ABSTRACT

The approval of 6 new agents for the treatment of colorectal cancer over the past decade, along with the development of numerous combination regimens, has led to increased attention to the complications associated with these therapies. Although each of the newer agents provides clinical benefits compared to previous standards of care, each is also associated with unique toxicities, including diarrhea, peripheral neuropathy, rash, and hypertension. Therefore, the challenge is to prevent and manage these toxicities appropriately. This article reviews common toxicities associated with fluorouracil/leucovorin, irinotecan, oxaliplatin, capecitabine, cetuximab, bevacizumab, and panitumumab that have a high impact on patients and the healthcare system. It also provides strategies for prevention and guidelines for effective management of specific toxicities. In addition, the article addresses the significance and clinical utility of the UGT1A1 molecular assay in detecting patients with the UGT1A1*28 polymorphism, a marker of increased risk for toxicity with irinotecan therapy. (Adv Stud Pharm. 2007;4(10):285-293)

PROCEEDINGS

PREVENTING AND MANAGING THE COMPLICATIONS OF COLORECTAL CANCER TREATMENT*

John M. Valgus, PharmD, BCOP†

T he addition of newer agents with activity against colorectal cancer (CRC) has resulted in improved treatment outcomes. Whether these drugs are given alone or combined with standard chemotherapy and/or with each other in multidrug regimens, they provide benefits such as improved disease control and increased survival.

However, these benefits come at a cost because each of the newer drugs is associated with significant toxicities, as is therapy with fluorouracil (FU) and leucovorin (LV). Although some of these toxicities are amenable to preventive strategies, others are not. In either case, appropriate management is essential, particularly when the toxicity is severe or appears to be worsening.

Drug-specific toxicities with a high impact on patients and the healthcare system are outlined in Table 1. These toxicities, as well as their prevention and management, are discussed in greater detail later in this article in the context of the drugs with which they are associated.

FLUOROURACIL AND LEUCOVORIN

It has long been known that the toxicity profile of FU/LV is dependent on the method used to administer FU. As demonstrated in one study, bolus infusion was associated with a significantly higher incidence of grade 3 and 4 bone marrow suppression (leukopenia) and grade 3 stomatitis than continuously infused FU.1 In contrast, infusional FU was associated with a significantly higher incidence of grade 1 to 4 palmar-plantar erythrodysthesia (hand-foot syndrome) than bolus FU (23% vs 0%). In the clinical setting, diarrhea is also much more common with infusional FU.

In general, leukopenia associated with bolus FU alone does not translate into a risk of febrile neutropenia and white blood cell growth factors are not routinely recommended. However, leukopenia should be
borne in mind when agents known to increase myelosuppression are added to regimens utilizing bolus FU.

Stomatitis has long been recognized as a toxicity of chemotherapy. It is associated with many agents and is seen in patients with CRC, head and neck cancers, and other malignancies. It is also one of the most difficult toxicities to manage. Early data suggested that using ice chips during the bolus infusion of FU was helpful, but this approach is probably not appropriate for patients receiving combination therapy with FU/LV and other agents, particularly oxaliplatin.

To date, there are no effective agents to prevent stomatitis in patients with solid tumors, but trials investigating preventive agents in this setting are under way.

The mechanisms underlying the development of hand-foot syndrome with infusional FU are poorly understood, although abnormal levels of thymidylate synthase in keratinocytes have been implicated as a possible cause. Mild cases of hand-foot syndrome can be alleviated by various lotions, but more severe cases require a reduction in the FU dose or discontinuation of FU altogether.

CAPECITABINE

Capecitabine is an oral agent that is also associated with diarrhea, stomatitis, and hand-foot syndrome. One study comparing capecitabine with bolus FU/LV as first-line therapy for metastatic CRC found a significantly lower incidence of grade 3/4 stomatitis, but a significantly higher incidence of grade 3 hand-foot syndrome with capecitabine. One reason for the higher incidence is that capecitabine is an FU pro-drug that mimics the infusional delivery of FU.

