More cancer therapies are being administered via an oral route. This paradigm shift in providing cancer treatment has been met with both excitement and significant challenges for oncology practitioners. Multiple factors can impact the ability for patients to initiate and stay on oral cancer therapy. A major factor in patient adherence with oral cancer therapies is management of side effects. Side effects from therapy not only have a negative impact on a patient’s quality of life but also can cause serious complications. In addition, they can impact the patient’s ability to stay on therapy at optimal doses. New strategies must be designed for educating patients and caregivers, as well as for patient management and follow-up. When side effects are not managed appropriately, patients are less likely to want or be able to adhere to established treatment plans. This article explores several challenges related to the use of oral cancer therapies, with a focus on side effects seen with various classes of new targeted agents. Evidence-based practice strategies and areas in need of additional exploration and research are reviewed.

Issues Impacting Successful Use of Oral Cancer Therapies

Although the prevalence of oral oncology agents is expanding rapidly, many factors impact their successful use. With patients taking these medications away from the clinic, the healthcare team may not be aware of many of these issues. Four areas that impact the use of oral oncology agents include financial issues, patient education, adherence issues, and toxicity management.

Financial Issues

Once the prescription is written for an oral cancer agent, the patient may not be able to fill it without obtaining prior authorization from their insurance provider. Oncology practices may not have individuals in place to assist patients with this process. Delays in obtaining a preauthorization can result in patients not having started medication by the time of their next scheduled appointment. Patients may believe the provider has this information and may not contact the provider to share it.

Copay amounts vary widely. With treatment costs of as much as $10,000 a month, a copayment of even 5% can be prohibitive. Patients may choose to decline the prescription and not notify their healthcare provider until their next visit. Delays may occur as assistance programs are sought. Although some pharmaceutical companies offer assistance via the provision of copay assistance cards, these cards typically are not available to patients on Medicare Part D because of government regulations. Patients on Medicare often are dealing with the problem of being in the so-called donut hole, with excessive copays beyond their means (Barefoot, Blecher, & Emery, 2009; Hede, 2009; Maloney & Kagan, 2011).
Patients also may be given reduced quantities (e.g., a two-week supply) despite what has been ordered. Mechanisms must be in place to verify that patients are able to obtain initial and subsequent refills on oral therapies, including whether prescribed quantities are the same as what has been dispensed.

In addition, financial issues occur related to patients abandoning or quitting their oral oncology therapy. For example, patients on Medicare with incomes lower than $40,000 were 20% more likely to abandon their oral cancer therapy than those with incomes exceeding $75,000. The rate of abandonment of oral cancer therapy increased with higher cost sharing and also with increased numbers of concurrent medications (Community Oncology Alliance, 2011).

Patient Education

Patient education is a critical component in the plan of care for patients receiving oral cancer therapies. Although nurses typically are involved in providing patient education, often delivered while the patient is receiving an IV infusion, the clinic nurse may not know that a patient has been given a prescription for a new oral oncology agent. Practices may not have established a mechanism to ensure that the usual educational process takes place when a patient is starting a new oral chemotherapy agent.

Information that has not previously been part of typical patient education but is needed is described in Figure 2. Providing patient education in a variety of formats, including written information, can help patients take oral cancer therapies correctly and promote timely reporting of adverse reactions (Kav et al., 2010).

Drug interactions are common with many of the current targeted therapies. One metabolic pathway frequently affected is the CYP3A4 pathway, which plays a significant role in drug metabolism. Patients taking concomitant medications that are either inhibitors or inducers of this pathway are at risk for problems with cancer therapy metabolism (Barton, 2011). Patients should be instructed not to take any medications (prescribed or over the counter) unless their healthcare provider is aware. Accurate medication reconciliation at the time of each clinic visit is imperative.

If patients have access to a vast number of information sources. Recommending previously reviewed relevant websites can be helpful. Part of effective patient education is to establish open communication with patients that encourages them to share information they have obtained from other sources so that misleading or harmful information can be addressed in a timely fashion.

