes ($n = 687$)[b]	86	10	2	2
Taxane alone ($n = 286$)	85	15	0	0

[a] EGF100151

[b] EGF10009, EGF10021, and EGF30001

Lapatinib in combination with taxanes (n = *687)*

Forty-eight percent of patients treated with lapatinib combined with paclitaxel or docetaxel (EGF10009, EGF10021, and EGF30001) experienced diarrhea events (Table 4). Distribution of diarrhea events by grade was similar to that reported for the lapatinib monotherapy studies; most diarrhea events were grade 1/2, and 3 and four events occurred in <10% of patients. Notably, a higher incidence of diarrhea events was reported in the two phase I studies that enrolled patients with refractory tumors, EGF10009 (82%) and EGF10021 (71%). An average of two diarrhea events occurred in patients who received lapatinib–taxane combination therapy. The median time to onset of diarrhea was 8 days; 37% of patients had a diarrhea event within 6 days of treatment initiation and diarrhea events lasted <10 days in 71% of patients. The median duration of diarrhea was similar by grade (3–4 days; Table 5). Four percent of patients treated with lapatinib–taxane combination therapy experienced diarrhea as an SAE; there were no fatal diarrhea SAEs. Overall, 84% of diarrhea AEs were considered treatment-related. Most diarrhea events were managed without recorded medical intervention (Table 6). Diarrhea events rarely led to treatment discontinuation (2%), and almost all events resolved.

Twenty-six percent of patients treated with taxane monotherapy experienced diarrhea events, 81% of which were deemed treatment-related. Grade 1/2 events occurred in 24% of patients, and grade 3 events occurred in 1% of patients. There were no grade 4 events. Diarrhea events in patients treated with taxane monotherapy had a median onset of 22 days and a median duration of 3 days. Diarrhea as an SAE was reported in <1% of patients. Ninety-eight percent of events resolved, and there were no treatment withdrawals.

Management of diarrhea events

Several SAEs, including death, as a result of septic shock and diarrhea occurred early in the lapatinib–paclitaxel combination study (EGF30001; Fig. 1). However, introduction of supportive measures as outlined in the American Society of Clinical Oncology (ASCO) treatment guidelines for cancer therapy-induced diarrhea (Table 7) [2] significantly decreased the frequency and severity of gastrointestinal complications. As a result, GlaxoSmithKline recommended that diarrhea events that occurred in other lapatinib clinical studies should be managed using the ASCO guidelines. As outlined in these guidelines, most uncomplicated cases of diarrhea (grade 1/2) were treated in an outpatient setting. In addition to dietary modification, lapatinib and cytotoxic chemotherapy were withheld in patients with grade 2 diarrhea until symptoms resolved. High-dose loperamide at an initial dose of 4 mg followed by 2 mg every 4 h was administered until 12 h elapsed without loose motions. In patients who were refractory to loperamide, octreotide therapy was initiated. Oral antibiotics were also added as needed. Patients with more complicated diarrhea (grade 3/4 diarrhea, grade 1/2 diarrhea with complicating features, or progression of grade 1/2 to grade 3/4 diarrhea) were hospitalized and received octreotide, intravenous fluids, and/or antibiotics. If necessary, a brief (up to 14 days) interruption or reduction in the dose of lapatinib or chemotherapy was implemented until symptoms of diarrhea resolved.

Discussion

These analyses of 2,201 patients enrolled in seven lapatinib monotherapy studies and four lapatinib combination studies (three studies with taxanes and one study with capecitabine) demonstrated that lapatinib-induced diarrhea is usually low-grade, self-limiting, and manageable. Severe (grade 3) diarrhea occurs in <10% of patients, and grade 4 diarrhea occurs rarely. Notably, the addition of chemotherapy (either taxanes or capecitabine) does not substantially increase the overall incidence or severity of diarrhea, particularly when proactive management