Management of stomatitis and hand-foot syndrome related to capecitabine therapy is the same as with FU.

IRINOTECAN

Irinotecan belongs to the camptothecin class of topoisomerase inhibitors and has considerable activity against CRC. It is also known as CPT-11, leading many to say in jest that the chemical abbreviation not only denotes the drug class, but also stands for “Can’t Predict Toxicity.” Recent developments in pharmacogenetics have helped clinicians identify individuals who may be at higher risk for these toxicities.

METABOLISM AND UGT1A1

The complex metabolism of irinotecan involves many proteins, including human carboxylesterase isoforms 1 and 2 to activate irinotecan to its active metabolite SN-38; cytochrome P450 isoforms 3A4 and 3A5 to mediate the oxidation of the parent compound to irinotecan; UGT1A1 (the 1A1 isofrom of uridino-glucuronosil transferase) to catalyze glucuronidation of SN-38; multiresistance protein isoform 2 to allow the cellular excretion of SN-38 glucuronide (SN-38G); and the multidrug resistance gene, encoding for P-glycoprotein, to permit excretion of irinotecan from the cell. Polymorphisms in the genes encoding for all of these proteins have been described.

Much of the antitumor activity and toxicity of irinotecan is due to SN-38, which is affected by any alteration in UGT1A1. In particular, it is the UGT1A1*28 polymorphism, the result of 7 (TA) repeats in the promoter region of chromosome 2 instead of 6 (TA) repeats, that is associated with the increased toxicity of irinotecan. The extra (TA) repeat results in reduced gene expression of UGT1A1 and reduced glucuronidation of SN-38. The UGT1A1*28 is also associated with Gilbert’s syndrome, a mild form of hyperbilirubinemia.

A review of several studies investigating the relationship between irinotecan toxicity and the homozygous UGT1A1*28 genotype found an increased risk for grade 4 leukopenia and lower absolute neutrophil count nadirs. Although risk varied from study to

| Table 1. Common Toxicities Associated with Colorectal Cancer Therapies |
|-----------------------------|----------------|
| Therapy                     | Toxicity                  |
| FU/LV, capecitabine, irinotecan | Diarrhea                 |
| FU/LV, capecitabine           | Mucositis/stomatitis      |
| FU/LV, capecitabine           | Hand-foot syndrome        |
| Irinotecan, FU/LV, capecitabine| Myelosuppression          |
| Oxaliplatin                  | Peripheral neuropathies   |
| Oxaliplatin, FU/LV, capecitabine, irinotecan | CINV |
| Cetuximab, panitumumab, other EGFR inhibitors | Rash |
| Cetuximab, panitumumab        | Hypersensitivity reactions |
| Bevacizumab                  | Hypertension              |
| Bevacizumab                  | Proteinuria               |

CINV = chemotherapy-induced nausea and vomiting; EGFR = epidermal growth factor receptor; FU/LV = fluorouracil/leucovorin.
study, one trial found that 50% of patients who were homozygous for UGT1A1*28 developed grade 3/4 neutropenia versus approximately 15% of those who were not homozygous. Findings regarding diarrhea were conflicting, with some studies demonstrating an increased risk of severe diarrhea in homozygous patients, whereas others did not.4

The link between homozygosity for UGT1A1*28 and increased risk for irinotecan toxicity, as well as the commercial availability of a UGT1A1 molecular assay (Invader, Third Wave Technologies, Inc., Madison, WI) that was approved by the US Food and Drug Administration (FDA) in August 2005, is 100% accurate in identifying this polymorphism compared to DNA sequencing, and requires as little as 4 to 5 hours of processing time, raises several important questions. For example, how useful is this assay in clinical practice? Should all patients be genotyped before they receive irinotecan? Should the irinotecan dose be reduced by 25% in homozygous patients, as recommended by the drug’s manufacturer,8 or should irinotecan be given to these patients at all? Should better supportive care, growth factors, prophylactic antibiotics, and/or closer follow-up be instituted instead? Given the wide range of opinions on this issue, there are no definitive answers.

