Lapatinib Side-Effect Management

Cynthia Frankel, RN, OCN®, and Frances M. Palmieri, RN, MSN, OCN®, CCRP

Lapatinib is an oral dual tyrosine kinase inhibitor targeting epidermal growth factor receptor and HER2. Diarrhea and dermatologic adverse events are reported commonly by patients treated with lapatinib. Diarrhea can range from mild to severe based on the agents used in combination with lapatinib. The adverse events may diminish quality of life, reduce treatment adherence, and lead to discontinuation of therapy. Consequently, proactive management of diarrhea is crucial, especially in patients receiving lapatinib in combination with other agents that also cause diarrhea. As the utility of lapatinib expands, crucial proactive diarrhea-management and dose-reduction strategies are evolving to decrease the likelihood of grade 3 or 4 toxicity. With regard to dermatologic adverse events, most are mild to moderate in severity, are of limited duration, and frequently do not require treatment intervention. However, in some patients, management of dermatologic adverse events is of great importance. This article reviews data regarding diarrhea and dermatologic adverse events in patients treated with lapatinib and summarizes the key role that oncology nurses play in educating patients about the potential for adverse events and the importance of preventive measures, ongoing surveillance, appropriate treatment, and dose reductions.

At a Glance

- Diarrhea and dermatologic adverse events are among the most common toxicities in patients treated with lapatinib alone or in combination.
- Most diarrhea and dermatologic adverse events in patients treated with lapatinib are mild to moderate in severity, are of limited duration, and do not require treatment interruption.
- Proactive management of diarrhea is crucial, especially in patients receiving lapatinib in combination with other agents that also cause diarrhea.

Cynthia Frankel, RN, OCN®, is the director of breast cancer research and development at Memorial Healthcare System in Hollywood, FL; and Frances M. Palmieri, RN, MSN, OCN®, CCRP, is the manager of the Breast Clinic and Breast Cancer Program at the Mayo Clinic in Jacksonville, FL. Mention of specific products and opinions related to those products do not indicate or imply endorsement by the Clinical Journal of Oncology Nursing or the Oncology Nursing Society. (First submission January 2009. Revision submitted April 2009. Accepted for publication April 18, 2009.)

Digital Object Identifier:10.1188/10.CJON.223-233
Discusses appropriate strategies that may be employed for the assessment and management of diarrhea and dermatologic adverse events.

Diarrhea

Diarrhea induced by cancer therapy is a significant source of morbidity and mortality and can negatively affect quality of life (Arbuckle, Huber, & Zacker, 2000; Arnold et al., 2005; Benson et al., 2004; Sharma, Tobin, & Clarke, 2005). Loss of fluids and electrolytes associated with persistent or severe diarrhea can result in life-threatening complications, including dehydration, renal insufficiency, and electrolyte imbalances, and may contribute to cardiovascular morbidity. Patients with therapy-induced neutropenia who develop diarrhea are at increased risk of infectious complications, including sepsis (Sharma et al., 2005). Diarrhea also can result in treatment modifications, including dose reductions, delays, and discontinuation. About 25% of patients treated with EGFR or HER2 monoclonal antibodies (e.g., cetuximab, trastuzumab), 40% of patients treated with taxanes (e.g., paclitaxel, docetaxel), 50% of patients treated with EGFR tyrosine kinase inhibitors (e.g., gefitinib, erlotinib), and 60% of patients treated with capecitabine experience diarrhea. The incidence and severity of diarrhea generally are higher when the agents are administered as combination therapy (AstraZeneca Pharmaceuticals LP, 2005; Bristol-Myers Squibb Co., 2003; Genentech Inc., 2008; ImClone Systems Inc., 2007; OSI Pharmaceuticals, Inc., 2007; Roche Pharmaceuticals, 2006; sanofi-aventis, 2006).