The process for patient education varies between practices. When patients are given prescriptions for oral cancer medica-

**FIGURE 1. Potential Advantages of Oral Cancer Therapy**

- Easier management of work schedules for employed patients
- Drivers not needed for infusion appointments
- Decreases need for IV access
- Eliminates need for implanted ports
- Potential decrease in clinic visits
- Decrease in time spent in clinic
- More time with family and friends
- Possible increase in exposure of tumor to agent

Adherence Issues

Whether patients take medications as intended can be influenced by many factors. Finances and education, as previously discussed, have the potential to impact adherence. If a patient does not understand the importance or benefit of therapy, adherence can be affected (Barton, 2011).

Several studies have identified factors that affect adherence, as well as strategies to improve patient adherence with oral therapies (Schneider, Hess, & Gosselin, 2011). The literature has shown adherence rates with oral cancer therapies to range from 16%–100% (Given, Spoelstra, & Grant, 2011). Variation includes both under- and overadherence (Ruddy, Mayer, & Partridge, 2009; Spoelstra, Given, Given, & Grant, 2011). Factors that can play a role in patient adherence are shown in Figure 3.

Toxicity Management

The toxicities experienced by patients on oral cancer therapies may play the most important role in patients maintaining optimal doses of therapy. When not managed adequately, side effects can result in dose modifications, interruptions, or discontinuation of treatment. When optimal dosing is not maintained, response can be compromised and patients can experience toxicities from treatment without clinical benefit (Ruddy et al., 2009).

Patients may choose not to report side effects for a variety of reasons. If patients fear being taken off treatment, they may delay reporting therapy-related toxicities. They also may be unable to differentiate side effects exceeding expected adverse events that require reporting (Simchowitz et al., 2010).

A variety of strategies must be used to effectively manage the toxicities associated with oral therapies. Patients and caregivers require an understanding of the goals of therapy, anticipated side effects, and at what point side effects necessitate notifying a member of the healthcare team. Patients also require education on self-care strategies (see Figure 4). Patients should be seen soon after starting a new oral cancer therapy (determined by the individual patient situation) to evaluate for early toxicities and to reinforce prior teaching. That also provides an opportunity to identify and address any questions or concerns with treatment.

**FIGURE 2. Patient Questions Regarding Oral Agent Administration**

- How many pills should be taken per day?
- Are any pills taken at the same time?
- Do I take the pills every day?
- What do I do if I miss a pill?
- Do the pills have to be taken on an empty stomach?
- What do I do if I vomit after taking a pill?
- Do I need to take special precautions with body fluids?
- Do any special handling requirements exist for the pills?
- How do I dispose of unused medications?
Avoid foods that cause increased irritation. Avoid use of alcohol-based mouthwashes. Explain when symptoms need to be reported to healthcare providers. Report sleep disturbances. Have patients obtain antidiarrheal preparations to have at home at 
Suggest diet modifications (e.g., diet of bananas, rice, applesauce, and 
Lack of provider availability 
Inability to obtain financial assistance 
Delays in obtaining refills 
Delays in follow-up after starting treatment 
Avoid activities leading to excessive pressure on feet. Identify current bowel elimination patterns.

Managing Select Toxicities

The various classes of oral cancer agents share common side effects and toxicities (see Figure 5). Although all treatment-related side effects have the potential to alter quality of life and the ability to maintain patients on treatment, the following side effects, including suggestions for their management, will be covered in this article: diarrhea, dermatologic toxicities, mucositis, and fatigue (see Figure 6).

Diarrhea

Chemotherapy has been associated with diarrhea rates ranging from 50%–80% (Muehlbauer et al., 2009). The majority of research pertaining to diarrhea in the oncology patient population has focused on IV chemotherapy. The incidence of diarrhea with oral cancer therapies is completely variable, based on the patient’s typical bowel patterns, individual characteristics, agent used, and other patient comorbidities. Diarrhea has an incidence rate of 27%–87% with tyrosine kinase inhibitor (TKI) therapies; 25% of those reach a grade 3 toxicity level (Appleby, Morrissey, Bellmunt, & Rosenberg, 2011; Hirsch, 2011) (see Table 1).