**Irinotecan-Induced Diarrhea**
The impact of irinotecan-induced diarrhea received worldwide attention in 2001 when 2 large trials demonstrated a significantly increased risk of early death (ie, within 60 days of initiating therapy) in patients receiving irinotecan and bolus FU/LV.9 Both trials—the North Central Cancer Treatment Group protocol N9741, which involved patients with metastatic CRC, and the Cancer and Leukemia Group B protocol C89803, which involved patients receiving adjuvant therapy—were suspended early, and an independent panel was convened to review the causes of these early deaths.

The panel concluded that deaths in both studies were more common in patients receiving irinotecan and were related, in the majority of cases, to gastrointestinal toxicities, primarily diarrhea.7

This led the American Society of Clinical Oncology (ASCO) to update its guidelines for the treatment of diarrhea induced by cancer therapy.10 In essence, patients with complicated diarrhea (ie, grade 3/4 diarrhea [>7 stools/day] or grade 1/2 diarrhea plus at least 1 of 8 complicating signs or symptoms [cramp-ing, nausea/vomiting, decreased performance status, fever, sepsis, neutropenia, frank bleeding, and dehydration]) should be hospitalized immediately, treated aggressively with intravenous hydration and electrolyte replacement, and monitored closely. In this way, it is hoped that deaths may be averted.

Patients with uncomplicated diarrhea (ie, grade 1/2 with no complicating signs or symptoms) should be treated conservatively with dietary modification, oral hydration, instructions to report any increase in stool frequency, fever, and symptoms such as dizziness upon standing, and loperamide as necessary. In patients with grade 2 diarrhea, cytotoxic chemotherapy should be held until symptoms resolve, and dose reduction should be considered.

**Oxaliplatin**
Acute and cumulative peripheral neuropathies are common and often dose-limiting toxicities associated with oxaliplatin.11 Acute neuropathies, which occur during or immediately after the infusion and are rapidly reversible, are characterized by paresthesias/dysesthesias in the hands, feet, and perioral region, where jaw tightness is sometimes present as well. They are triggered or enhanced by exposure to cold. Pharyngolaryngo-dysesthesia, with complaints of shortness of breath despite normal respiratory status, is also seen. Acute dysesthesias related to exposure to cold appear to be exclusive to oxaliplatin, as they are not seen with other platinum compounds.

Cumulative neuropathies, by comparison, occur after long-term administration of oxaliplatin, and are characterized by deep sensory loss, sensory ataxia, and functional impairment.11 They are similar to the neurotoxicities observed with cisplatin and are correlated with the cumulative dose of oxaliplatin. Cumulative doses above 500 mg/m² are associated with a significantly higher risk of neurotoxicity. In most cases, the neuropathies are reversible, but in some cases they are not.

Strategies to prevent and/or treat oxaliplatin-induced peripheral neuropathies are summarized in Table 2.11 Although these strategies have been studied in a variety of investigations, better trials are needed to confirm their effectiveness. Glutathione in particular warrants additional study in the chronic setting, in which it holds more promise than in the acute setting because its mechanism of action prevents the accumulation of platinum adducts. Calcium-magnesium infusions also warrant further scrutiny. Although early data
demonstrated efficacy in preventing oxaliplatin-induced neurotoxicity, an interim analysis of a recently terminated trial indicated that the addition of these infusions for neuroprophylaxis in patients receiving an oxaliplatin (FOLFOX [FU/LV plus oxaliplatin]) and bevacizumab regimen was associated with a possible reduction in the rate of response to therapy.12

CETUXIMAB AND PANITUMUMAB

RASH

Acneiform rash is the most commonly reported side effect of therapy with inhibitors of the epidermal growth factor receptor (EGFR), such as the monoclonal antibodies (mAbs) cetuximab and panitumumab. A typical rash with macules and discoloration is shown in both panels of Figure 1.13

Studies evaluating cetuximab, panitumumab, and other inhibitors of EGFR have found that the rash occurs in 50% to 100% of patients and appears to be dose dependent. The rash also appears to be associated with antitumor activity, with higher response rates to therapy seen in patients with higher grades of rash. In fact, ongoing studies are evaluating the theory of utilizing dose titration to induce the rash and improve drug efficacy.