Diarrhea and Lapatinib

Diarrhea is a common adverse event in patients treated with lapatinib. Among 2,093 patients with solid tumors, an increased frequency of diarrhea was reported in patients treated with lapatinib monotherapy, lapatinib plus capecitabine, and lapatinib plus taxanes (Crown et al., 2008) (see Figure 1). About 40% of patients treated with lapatinib alone or in combination experienced a first diarrhea event within six days of treatment initiation, and the median duration of diarrhea events was seven to nine days. Most diarrhea events (80% or more) resolved without treatment intervention. Diarrhea events infrequently resulted in treatment interruption (9%), dose adjustment (3%), or treatment discontinuation (2%) (Crown et al., 2008). Older adult patients (70 years or older) experienced more diarrhea events compared with younger patients; however, the onset, severity, and resolution of diarrhea events were similar in older adult patients and in patients younger than 70 years.

Preliminary results have been reported from two adjuvant studies that evaluated the safety of paclitaxel-trastuzumab-lapatinib (PTL) combination therapy after doxorubicin and cyclophosphamide (AC) in patients with HER2-positive breast cancer (Dang et al., 2008; Johnson et al., 2008). In a pilot study of dose-dense AC followed by PTL, grade 3 diarrhea was reported in 12 of 38 patients (32%) who received lapatinib at an initial dose of 1,000 mg per day (Dang et al., 2008). Lapatinib dose reduction was required in 50% of patients. The incidence of grade 3 diarrhea in this study was substantially higher than that previously reported with lapatinib-based therapy (less than 10% as monotherapy or combination therapy) (Crown et al., 2008). The second study (Mayo Clinic Cancer Research Consortium study RC0639), ongoing at the time of this article, enacted lapatinib dose modification because of an increased incidence of grade 3 or 4 diarrhea observed on administering the PTL regimen after four cycles of AC (Johnson et al., 2008). More aggressive treatment guidelines have been adopted to address this toxicity, including administration of a reduced dose of lapatinib (750 mg per day) at the start of the PTL regimen. After the PTL regimen is completed, the starting dose of lapatinib (1,000 mg per day) resumes during subsequent treatment with lapatinib plus trastuzumab.

Although no pharmacokinetic interactions have been observed with most chemotherapy agents, a previous study reported that coadministration of lapatinib and paclitaxel resulted in an approximately 20% increase in systemic exposure to both agents (EGF10009) (Burris, in press). This finding suggests a possible increase in the potential for diarrhea in patients who receive combination therapy with the two agents.

During the early clinical development of lapatinib, high rates of grade 3 diarrhea (30%) were reported in a study that combined lapatinib with weekly paclitaxel but did not include proactive diarrhea management (Cristofanilli et al., 2006). The incidence of grade 3 or higher diarrhea was lower (5%) when patients were actively managed for diarrhea events. In a phase III study of lapatinib plus paclitaxel every three weeks that did not include proactive diarrhea management at study inception, the incidence of grade 3 or higher diarrhea was 15% and several patients developed serious diarrhea-related complications, including three who died as a result of septic shock (Di Leo et al., 2008). The severity of gastrointestinal complications declined substantially after the introduction of proactive diarrhea-management strategies, and no additional deaths occurred related to gastrointestinal complications.
Mechanism of Gastrointestinal Toxicity

Although not entirely understood, diarrhea is believed to stem from loss of intestinal absorption as a result of chemotherapy-mediated injury to epithelial cells. Previous studies have demonstrated that chemotherapy agents exert cytotoxic effects on the rapidly dividing crypt cells in the intestinal epithelium, which may result in a relative loss of intestinal-absorptive capacity compared with secretory capacity (Baskerville & Batter-Hatton, 1977; de Roy van Zuidewijn, Schillings, Wobbes, Hendriks, & de Boer, 1992). Cytotoxic destruction or augmentation of enzymes involved in the digestion of proteins and carbohydrates also may alter osmotic gradients in the gut and contribute to decreased reabsorption and increased secretion of fluid and electrolytes in the stool (Wadler, Haynes, & Wiernik, 1995). In contrast, lapatinib is not a cytotoxic agent and should not adversely affect the integrity of the intestinal epithelium. Preliminary studies demonstrated that the incidence of diarrhea in patients treated with lapatinib was related to the oral dose but not the serum concentration of lapatinib, suggesting that lapatinib toxicity may evolve from a local effect on the intestinal epithelium. However, the mechanism is unknown (Burris et al., 2005). A study is planned to further investigate the mechanism of lapatinib-associated diarrhea.

