

Safety Profile and Clinical Recommendations for the Use of Lapatinib

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Key Words

Lapatinib · Tolerability · Rash · Diarrhea · Clinical management

Summary

The toxicity profile of agents blocking the epidermal growth factor receptor pathway excludes many of the severe side effects commonly observed with cytotoxic chemotherapy. Like other tyrosine kinase inhibitors, lapatinib is generally well tolerated. Lapatinib exhibits specific toxicities, the most common being diarrhea and rash, which are mostly mild to moderate in severity. Cardiac toxicity is rarely seen with lapatinib. Generally, lapatinib-associated toxicities are manageable.

Schlüsselwörter

Lapatinib · Verträglichkeit · Hautveränderungen · Diarrhö · Klinisches Management

Zusammenfassung

Unter Anti-EGFR(epidermal growth factor receptor)-Therapeutika treten viele der schweren Nebenwirkungen nicht auf, die häufig unter Chemotherapie gesehen werden. Wie andere Tyrosinkinasehemmer wird auch Lapatinib allgemein gut vertragen. Zu den häufigsten Nebenwirkungen gehören Hautveränderungen («Rash») und Diarrhö, die beide meist von leichtem bis moderatem Schweregrad sind. Kardiale Toxizitäten sind unter Lapatinib nur selten. Generell lassen sich die Lapatinib-assoziierten Nebenwirkungen gut beherrschen.

Introduction

Contrary to standard chemotherapy agents which affect most replicating cells, drug-induced blockade of ErbB family members targets specific signaling pathways that are essential for tumor cell proliferation and survival. Therefore, treatment with these targeted therapies excludes many of the severe systemic and particularly hematopoietic side effects often seen with cytotoxic chemotherapy. However, as anti-ErbB1 treatment is increasingly part of the therapeutic armamentarium for the treatment of different malignancies, commonly occurring adverse events blocking the ErbB1 pathway have been identified. These reactions are caused by coincident inhibition of receptor activity in tissues that depend on ErbB1 signaling

for physiological function. ErbB1 is expressed on nearly all body cells, particularly those of epithelial origin such as skin, liver, and the gastrointestinal tract, but not on hematopoietic cells [1, 2]. As a consequence, the most commonly encountered toxic effects from agents blocking the epidermal growth factor receptor (EGFR) are rash and diarrhea, as well as hepatic disorders. ErbB2 (HER2)- and ErbB1-inhibiting therapies have also resulted in cardiotoxicity. Yet, these adverse events appear to differ in frequency and severity within the various ErbB1-targeting agents. In conclusion, awareness as well as improved understanding and proper management of these side effects are crucial in order to increase patients' compliance, adherence and persistence, and to ensure quality of life and overall treatment success.

Tolerability in Clinical Phase III Trials

The safety of lapatinib has been evaluated in clinical trials involving more than 3,500 patients [3]. The most frequently reported drug-related adverse events (>20%) in the pivotal phase III trial EGF 100151 with lapatinib plus capecitabine were gastrointestinal (diarrhea, nausea, and vomiting), dermatologic (palmar-plantar erythrodysesthesia and rash), and fatigue. In the combination arm, 60% of women experienced diarrhea (27% grade 1, 20% grade 2, 12% grade 3, and 1% grade 4), versus 39% in the capecitabine monotherapy arm (14% grade 1, 14% grade 2, 11% grade 3) ($p < 0.001$) [4]. In the combination group, 27% of patients developed rash compared to 15% in the capecitabine monotherapy arm ($p = 0.011$) [4]. The vast majority of rash cases were mild to moderate (grade 1 or 2), with grade 3 rash seen in 1% of patients in both the combination arm and the capecitabine monotherapy arm. As compared with capecitabine alone, lapatinib plus capecitabine was not associated with an increase in either serious toxic effects or rates of discontinuation related to adverse events. Adverse events led to discontinuation of treatment in 22 women in the combination therapy group (13%) and in 18 women in the monotherapy group (12%). There were no differences in the mean left ventricular ejection fraction (LVEF) by echocardiography or multiple gated acquisition (MUGA) scanning between the two groups at scheduled assessments in the EGF 100151 trial [4]. In the combination arm, 4 women experienced asymptomatic and reversible cardiac dysfunction considered to be treatment-related, while 1 patient in the capecitabine monotherapy group suffered from a cardiac event unrelated to treatment, that remained unresolved. No symptomatic cardiac events were observed, and there were no withdrawals from treatment due to declines in LVEF, no cases of congestive heart failure (CHF), and no decreases in the mean LVEF values in the group receiving lapatinib.