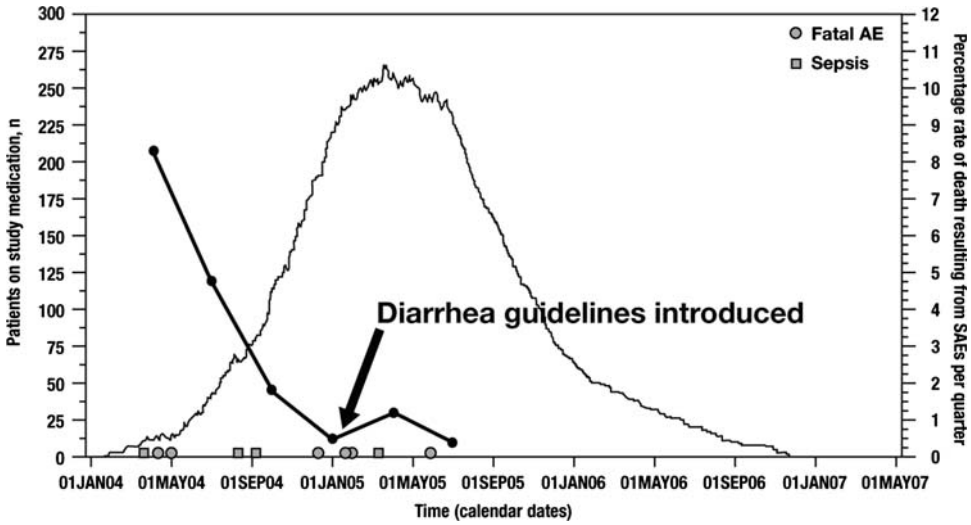

Fig. 1 EGF30001: effect of diarrhea management guidelines on death rates resulting from serious adverse events (SAEs)

guidelines are in place. Diarrhea generally occurs early in the course of treatment (<1 week) and is usually of limited duration (median of 4–5 days). Most diarrhea events resolve and do not require lapatinib dose reduction, interruption, or discontinuation. Although the elderly (>70 years) patient population was small, the incidence of diarrhea events was comparable to that observed in younger patients and does not represent a particular concern in the elderly.

A small group of patients (10–15%) developed clinically significant diarrhea that was of concern, especially in those receiving concomitant myelosuppressive chemotherapy. Several diarrhea events that culminated in serious consequences, including death, as a result of septic shock, were reported early in a lapatinib–paclitaxel combination study in patients who were experiencing diarrhea and severe myelosuppression [15]. Further experience with lapatinib, a better understanding of the side effect profile of lapatinib, and early introduction of supportive care significantly decreased the frequency and severity of gastrointestinal complications. Consequently, most recent lapatinib clinical studies incorporate proactive diarrhea management, and lapatinib dose adjustments, interruptions, or discontinuations should only be necessary in patients with persistent diarrhea.

The mechanism underlying EGFR-related diarrhea has not been completely elucidated. Several important observations resulted from phase I studies that evaluated the relationship between pharmacokinetic parameters and side effects in patients with metastatic solid tumors who were treated with lapatinib, either as monotherapy or in combination with taxanes and capecitabine [12]. It was shown that the frequency of diarrhea was related to the dose but not the

Table 7 ASCO recommended guidelines for the management of treatment-induced diarrhea [2]

Diarrhea CTC grade	Management
Uncomplicated grade 1–2	• Stop all lactose-containing products • Drink 8 to 10 large glasses of clear liquids per day • Eat frequent small meals
Grade 2	• Hold cytotoxic chemotherapy and consider lapatinib dose reduction • Administer standard dose of loperamide: initial dose, 4 mg, followed by 2 mg every 4 h or after every unformed stool – Consider continuation of loperamide until diarrhea-free for 12 h
Grade 3 or 4 diarrhea or grade 1 or 2 diarrhea with complicating features[a]	• Consider hospital admission • Administer octreotide [100–150 μg SC BID or IV (25–50 μg/h) if dehydration is severe, with dose escalation up to 500 μg TID] • Use intravenous fluids as appropriate • Use prophylactic antibiotics as needed (e.g., fluoroquinolones), especially if diarrhea is persistent beyond 24 h or there is fever or grade 3–4 neutropenia • Hold both cytotoxic chemotherapy and lapatinib