Assessment and Proactive Management of Diarrhea in Patients Treated With Lapatinib

When lapatinib is administered alone or in combination with cytotoxic agents, the onset of diarrhea should be anticipated. No clinical guidelines are designed specifically for the management of lapatinib-associated diarrhea. Instead, practical management recommendations are based on the American Society of Clinical Oncology (ASCO) guidelines for the management of cancer treatment-induced diarrhea (Benson et al., 2004). According to the guidelines, patients should be interviewed to assess the presence and severity of diarrhea. Patients with diarrhea should receive appropriate dietary and pharmacologic interventions depending on whether their diarrhea is classified as uncomplicated or complicated (see Figure 2). Patients enrolled in ongoing adjuvant clinical studies using lapatinib as monotherapy or combination therapy should be monitored as outlined in the study protocols.

**Patient assessment:** Patient education is critical in managing diarrhea. Detailed, directed assessment of the patient for signs and symptoms of diarrhea will assist the patient in notifying the nurse or physician and receiving early and appropriate intervention. Before the start of treatment, baseline bowel habits must be recorded to assess changes during treatment. A diary card can be provided to patients to record daily diarrhea experiences. Instruct patients how to accurately complete the diary and about the importance of returning it for review at each clinic visit. During each visit, review the diary and assess the number and composition of stools relative to baseline, the duration and severity of diarrhea symptoms, lapatinib dosing, and the use of antidiarrheal medications. Some patients may be reluctant to report diarrhea events because they fear that it will result in interruption or discontinuation of therapy. Therefore, asking specific questions will assist in obtaining accurate information. Explain to patients before the start of treatment that adverse events and dose modifications are common and that accurate reporting of diarrhea events will result in the safest and most effective therapy. During the physical examination, perform an examination of the abdomen and rectal area and record weight and vital signs.

**Dosage and administration of lapatinib:** Verify that the appropriate dose and administration procedure are being maintained in patients being treated with lapatinib who present with diarrhea. The approved dose of lapatinib is 1,250 mg per day (five 250 mg tablets per day) taken continuously in combination with capecitabine 2,000 mg/m² per day during days 1-14 of each 21-day treatment cycle (GlaxoSmithKline, 2008). Lapatinib is administered as a once-daily dose at least one hour before or one hour after a meal; dividing the daily dose is not recommended. In addition, lapatinib tablets should not be crushed, split, or dissolved. Capecitabine is administered orally in two divided doses approximately 12 hours apart and is taken with food or within 30 minutes after food. If a day’s dose is missed, the patient should be instructed not to double the dose the next day. Strong CYP3A4 inhibitors and inducers are to be avoided (see Figure 3).

Patients should be instructed not to take lapatinib with food because of the highly unpredictable effect of food on lapatinib bioavailability. Administering lapatinib without food is the most effective way to reliably deliver a consistent dose.

**Assessment of the severity and complexity of diarrhea:** Diarrhea is defined by the National Cancer Institute (2006) in terms of the number of bowel movements per day above baseline (see Figure 4). According to the ASCO treatment guidelines, the most appropriate intervention for cancer treatment-induced diarrhea is based on the patient’s symptoms, which are classified as “uncomplicated” or “complicated” (Benson et al., 2004). Patients with grade 1 or 2 diarrhea with no other complicating signs or symptoms are classified as uncomplicated and managed conservatively. Patients with grade 1 or 2 diarrhea and additional risk factors are classified as complicated; such patients need further evaluation and may require more aggressive management. Patients with grade 3 or 4 diarrhea are classified as complicated and always require aggressive management.