This safety profile of the small-molecule dual tyrosine kinase inhibitor (TKI) was confirmed by the data of the second phase III trial evaluating the efficacy of lapatinib in combination with paclitaxel as first-line therapy in 579 women with metastatic breast cancer (EGF 30001) [5]. Diarrhea was the most common adverse event, experienced by 58% of women in the combination arm and 26% in the paclitaxel monotherapy group ($p < 0.0001$). Rash was seen in 43% of women in the lapatinib/paclitaxel arm versus 21% receiving paclitaxel monotherapy ($p < 0.0001$). Lapatinib combined with paclitaxel was associated with a 2.7% incidence of fatal adverse events (mainly sepsis associated with diarrhea), compared with a 0.6% incidence in the paclitaxel/placebo arm. According to the authors, most of these fatal events occurred early in the accrual period and decreased sharply with time. Increased experience treating these adverse events and the introduction of proactive guidelines for managing lapatinib-related diarrhea during the study likely contributed to the reduced in-

cidence and severity of diarrhea episodes. Six patients (2%) in each treatment group of the EGF 30001 trial had a decrease in LVEF [5]. Five of 6 patients in each group experienced an asymptomatic LVEF decrease that met protocol-defined serious adverse event (SAE) criteria. None of these events required a dose/schedule adjustment or resulted in treatment withdrawal or death. Decreases in LVEF were considered treatment-related in 3 of 6 patients in the paclitaxel/lapatinib arm and in 4 of 6 patients in the paclitaxel/placebo group. All events occurred more than 28 days after treatment initiation.

Diarrhea and Clinical Management

To characterize diarrhea events in cancer patients treated with lapatinib as monotherapy or in combination with capecitabine or taxanes, Crown et al. [8] conducted a pooled analysis of 9 clinical trials (phase I, II, or III) in patients with metastatic cancer. 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. Diarrhea occurred in 55% of lapatinib-treated patients and 24% of patients not receiving lapatinib. All-grade diarrhea experienced 51% of patients treated with lapatinib monotherapy and 65% under lapatinib plus capecitabine. In a separate analysis, 48% of women receiving lapatinib plus a taxane experienced diarrhea. Overall, most diarrhea events were low-grade 1/2, requiring infrequent lapatinib dose modification or interruption. Grade 3 events occurred in <10% of patients, and grade 4 events were rare ($< \text{or} = 1\%$). 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 did not cause severe diarrhea when proactive monitoring and intervention was introduced.

Management of diarrhea is crucial to prevent more serious complications in lapatinib-treated patients. Therefore, Chat-sipiroios and Jackisch [from 9–14] developed a useful algorithm which can be applied by nurses/office assistants (fig. 1) and physicians (fig. 2). If a patient experiences mild to moderate (grade 1 or 2) diarrhea, dietary measures like avoiding all lactose-containing products, staying well hydrated, eating frequent small meals, as well as administering standard doses of loperamide are indicated. Diarrhea has to be controlled after 24 h. If there is no improvement seen after 24 h, if the patient experiences severe diarrhea or has complicating features such as severe cramping, severe nausea or vomiting, fever or dehydration, she has to be seen by a physician, and inpatient hospi-