Although often seen early after the start of treatment, diarrhea can begin after months of therapy and continue throughout the course of treatment (Hutson et al., 2010). The exact mechanism causing diarrhea with TKIs is not completely understood. Etiologies include changes to intestinal microflora as well as dysmotility related to the effect of agents on Cajal cells responsible for intestinal motility (Larkin et al., 2013).

Recommendations for the management of diarrhea largely have been based on anecdotal or experiential information, even in established guidelines. Dietary alterations should be recommended as an initial strategy. As the frequency of stools increases, the addition of psyllium and loperamide can be instituted. Patients require instruction on the number of pills that can be taken and when diarrhea warrants contacting the healthcare team. Symptoms such as dizziness, weakness, or fever will need to be evaluated more expeditiously and may require clinic evaluation. Patients with excessive diarrhea reaching grade 2 or more should be evaluated for dose interruption or modification, as well as the need for IV hydration.

Clinical guidelines for the management of diarrhea caused by oral cancer therapies are lacking. Treatment for more severe
diarrhea includes limited recommendations for diphenoxylate-atropine, octreotide, and tincture of opium (Eisen et al., 2012; Gibson et al., 2013; Shaw & Taylor, 2012; Stein, Voigt, & Jordan, 2010). Persistent diarrhea should prompt consideration of stool evaluation for possible infectious etiologies, as well.

**Dermatologic Toxicities**

The type and severity of dermatologic toxicity varies based on the classification of oral cancer therapy. Toxicities can be as mild as simple dryness of skin to severe skin alterations such as erythema multiforme major (Stevens-Johnson syndrome). Skin condition at the start of therapy is not necessarily predictive for the development of dermatologic toxicity.

Dermatologic toxicity is an expected side effect in patients receiving epidermal growth factor receptor (EGFR) inhibitors. EGFR plays an important role in the maintenance of the epidermis, and is found in keratinocytes within the basal and suprabasal layers of the epidermis and outer root sheath of hair follicles (Lacouture et al., 2011). Skin toxicities include rash, xerosis, paronychia, hair changes, hypertrichosis, and trichomegaly (Potthoff et al., 2011; Sun, 2012; Wu, Balagula, Lacouture, & Anadkat, 2011).

The dermatologic toxicities of other oral cancer therapies are seen less frequently, but can be equally challenging. Those toxicities include rash, pruritus, desquamation, depigmentation, trichomegaly, paronychia, subungal hemorrages, and photosensitivity (Bonny, Buyse, & Brochez, 2011; Borovicka et al., 2011; Rosen, Wu, Damse, Sherman, & Lacouture, 2012). Unique to the BRAF inhibitor class is the development of keratoacanthomas or squamous cell cancers (Puzanov & Flaherty, 2010). The pathophysiology of dermatologic toxicities in these classes of agents is somewhat less well understood, but is still felt to be based on the inhibitory effect of agents on signaling pathways that regulate cell growth and tissue repair.

Dermatologic toxicity management should be based on the grade of toxicity as well as on the physical and psychological impact on the patient. Patient education regarding the potential for dermatologic toxicity is crucial at the start of therapy. Proactive measures to protect skin should be discussed, including avoiding excessive sun exposure. Data exist to support the use of minocycline or doxycycline prophylactically in patients receiving EGFR inhibitors (Baas et al., 2012; Balagula, Garbe, et al., 2011; Eaby, Culkin, & Lacouture, 2008; Lacouture et al., 2010).