**Management of uncomplicated diarrhea:** Management of uncomplicated diarrhea consists of dietary modification, maintenance of adequate fluid intake, and appropriate pharmacologic intervention. At the onset of grade 1 or 2 diarrhea, instruct patients to stop consuming lactose-containing products because of the potential for lactose intolerance. Patients should be advised to follow the BRAT (bananas, rice, applesauce, and toast) diet until symptoms resolve (Benson et al., 2004). This diet may be expanded slowly to include readily digestible foods (e.g., lean meats, scrambled eggs) as tolerated. Vegetables such as cabbage, Brussels sprouts, and broccoli should not be consumed because of the risk of increased abdominal cramping and bloating. Patients also should be advised to avoid fried, fatty, and spicy foods.

Emphasize to patients that food intake is of minimal importance during acute episodes of diarrhea but that maintenance of adequate hydration is critical. Clarify that patients must drink 8–10 glasses of clear liquids each day, which should include not only water but also clear fluids containing salt and sugar.
Figure 2. Algorithm for Assessment, Management, and Treatment of Lapatinib-Associated Diarrhea

**Evaluate**
- Obtain history of onset and duration of diarrhea.
- Describe number of stool and stool composition.
- Assess patient for fever, dizziness, abdominal pain or cramping, and weakness.
- Medications profile
- Dietary profile

**Uncomplicated**
CTC grade 1 or 2 diarrhea with no complicating signs or symptoms

**Complicated**
CTC grades 3 or 4 diarrhea or grade 1 or 2 with one or more of these signs or symptoms:
- Cramping
- Nausea or vomiting (≥ grade 2)
- Decreased performance status
- Fever
- Sepsis
- Neutropenia
- Frank bleeding
- Dehydration

**Management**
- Discontinue lactose products and alcohol.
- Drink 8–10 large glasses of clear liquids per day.
- Eat frequent small meals (e.g., bananas, rice, applesauce, toast).
- Record number of stools and report life-threatening symptoms (dizziness or fever).
- Grade 2 diarrhea: Hold cytotoxic chemotherapy and consider lapatinib dose reduction until symptoms resolve.

**Treatment**
- Administer standard dose of loperamide after every unformed stool.
- Consider clinical trial.

Diarrhea resolving
- Continue instruction for dietary modification.
- Gradually add solid food to eat.
- Discontinue loperamide after 12-hour diarrhea-free interval.

Diarrhea resolved
- Continue instruction for dietary modification.
- Gradually add solid food to eat.
- Discontinue loperamide after 12-hour diarrhea-free interval.

Diarrhea unresolved
- Reassess 12–24 hours later.

Persistent diarrhea (grade 1 or 2): loperamide every two hours or diphenoxylate and atropine (two tablets) three or four times per day. Start oral antibiotics.

Diarrhea unresolved
- Reassess 12–24 hours later.

Persistent diarrhea (grade 1 or 2)
- Evaluate in office or outpatient center.
  - Perform stool workup.
  - Check complete blood count and electrolytes.
  - Perform abdominal examination.
  - Replace fluids and electrolytes.
  - Consider complete bowel rest for 12–24 hours (nothing by mouth).
  - Discontinue loperamide and begin diphenoxylate and atropine or octreotide.
  - Consider lapatinib dose reduction or discontinue lapatinib based on tolerance.

Admit to hospital
- Administer octreotide.
- Start IV fluids and antibiotics.
- Stool workup, complete blood count, and electrolyte profile
- Discontinue chemotherapy until symptoms resolve; restart chemotherapy at reduced dose.