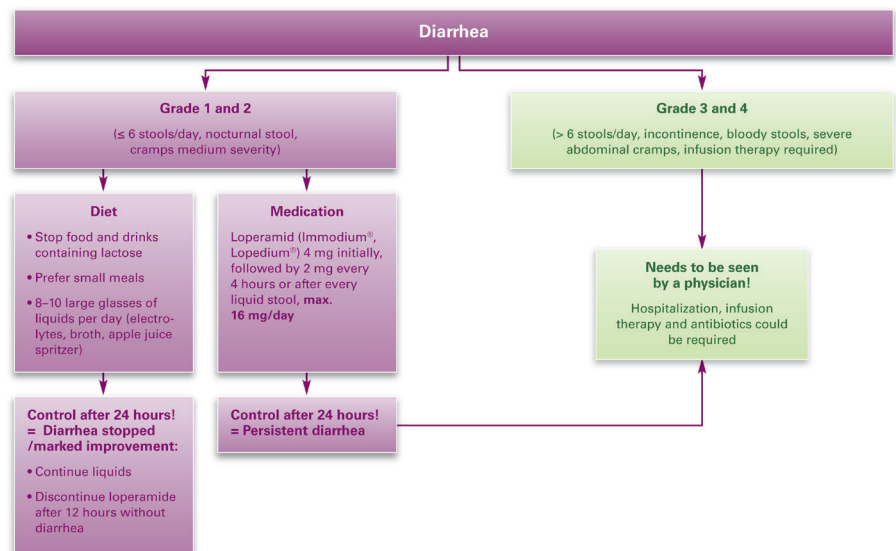


Fig. 1. Management algorithm for lapatinib-associated diarrhea for nurses/office assistants developed by the author and C. Jackisch from [9–14].

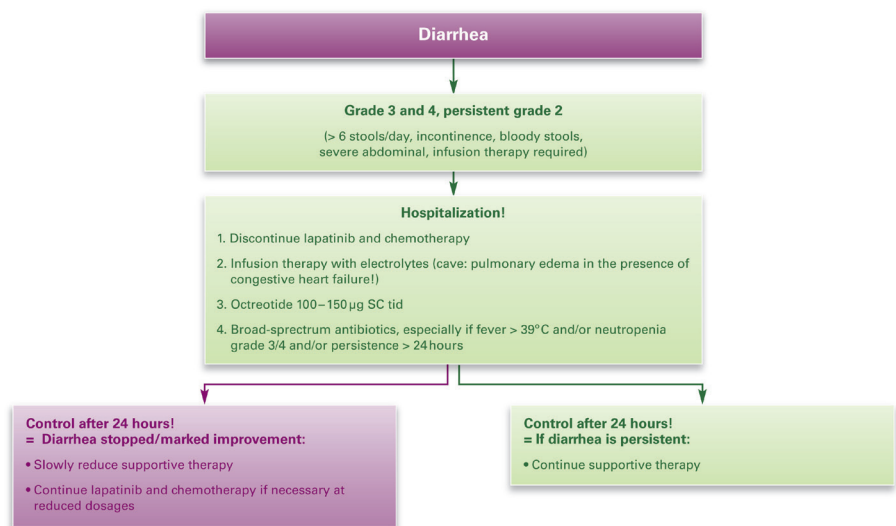


Fig. 2. Management algorithm for lapatinib-associated diarrhea for physicians developed by the author and C. Jackisch from [9–14].

talization should be considered (fig. 2). Further doses of lapatinib and chemotherapy should be held; intravenous (IV) fluids, octreotide 100–150 µg subcutaneously 3 times daily (not licensed in Germany for this indication), and antibiotics might be required. Repeated administration of lapatinib should be delayed until the patient recovers.

Rash and Clinical Management

Skin reactions are common in patients receiving ErbB1-targeted treatments, regardless of therapy type (i.e. ErbB1 TKIs or monoclonal antibodies). ErbB1 activation mediates essential functions in the skin such as the promotion of keratinocyte proliferation, survival and motility, and the regulation of differentiation and keratinization [15]. In wounded

skin, the ErbB1 receptor is transiently up-regulated, and is an important contributor to the proliferative and migratory aspects of wound re-epithelialization. Therefore, blocking the ErbB1 pathway at the skin level can result in abnormal proliferation, migration, and differentiation of target cells, and consequent disruption of the integrity of the skin with recruitment of inflammatory cells. The most commonly seen skin reaction with ErbB1 inhibitors is a follicular acneiform eruption, also termed acne-like rash or folliculitis, characterized by inflammatory papules and pustules most often seen on the face, chest, and back [3]. The distribution is called ‘acneiform’ because the lesions are present at sites with large numbers of pilosebaceous units such as the scalp, face, neck, and upper trunk. However, the characteristic rash is different from classic acne vulgaris because of its lack of comedones.