SC, subcutaneous; BID, twice daily; TID, three times a day

[a] Grade III cramping, grade III nausea/vomiting, decreased performance status from baseline, >grade II fever, any sepsis, grade 3 or 4 neutropenia, grade III bleeding, or grade II dehydration

serum concentration of lapatinib, suggesting that lapatinib toxicity evolves from a local effect on the gut epithelium [12]. Pharmacokinetic interactions were reported when lapatinib was combined with paclitaxel [16]. Coadministration of lapatinib and paclitaxel in patients with metastatic solid tumors resulted in an approximately 20% increase in systemic exposure (area under the concentration–time curve) to both drugs [16, 17]. In contrast, lapatinib combined with either docetaxel or capecitabine did not result in detectable pharmacokinetic interactions [15].

Some chemotherapy agents exert cytotoxic effects on the rapidly dividing crypt cells in the intestinal epithelium, which may lead to a relative loss of intestinal-absorptive capacity compared with secretory capacity [18, 19]. Furthermore, cytotoxic destruction or augmentation of enzymes involved in the digestion of proteins and carbohydrates may also alter osmotic gradients in the gut and contribute to decreased reabsorption and increased secretion of fluid and electrolytes in the stool, resulting in diarrhea [20]. The addition of paclitaxel, docetaxel, or capecitabine to lapatinib treatment may increase the incidence of diarrhea events; however, diarrhea events are manageable in patients who receive combination therapy.

Diarrhea is a recognized side effect of EGFR inhibitors [21]. The incidence and severity of diarrhea in lapatinib-treated patients is similar to results reported for other EGFR inhibitors. Diarrhea of any grade was noted in 48% of patients with non-small cell lung cancer (NSCLC) treated with gefitinib 250 mg/day (1% had grade 3/4) [22]. Any grade diarrhea was observed in 54% of patients with NSCLC treated with erlotinib 150 mg; 6% of patients developed severe (grade 3/4) diarrhea [23]. Similar to the current analysis, other EGFR therapies are also associated with higher incidences and severities of diarrhea when administered as combination therapy. Any grade diarrhea was reported in 25% of patients with colorectal cancer treated with cetuximab monotherapy (2% had grade 3/4) [24]. However, 72% of patients treated with cetuximab combination therapy experienced diarrhea (22% had grade 3/4). Similarly, diarrhea developed in 25% of patients with metastatic breast cancer treated with trastuzumab monotherapy and in 45% of patients treated with trastuzumab combined with paclitaxel or anthracyclines [25]. Paclitaxel monotherapy is associated with a diarrhea incidence rate of 38% [26]. In addition, diarrhea developed in 39% of patients treated with docetaxel monotherapy (5% had grade 3/4) [26]. Fifty-seven percent of patients with metastatic breast cancer who received capecitabine monotherapy reported all grade diarrhea (15% had grade 3/4) [27]. The incidence of diarrhea in patients treated with lapatinib–capecitabine combination therapy was similar in the current analysis (65%). Diarrhea has also been reported to occur in placebo-treated patients who participate in clinical studies (all grade, 13–27%; <1% had grade 3/4) [23, 28, 29].

The onset of diarrhea events in lapatinib-treated patients is similar to that reported for other EGFR tyrosine kinase inhibitors. Diarrhea events occurred in gefitinib-treated patients within the first month of therapy, and only 2% of patients discontinued therapy because of diarrhea [22]. Similarly, the median time to onset of diarrhea in erlotinib-treated patients was 12 days and dose reduction and treatment discontinuation occurred in 1% of patients [23].

Consistent with EGFR-related mechanism-based toxicity, most diarrhea events in lapatinib-treated patients were mild to moderate in severity, had an early onset, and were of short duration. The majority of events resolved and did not require lapatinib dose adjustment or treatment interruption. Serious cases of diarrhea occurred rarely; however, these events may pose a clinical problem, especially in patients treated with lapatinib in combination with chemotherapy. Consequently, proactive diarrhea management is strongly recommended when lapatinib is administered in combination with chemotherapy.

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