CTC—National Cancer Institute Common Toxicity Criteria

**Figure 2. Algorithm for Assessment, Management, and Treatment of Lapatinib-Associated Diarrhea**

Dermatologic adverse events are very common with EGFR inhibitors and typically occur in more than 50% of patients treated with the agents (Agero et al., 2006; Perez-Soler & Saltz, 2005). Dermatologic adverse events include xerosis (dry skin), pruritus (itching), paronychia (nail and periungual alterations), abnormalities of hair growth (alopecia of the scalp, trichomegaly of the eyelashes, and hypertrichosis of the face), and telangiectasia (dilation of small blood vessels) (Lacouture & Lai, 2006; Segaert & Van Cutsem, 2005). However, the most commonly reported dermatologic event is a papulopustular reaction described as acne, acniform rash, or rash (Busam et al., 2001). The rash usually develops on the face or upper trunk and peaks in severity associated with EGFR inhibitors appears to be dose dependent (Bruno, Mass, & Jones, 2003) and, in general, tends to occur more frequently and with greater severity in patients treated with anti-EGFR monoclonal antibodies versus small-molecule tyrosine kinase inhibitors (Sipples, 2006). A number of studies also have suggested that the development of skin rash may be a useful surrogate marker of clinical efficacy (Burtness, Goldwasser, Flood, Mattar, & Forastiere, 2005; Clarke, Perez-Soler, & Siu, 2003; Cunningham et al., 2004; Perez-Soler, 2006; Perez-Soler et al., 2004). This relationship has been studied most extensively for the EGFR inhibitor erlotinib; several clinical studies have demonstrated a positive correlation between the severity of skin rash and tumor response or survival in patients treated with erlotinib (Clarke et al., 2003; Perez-Soler, 2006; Perez-Soler et al., 2004). Similar relationships also have been established for cetuximab and gefitinib (Burtness et al., 2005; Cunningham et al., 2004; Perez-Soler, 2006).

Dermatologic adverse events include xerosis (dry skin), pruritus (itching), paronychia (nail and periungual alterations), abnormalities of hair growth (alopecia of the scalp, trichomegaly of the eyelashes, and hypertrichosis of the face), and telangiectasia (dilation of small blood vessels) (Lacouture & Lai, 2006; Segaert & Van Cutsem, 2005). However, the most commonly reported dermatologic event is a papulopustular reaction described as acne, acniform rash, or rash (Busam et al., 2001). The rash usually develops on the face or upper trunk and peaks in severity associated with EGFR inhibitors appears to be dose dependent (Bruno, Mass, & Jones, 2003) and, in general, tends to occur more frequently and with greater severity in patients treated with anti-EGFR monoclonal antibodies versus small-molecule tyrosine kinase inhibitors (Sipples, 2006). A number of studies also have suggested that the development of skin rash may be a useful surrogate marker of clinical efficacy (Burtness, Goldwasser, Flood, Mattar, & Forastiere, 2005; Clarke, Perez-Soler, & Siu, 2003; Cunningham et al., 2004; Perez-Soler, 2006; Perez-Soler et al., 2004). This relationship has been studied most extensively for the EGFR inhibitor erlotinib; several clinical studies have demonstrated a positive correlation between the severity of skin rash and tumor response or survival in patients treated with erlotinib (Clarke et al., 2003; Perez-Soler, 2006; Perez-Soler et al., 2004). Similar relationships also have been established for cetuximab and gefitinib (Burtness et al., 2005; Cunningham et al., 2004; Perez-Soler, 2006).

**Figure 3. CYP3A4 Inhibitors and Inducers to Avoid in Combination With Lapatinib**

*Note. Based on information from GlaxoSmithKline, 2008.*
keratinocyte apoptosis and tissue damage (Kari, Chan, Rocha de Quadros, & Rodeck, 2003). This tissue damage is believed to account for the majority of dermatologic adverse events, including tenderness, papulopustules, and periungual inflammation (Lacouture & Lai, 2006).