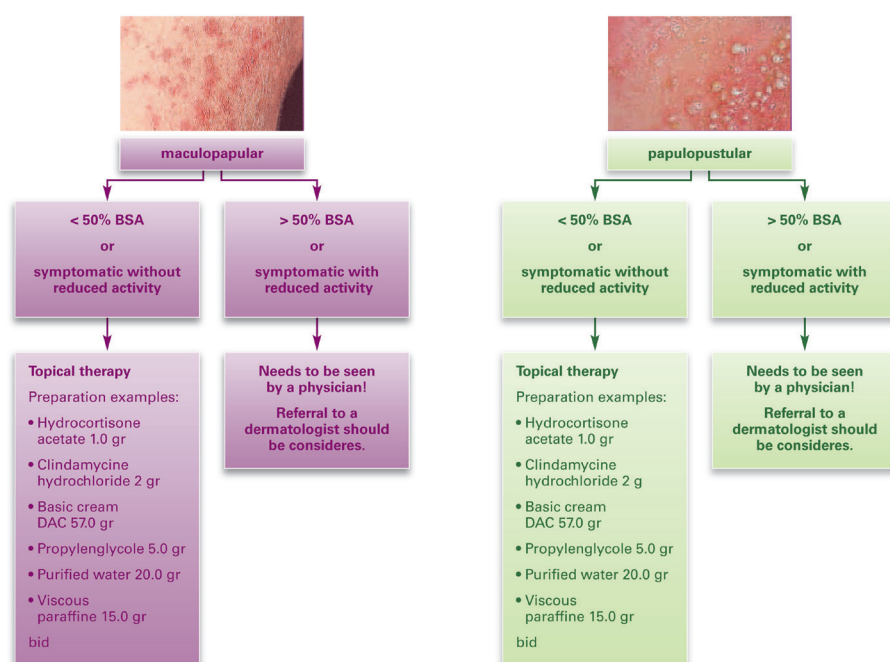


Fig. 3. Management algorithm for lapatinib-associated rash for nurses/office assistants adapted by the author and C. Jackisch from [18].