Treatment of rashes that meet the criteria for grade 2 or higher include an evaluation for dose interruptions or modifications. Pruritic symptoms can be managed with nonpharmacologic measures such as tepid showers, ice, or emollient creams. More severe pruritus may require diphenhydramine, cholestyramine, or hydroxyzine. In addition, the use of antibiotics such as minocycline, doxycycline, or clindamycin and/or steroids (oral or topical) should be considered (Baas et al., 2012; Balagula, Garbe, et al., 2011; Burtness et al., 2009; Gandhi, Oishi, Zubal, & Lacouture, 2010). Individual patient presentations may necessitate referral to dermatology, with a preference for those specializing in oncodermatology (Balagula, Rosen, & Lacouture, 2011). Prompt management of dermatologic toxicities may prevent discontinuation of therapy. Patients need to understand that early reporting can result in the best outcomes. In many cases, temporary dose interruptions or modifications can be made and patients can continue on treatment.

Hand-foot skin reactions present another dermatologic challenge. One typical presentation is erythema over pressure points on the hands and feet. These areas become exquisitely tender and can blister and peel. The extent can be severe enough to prohibit patient ambulation because of pain. Feet can develop thickened areas with patchy hyperkeratoderma over high-pressure areas. The pathophysiology of hand-foot skin reactions is believed to be related to the effect that various TKIs have on keratinocyte differentiation and possibly the inability of the most distal capillary
endings to repair themselves following injury (Degen et al., 2010; Ravaud, 2011; Rosenbaum, et al., 2008). Prophylactic measures to protect hands and feet are part of initial patient education when starting treatment. Early supportive measures such as gel inserts in shoes, frequent emollient cream application, and careful shoe selection may be adequate (Edmonds et al., 2012; Worthington, 2011) on chemotherapy-related mucositis identification. Whenever possible, problem areas should be addressed prior to the initiation of treatment. Patients should be instructed on measures to promote optimal oral hygiene (e.g., regular brushing of teeth with a mild toothpaste; soft-bristled toothbrush; mouth rinses using non-alcohol, hydrogen peroxide, or iodine-based rinses). A solution of salt and soda (1:1 in one quart water) can be used to rinse three or four times daily. A meta-analysis by Worthington (2011) on chemotherapy-related mucositis identified cryotherapy (ice chips) as the most effective treatment.

Patients should be instructed to contact their provider if any ulcerations appear. Early changes can be managed with supportive measures such as avoiding irritating foods and incorporating bioadherent mouth rinses or gels. Possible drug interactions should be considered prior to instituting rinses that contain antifungal agents. Grade 3 or higher toxicity requires a break in therapy. Treatment can be reinitiated when symptoms return to baseline or grade 1 (Eisen et al., 2012; Hudes et al., 2011).

### Mucositis

Mucositis can develop with any of the TKIs, but has been reported at frequencies of more than 70% in patients receiving mammalian target of rapamycin (mTOR) inhibitors (Martins et al., 2013). Symptoms can range from an irritating sensation in the mouth to the development of large aphthous ulcerations. Patients initiating oral oncolytics require a careful evaluation of the oral cavity for problems with the oral mucosa or dentition.

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>Increase of less than four stools per day over baseline; mild increase in ostomy output compared to baseline</td>
<td>Increase of four to six stools per day over baseline; moderate increase in ostomy output compared to baseline</td>
<td>Increase of more than seven stools per day over baseline; incontinence; severe increase in ostomy output compared to baseline; limiting self-care ADL</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Fatigue relieved by rest, limiting instrumental ADL</td>
<td>Fatigue not relieved by rest, limiting instrumental ADL</td>
<td>Fatigue not relieved by rest, limiting self-care ADL</td>
<td>—</td>
</tr>
<tr>
<td>Hand-foot skin reaction</td>
<td>Minimal skin changes or dermatitis (e.g., erythema, edema, hyperkeratosis without pain)</td>
<td>Skin changes (e.g., peeling, blisters, bleeding, edema, hyperkeratosis) with pain; limiting instrumental ADL</td>
<td>Severe skin changes (e.g., peeling, blisters, bleeding, edema, hyperkeratosis) with pain, limiting self-care ADL</td>
<td>—</td>
</tr>
<tr>
<td>Mucositis</td>
<td>Asymptomatic or mild symptoms; intervention not indicated</td>
<td>Moderate pain; not interfering with oral intake; modified diet indicated</td>
<td>Severe pain; interfering with oral intake</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
</tr>
<tr>
<td>Rash</td>
<td>Acneiform: Papules and/or pustules covering less than 10% BSA; may or may not be associated with symptoms of pruritus or tenderness</td>
<td>Papules and/or pustules covering 10%–30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact, limiting instrumental ADL</td>
<td>Papules and/or pustules covering more than 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated</td>
<td>Papules and/or pustules covering any BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life-threatening consequences</td>
</tr>
<tr>
<td>Maculo-papular</td>
<td>Macules or papules covering less than 10% BSA with or without symptoms (e.g., pruritus, burning, tightness)</td>
<td>Macules or papules covering 10%–30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL</td>
<td>Macules or papules covering more than 30% BSA with or without associated symptoms; limiting self-care ADL</td>
<td>—</td>
</tr>
</tbody>
</table>