In Patients Treated With Lapatinib

Dermatologic adverse events are among the most commonly reported side effects in patients treated with lapatinib. In a pooled analysis of 2,093 patients with advanced or metastatic cancer, dermatologic adverse events were reported in 58% of patients treated with lapatinib monotherapy and in 74% of patients treated with lapatinib plus either capecitabine or paclitaxel compared with 53% of patients not receiving lapatinib therapy (Lacouture et al., 2008). Most were mild to moderate in severity (approximately 60%); grade 3 events occurred infrequently (6%), and no grade 4 events were reported. Rash was the most common dermatologic adverse event in patients receiving lapatinib (43%; grade 3, 4%). In contrast to other EGFR inhibitors (e.g., gefitinib, cetuximab), rash tended to localize more frequently on the trunk and infrequently on the face (see Figure 5). Based on currently available evidence, the incidence and severity of rash in patients treated with lapatinib do not appear to correlate with lapatinib plasma concentrations or clinical response. The incidence of hand-foot syndrome was higher in patients treated with lapatinib plus capecitabine (53%) compared with patients treated with capecitabine monotherapy (51%) or lapatinib monotherapy (< 1%); therefore, hand-foot syndrome most likely is related to capecitabine rather than lapatinib (Roche Pharmaceuticals, 2006). Approximately 40% of dermatologic adverse events occurred during the first two weeks of lapatinib treatment, and the median duration of the events was 29 days. Most resolved without treatment intervention (88%); dose interruption occurred in 7% of patients, adjustment in 3%, and discontinuation in 1%.

Management

Education regarding possible dermatologic adverse events should occur before the start of lapatinib therapy. Emphasize that not all patients experience dermatologic adverse events and that the events are temporary (i.e., self-limiting) and tend to diminish in intensity with continued lapatinib exposure. Discuss effective strategies to prevent and manage the physical and psychological symptoms associated with dermatologic adverse events, and provide a realistic appraisal regarding the potential for success with these approaches. Highlight the importance of
early treatment intervention and encourage patients to contact their healthcare providers if they develop adverse events that appear to be serious, continue for a prolonged period, are intolerable, or interfere with daily activities. Handouts may enhance discussion with patients; include details of print and online resources that provide further information.

**Risk Reduction**

The primary goal of any program designed to manage dermatologic adverse events is to proactively reduce the risk for their development. On initiation of therapy, patients are advised to use lukewarm water, avoid soap, and moisturize dry areas of the skin twice daily with a thick, alcohol-free emollient. Because skin rash tends to occur more frequently in photoexposed areas of the skin, encourage patients to minimize exposure to sunlight and use a broad-spectrum sunscreen with a sun protection factor of at least 30. Physical sunscreens, containing zinc oxide or titanium dioxide, are preferred over chemical sunscreens and are applied one or two hours before sun exposure and repeated when sun exposure is prolonged.

**Assessment and Treatment**

Very few controlled clinical studies have investigated treatment options for EGFR inhibitor-associated dermatologic adverse events; consequently, no evidence-based treatment recommendations have been established, and many of the more widely used treatment interventions are based on anecdotal reports. In general, the treatment intervention is tailored to the type and severity of the dermatologic adverse event. The severity of these events is usually classified according to the NCI-CTC criteria (National Cancer Institute, 2006).

Lapatinib treatment may be interrupted for as long as 14 days in patients with grade 3 or 4 dermatologic reactions. Consider lapatinib interruption for grade 2 dermatologic adverse events that do not improve after two weeks of therapy and significantly decrease quality of life. Rechallenge at 1,250 mg per day may be appropriate for patients with grade 3 or 4 dermatologic adverse events who recover to grade 1 or 2 within 14 days after interrupting lapatinib therapy. Lapatinib must be discontinued permanently if a grade 3 or 4 dermatologic adverse event is intolerable to the patient despite recommended treatment interventions. In addition, lapatinib should be discontinued immediately and permanently in the event of a life-threatening event (e.g., anaphylaxis, Stevens-Johnson syndrome, toxic epidermal necrolysis).