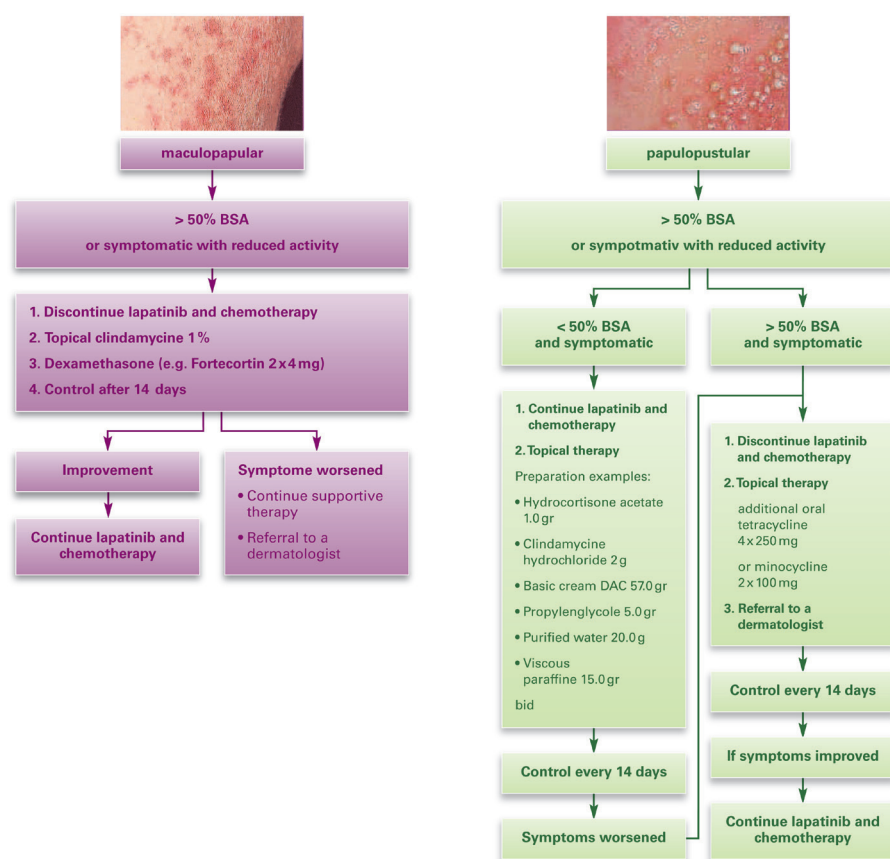


Fig. 4. Management algorithm for lapatinib-associated rash for physicians adapted by the author and C. Jackisch from [18].

Rash associated with ErbB1 inhibitors generally follows a well-characterized clinical course: Within the first week of treatment, patients experience sensory disturbance with erythema and edema [16]. From weeks 1 to 3, the papulopustular

eruption becomes manifest, followed by crusting at week 4. Despite successful treatment, erythema and dry skin may persist in the areas previously affected by the skin rash through weeks 4 to 6. Other less frequent dermatological side effects

Table 1. Potential drug-drug interactions with lapatinib, adapted from [3]

Drug class	Agent
CYP3A4 inducers	
Antibiotics	all rifamycin class agents (e.g. rifampicin, rifabutin, rifapentine)
Anticonvulsants	phenytoin, carbamazepine, barbiturates (e.g. phenobarbital)
Antiretrovirals	efavirenz, nevirapine
Glucocorticoids (oral)	cortisone (>50 mg), hydrocortisone (>40 mg), prednisone (>10 mg), methylprednisone (>8 mg), dexamethasone (>1.5 mg)
Other	St. John's Wort, modafinil
CYP3A4 inhibitors	
Antibiotics	clarithromycin, erythromycin, troleandomycin
Antifungals	itraconazole, ketoconazole, fluconazole (>150 mg daily), voriconazole
Antiretrovirals, protease inhibitors	delaviridine, nelfinavir, amprenavir, ritonavir, indinavir, saquinavir, lopinivir
Calcium channel blockers	verapamil, diltiazem
Antidepressants	nefazodone, fluvoxamine
Gastrointestinal agents	cimetidine, aprepitant
Other	grapefruit, grapefruit juice, amiodarone
Miscellaneous	
Antacids	Mylanta [®] , Maalox [®] , Tums [®] , Rennie [®] (1 h before and after lapatinib dosing)
Herbal supplements	gingko biloba, kava, grape seed, valerian, ginseng, echinacea, evening primrose oil
CYP = Cytochrome P450.	

include dry skin, pruritus, fissures, palmar-plantar rash, hyperkeratosis, and nail disorders.

In an overview of dermatologic events (DEs) in patients with metastatic cancer treated with lapatinib, Lacouture et al. [17] analyzed 9 clinical trials. Lapatinib was administered at doses ranging from 1,000 to 1,500 mg/day as monotherapy (n = 928) or in combination with paclitaxel or capecitabine (n = 491). Patients not treated with lapatinib comprised the control group. Dermatologic events included hand-foot syndrome, rash, hair disorder, dry skin, pruritus/urticaria, skin disorder, skin infection, and nail disorder. Overall, 58% of patients receiving lapatinib monotherapy, 74% of patients treated with lapatinib plus paclitaxel or capecitabine, and 53% of patients in the control group developed dermatologic events [17]. Among patients receiving lapatinib monotherapy, 55% experienced grade 1/2 DEs, 3% had grade 3 DEs. No grade 4 DEs were observed. The most common event was rash (43%); all other events occurred in ≤8% of patients. Most dermatologic side effects developed between days 1 and 14 after starting treatment, with a median duration of 29 days. In most patients, rash attributable to lapatinib resolved during treatment, following a temporary interruption in treatment, or after treatment cessation. A total of 3% of DEs led to a dose reduction of lapatinib, 7% resulted in dose interruption, and only 1% led to drug discontinuation. Compared to other ErbB1 inhibitors, lapatinib is associated with fewer and less severe skin events [17].