ADL—activities of daily living; BSA—body surface area

Note. Table courtesy of the National Cancer Institute, 2010.
Fatigue

Fatigue can be one of the most challenging symptoms to address, with reported incidence as high as 75% in patients with cancer whether they are on or off treatment (National Comprehensive Cancer Network [NCCN], 2013). Multiple etiologies are associated with cancer-related fatigue, including anemia, endocrinopathies, depression, and pain. Despite a moderate amount of nursing research conducted in this area, the so-called magic bullet for battling treatment-related fatigue remains elusive.

Patient evaluation at the start of oral cancer treatment includes assessment of the current fatigue level as well as education regarding fatigue that may be experienced as a result of therapy. NCCN (2013) developed guidelines for cancer-related fatigue, and described it as often being part of a symptom cluster that includes sleep disturbance, emotional distress, and pain. Patients should be evaluated for these symptoms as part of the general assessment for fatigue.

Evidence-based recommendations include addressing contributing factors when possible. Nonpharmacologic measures include increasing activity as tolerated, relaxation, massage, and measures to improve sleep patterns. Mixed reviews exist for treatments such as acupuncture or initiation of psychostimulants such as methylphenidate (Minton, Richardson, Sharpe, Hotopf, & Stone, 2011; NCCN, 2013). Increasing hydration is generally supported.

Patients receiving oral cancer therapy need to be monitored throughout the course of treatment for changes in fatigue. As changes are reported, evaluation will need to take place, as at the start of treatment, for other contributing factors. When significant increases in fatigue are believed to be specifically related to treatment, regimen modification should be considered.

Monitoring Patients

Limited formal direction exists on standard monitoring for patients receiving oral cancer therapy. The American Society of Clinical Oncology and the Oncology Nursing Society (ONS) updated their Chemotherapy Administration Guidelines in 2013 (Neuss et al., 2013). This new rendition strengthened the recommendations on prescribing patient education and ongoing monitoring for patients receiving oral cancer therapy. Recommendations now incorporate

- Including frequency of office visits and monitoring in the treatment plan
- Evaluating patient ability to obtain drug and addressing identified issues
- Assessing for factors that may influence initiation or adherence to the regimen

- Assessing for adherence and toxicity at each visit, with a plan to address any problems identified (Neuss et al., 2013).

These recommendations emphasize that oral cancer therapy must be regarded as seriously as its IV counterpart. As more institutions adopt these guidelines for practice, a greater number of patients likely will remain on optimal doses of treatment with improved management of toxicities of therapy.

Conclusions

Oral cancer therapies are not just here to stay, but continue to be major components of the oncology treatment armamentarium. With more patients receiving care outside of the infusion room setting, a greater need exists to develop improved strategies for assessment, patient education, toxicity management, and ongoing monitoring of care.

Nurses are the ultimate advocates for patients undergoing treatment for cancer with oral agents. Their ability to educate patients, caregivers, and other staff on the best approaches to manage symptoms can significantly improve patient quality of life and help patients stay on treatment. The increasing number of new therapies may bring new challenges to the entire healthcare team but, most importantly, they bring greater hope to patients with a cancer diagnosis.

References