Most dermatologic adverse events in patients treated with lapatinib are mild to moderate in severity and of limited duration. Most events do not require lapatinib dose adjustments and are managed with established standard therapeutic regimens used to treat similar dermatologic conditions. Dermatology consultation is encouraged for patients with extensive or symptomatic grade 3 or 4 dermatologic adverse events; those with chronic, persistent, or recurring lower-grade events; and in cases where physicians require another opinion regarding the treatment course of action (Purdom & Ohinata, 2007). In general, proactive management of such events is recommended, and inter-

---

**Figure 6. Algorithm for Management of Lapatinib-Associated Skin Rash**


<table>
<thead>
<tr>
<th>Dermatologic reaction</th>
<th>Maculopapular</th>
<th>Papulopustular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 50% BSA or symptomatic, not affecting activities of daily living</td>
<td><strong>Hold treatment.</strong></td>
<td><strong>Hold treatment.</strong></td>
</tr>
<tr>
<td><strong>Topical corticosteroids</strong></td>
<td><strong>Topical corticosteroids</strong></td>
<td><strong>Topical corticosteroids</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Re-evaluate in two weeks for rechallenge.</strong></td>
<td><strong>Re-evaluate in two weeks.</strong></td>
</tr>
</tbody>
</table>

| Less than 50% BSA; asymptomatic | **Continue treatment.** | **Continue treatment.** |
| **Topical corticosteroids** | **Topical corticosteroids** | **Oral semisynthetic tetracyclines** |
| | | **Re-evaluate in two weeks.** |

| 50% or more BSA or symptomatic | **Continue treatment.** | **Continue treatment.** |
| **Topical corticosteroids** | **Topical corticosteroids** | **Oral semisynthetic tetracyclines** |
| | | **Re-evaluate in two weeks.** |

| Improvement in BSA involvement or symptoms | **Resume treatment.** |
| **Continue treatment.** |

**BSA—body surface area**
ventions should be tailored toward the type and severity of the dermatologic adverse event.

**Rash:** Application of topical corticosteroids (e.g., hydrocortisone 1% or 2.5% cream) may provide symptomatic relief for patients with rash (see Figure 6). Culture-driven, topical, or systemic antibiotics are indicated for superinfected lesions. Administration of oral corticosteroids for a limited period (maximum of 14 days) may help patients to remain on treatment. Re-evaluate patient response to treatment after two weeks.

**Paronychia:** Paronychia is a painful inflammation of the tissue around the fingernails and toenails that may render nail folds susceptible to infection (see Figure 7). Patients with paronychia are encouraged to use a daily emollient (ammonium lactate 12% cream or urea 40% cream) to prevent skin fissuring (see Figure 8) (Lacouture, Cotliar, & Mitchell, 2007). If edema or erythema is present, a high-potency topical corticosteroid (e.g., clobetasol ointment, fluandrenolide adhesive steroid tape) may be applied. Cultures should be obtained from infected lesions to determine appropriate systemic antibiotic therapy. Soaking fingertips in a solution of white vinegar and water (1:10) for five minutes per day also may be beneficial because of its bactericidal effect. If these interventions fail, intralesional corticosteroids (triamcinolone 10 mg/ml, 0.02 ml per lateral nail fold) or removal of the nail plate may be required.

**Xerosis and pruritus:** Patients are advised to apply highly occlusive emollients to prevent and alleviate xerosis or dry skin, except in regions where their application may further exacerbate lapatinib-associated skin rash (Lacouture et al., 2007). If no signs of skin inflammation exist (e.g., redness, sensitivity), the emollients may be mixed with 10% to 20% urea or 12% lactic acid to aid desquamation. Recommendations for care of sensitive skin and the use of hypoallergenic products that lack potential irritants and fragrances are advisable.