There are no clear evidence-based recommendations for management of lapatinib-associated rash. However, there is considerable experience in managing dermatologic events from other ErbB1-targeted agents [16]. An effective multidis-

ciplinary management as well as patient education are paramount to improve the symptoms and optimize clinical outcomes by minimizing the need for significant dose reductions or discontinuation. In general, patients should be advised to take appropriate sun protective measures, because sun-exposure can exacerbate rash severity on unprotected areas of the body. In addition, greasy ointments and skin care products that exsicate the skin should be avoided. Instead, frequent moisturizing with alcohol-free emollient creams is recommended.

For the management of skin rash, it is crucial to distinguish between papulopustular and maculopapular eruptions, to determine the extent of body surface area (BSA) affected, and to consider the severity of symptoms (fig. 3 and 4) [18]. Patients with less than 50% BSA and symptoms that do not affect activities of daily living can be treated with topical medications. If more than 50% BSA is affected, lapatinib and chemotherapy should be discontinued, and topical therapy should be given. Topical retinoids, like the antiacne medication tretinoin, are generally not recommended, because rash seen with lapatinib has a different pathophysiology than acne vulgaris [3]. Referral to a dermatologist is recommended if the skin toxicity does not improve within 1–2 weeks of treatment, or if the patient is severely symptomatic [16].

Cardiac Function and Clinical Management

Because of the cardiac toxicity associated with trastuzumab [19, 20], Perez et al. [21] analyzed the cardiac safety of lapatinib using prospective data collected in 44 clinical phase I, II,

and III studies. These data showed a very low rate of symptomatic CHF (0.2%) or asymptomatic cardiac events (1.4%) [21]. None of the 53 asymptomatic patients received cardiac-related treatment; no cardiac deaths were attributed to lapatinib. As concluded by the authors, this review of data from 44 clinical studies revealed low levels of cardiotoxicity for lapatinib [21]. However, given the similarities between trastuzumab- and lapatinib-induced cardiac toxicity, the cardiac safety consensus guidelines for the adjuvant use of trastuzumab of the Cardiac Guidelines Consensus Committee can serve as a basis also for patients on lapatinib therapy [3, 22]. Before initiating lapatinib, the baseline LVEF evaluated by MUGA scan or echocardiography should be $\geq 50\%$. Subsequent cardiac evaluations are recommended, using the same method as in the baseline evaluation [22]. Lapatinib administration should generally be avoided in patients with a subnormal LVEF.

Drug Interactions

The elimination of lapatinib occurs through hepatic metabolism primarily through cytochrome P450 (CYP)3A4 and excretion in feces [3]. Lapatinib inhibits CYP3A4 and CYP2C8 in vitro at clinically relevant concentrations [23]. Therefore, caution should be exercised when dosing lapatinib concurrently with medications with narrow therapeutic windows that are substrates of CYP3A4 or CYP2C8 (table 1) [3, 23]. Lapatinib undergoes extensive metabolism by CYP3A4. Concomitant administration of inducers or strong inhibitors of CYP3A4 significantly alter lapatinib concentrations (table 1) and should be avoided [23]. Antacids that modify gastric pH may affect the absorption of lapatinib and should generally be avoided for 1 h before and after lapatinib dosing.

Disclosure Statement

The author was a speaker and contributor to the meeting 'ErbB2 (HER2)-positives Mammakarzinom; 2. Münchner Brustkrebs-Symposium Update 2009', 23/24 October 2009 in Munich, sponsored by GlaxoSmithKline