Pruritus that arises from severe xerosis can be a difficult, chronic condition that, if left untreated, can result in widespread skin erosions and an increased risk of secondary skin infection. Pruritus may be treated with oral antihistamines (e.g., diphenhydramine, cetirizine, loratadine, hydroxyzine) (Lacouture et al., 2007). Pregabalin (75–100 mg twice daily) has been reported to be effective in the treatment of pruritus associated with EGFR inhibitors that fails to respond to oral antihistamines.

**Hair abnormalities:** No agents are known to be effective in the treatment of alopecia associated with the use of EGFR inhibitors; however, some patients have reported spontaneous improvement in hair growth after several months of continuous EGFR inhibitor therapy (Lacouture et al., 2007). Topical corticosteroids may relieve inflammation and papulopustules associated with the initial development of alopecia, thereby minimizing follicular inflammation and resultant hair loss. Hypertrichosis or excessive hair growth on the face may be alleviated via depilatory methods such as electrolysis and laser hair removal. Trichomegaly or long eyelashes and eyebrows may be alleviated with trimming.

**Management of Psychological Sequelae With Dermatologic Events**

Patients may benefit from cognitive behavioral strategies (e.g., guided imagery) for the management of the physical discomfort...
associated with dermatologic adverse events; cognitive behavioral therapy also may be useful in treating anxiety and depression that may arise from lack of social interaction (Purdom & Ohinata, 2007). Symptom reframing, which involves teaching patients that dermatologic adverse events should be anticipated and are common with treatment, may improve their ability to cope with the physical discomfort and effects on quality of life. Urge patients to conceptualize dermatologic adverse events as a reminder that they are actively coping with their cancer by undergoing treatment. Interpreting toxicities in a constructive manner (e.g., treatment is beneficial) as opposed to a negative manner (e.g., a reminder that they have cancer) will reduce the intensity of the physical discomfort and the adverse effects on quality of life.

**Conclusion**

Lapatinib is effective and well tolerated when administered as monotherapy or combination therapy to patients with HER2-positive breast cancer or other solid tumors. Diarrhea and dermatologic toxicities are among the most frequently reported adverse events in patients treated with lapatinib. Notably, diarrhea and dermatologic adverse events also have been reported in patients treated with other agents, including EGFR and HER2 monoclonal antibodies, EGFR tyrosine kinase inhibitors, capecitabine, and taxanes. Although rarely severe, diarrhea and dermatologic adverse events have the potential to impair quality of life and cause patients to become less adherent with lapatinib therapy. Consequently, proactive management of diarrhea and dermatologic adverse events is important, especially in patients receiving lapatinib in combination with paclitaxel or capecitabine. Application of the practical management recommendations developed for cancer therapy-induced diarrhea and EGFR-associated dermatologic toxicities is advisable in patients receiving lapatinib therapy. Oncology nurses should be aware of the potential diarrhea and dermatologic adverse events associated with lapatinib and should counsel patients about the importance of prevention, early detection, and appropriate treatment intervention. Early identification and rapid intervention may prevent the development of severe adverse events and avoid lapatinib dose reduction, interruption, or discontinuation. Effective communication between nurses and patients is crucial in ensuring that patients continue to gain uninterrupted benefit from lapatinib therapy.

The authors take full responsibility for the content of the article but thank Anne Marie Fitzmaurice, PhD, of ProEd Communication, Inc., supported by GlaxoSmithKline, for medical writing support. The content of this article has been reviewed by independent peer reviewers to ensure that it is balanced, objective, and free from commercial bias. No financial relationships relevant to the content of this article have been disclosed by the independent peer reviewers or editorial staff.

**Author Contact:** Cynthia Frankel, RN, OCN®, can be reached at cfrankel@mhs.net, with copy to editor at CJIONEditor@ons.org.

**References**


Cristofanilli, M., Boussen, H., Baselga, J., Lluch, A., Ben Ayed, F.,...


Acneform rash. *Seminars in Oncology Nursing*, 22(1, Suppl. 1), 28–34. doi: 10.1016/j.soncn.2006.01.013