References

- O'Keefe E, Battin T, Payne T Jr: Epidermal growth factor receptor in human epidermal cells: direct demonstration in cultured cells. *J Invest Dermatol* 1982;78:482–487.
- Harandi A, Zaida A, Stocker AM, Laber D: Clinical efficacy and toxicity of anti-EGFR therapy in common cancers. *J Oncol* 2009; Epub ahead of print.
- Moy B, Goss PE: Lapatinib-associated toxicity and practical management recommendations. *Oncologist* 2007;12:756–765.
- Geyer CE, Forster J, Lindquist D, et al.: Lapatinib plus capecitabine for HER-2-positive advanced breast Cancer. *N Engl J Med* 2006;355:2733–2743.
- Di Leo A, Gomez HL, Aziz Z, et al.: Phase III, double-blind, randomized study comparing lapatinib plus paclitaxel with placebo plus paclitaxel as first-line treatment for metastatic breast cancer. *J Clin Oncol* 2008;26:5544–5552.
- Crown JP, Burris HA, Jones S, et al.: Safety and tolerability of lapatinib in combination with taxanes (T) in patients with breast cancer (BC). *J Clin Oncol* 2007;25(suppl):38s, abstr 1027.
- Jones SF, Burris HA 3rd, Yardley DA, et al.: Lapatinib (an oral dual kinase inhibitor) plus weekly or every 3 week paclitaxel. 27th Annual San Antonio Breast Cancer Symposium 2004;abstr 1069.
- Crown JP, Burris HA 3rd, Boyle F, et al.: Pooled analysis of diarrhea events in patients with cancer treated with lapatinib. *Breast Cancer Res Treat* 2008;112:317–325.
- Arbuckle RB, Huber SL, Zacker C: The consequences of diarrhea occurring during chemotherapy for colorectal cancer: a retrospective study. *Oncologist* 2000;5:250–259.
- Benson AB, Ajani JA, Catalano RB: Recommended guidelines for treatment of cancer treatment-induced diarrhea. *J Clin Oncol* 2004;22:2918–26.
- Cascinu S, Barni S, Labianca R: Evaluation of factors influencing 5-fluorouracil-induced diarrhea in colorectal cancer patients. An Italian Group for the Study of Digestive Tract Cancer study. *Support Care Cancer* 1997;5:314–317.
- Rothenberg ML, Meropol NJ, Poplin EA: Mortality associated with irinotecan plus bolus fluorouracil/leucovorin: summary findings of an independent panel. *J Clin Oncol* 2010;19:3801–3807.
- Rosenoff S: Octreotide LAR resolves severe chemotherapy-induced diarrhea and allows continuation of full-dose therapy. *Proc Am Soc Oncol* 2003;22:778(abstr 3126).
- Wadler S, Benson AB, Engelking C: Recommended guidelines for the treatment of chemotherapy-induced diarrhea. *J Clin Oncol* 1998;16:3169–3178.
- Segaert S, Van Cutsem E: Clinical signs, pathophysiology and management of skin toxicity during therapy with epidermal growth factor receptor inhibitors. *Ann Oncol* 2005;16:1425–1433.
- Melosky B, Burkes R, Rayson D, Alcindor T, Shear N, Lacouture M: Management of skin rash during EGFR-targeted monoclonal antibody treatment for gastrointestinal malignancies: Canadian recommendations. *Curr Oncol* 2009;16:16–26.
- Lacouture ME, Laabs SM, Koehler M, et al.: Analysis of dermatologic events in patients with cancer treated with lapatinib. *Breast Cancer Res Treat* 2009;114:485–493.
- Moy B and Goss PE: Lapatinib associated toxicity and practical management recommendations. *Oncologist* 2007;12:756–765.
- Perez EA: Cardiac toxicity of ErbB2-targeted therapies: what do we know? *Clin Breast Cancer* 2008;8(suppl 3):S114.
- Slamon DJ, Leyland-Jones B, Shak S, et al.: Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 2001;344:783–792.
- Perez EA, Koehler M, Byrne J, Preston AJ, Rappold E, Ewer MS: Cardiac safety of lapatinib: pooled analysis of 3689 patients enrolled in clinical trials. *Mayo Clin Proc* 2008;83:679–686.
- Ewer MS, Perez EA, Baselga J, et al.: Cardiac safety guidelines for the adjuvant use of trastuzumab (Herceptin) in HER2-positive early breast cancer. *Breast* 2007;16(suppl 1):S63.
- Tyverb® full prescribing information, August 2009; us.gsk.com/products/assets/us_tyverb.pdf.