Although other ongoing trials are investigating strategies to prevent the rash, many experts question this line of research on the grounds that preventing the rash would largely obliterate the prognostic information it provides.

There is no gold standard for treating EGFR-induced rash, largely because the rash can vary from

<table>
<thead>
<tr>
<th>Grade</th>
<th>Macular</th>
<th>Pustular/ Papular</th>
<th>Dry Skin</th>
<th>Pruritus</th>
<th>Ulcerative</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Topical steroids</td>
<td>Clindamycin gel or lotion</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>2</td>
<td>Topical steroids</td>
<td>Oral antibiotics</td>
<td>Lotion (perfume, alcohol, dye free)</td>
<td>Antihistamine (topical or oral)</td>
<td>NA</td>
</tr>
<tr>
<td>3</td>
<td>Oral steroids</td>
<td>Oral antibiotics</td>
<td>Lotion</td>
<td>Antihistamine (oral)</td>
<td>Silver sulfadiazine</td>
</tr>
</tbody>
</table>

Table 2. Prophylaxis and/or Treatment of Oxaliplatin-Induced Peripheral Neuropathies

<table>
<thead>
<tr>
<th>Acute</th>
<th>Chronic (Cumulative)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avoid exposure to cold, drink warm liquids, cover mouth with hand to breathe in warmer air</td>
<td>Hold therapy; possibly reduce dose</td>
</tr>
<tr>
<td>Sodium channel blockers*</td>
<td>Sodium channel blockers*</td>
</tr>
<tr>
<td>Amifostine</td>
<td>Amifostine</td>
</tr>
<tr>
<td>Glutathione</td>
<td></td>
</tr>
<tr>
<td>Different oxaliplatin schedules†</td>
<td>Different oxaliplatin schedules†</td>
</tr>
<tr>
<td>Neuromodulating agents</td>
<td></td>
</tr>
<tr>
<td>Calcium-magnesium infusions‡</td>
<td></td>
</tr>
</tbody>
</table>

*Carbamazepine and gabapentin.
†Fractionated doses or stop-and-go therapy timed to the onset and abatement of neuropathy.
‡1 g of each before and after the oxaliplatin infusion is administered at some institutions.


Figure 1. EGFR Inhibitor-Induced Rash

EGFR = epidermal growth factor receptor.
Reprinted with permission from Van Cutsem. Oncologist. 2006;11:1010-1017.13

Figure 2. Algorithm for the Treatment of EGFR-Induced Rash

EGFR = epidermal growth factor receptor; NA = not applicable.
patient to patient. It can be macular, papular, or pustular, and higher grades may be accompanied by dry skin, pruritus, and ulcerative lesions. Therefore, any rash that develops shortly after the initiation of therapy with an EGFR inhibitor should be carefully evaluated. Many clinicians have found the treatment algorithms similar to the one presented in Figure 2 to be helpful. Nevertheless, more research is needed to better characterize the features of the rash to optimize treatment.

**Infusion Reactions**

Infusion reactions are fairly common with cetuximab, a humanized mAb, but far less common with panitumumab, a fully human mAb. Approximately 20% of patients receiving cetuximab and 4% of those receiving panitumumab experience a grade 1 to 4 infusion reaction.13,16 Approximately 3% of patients receiving cetuximab develop grade 3/4 reactions (of which <0.1% are fatal) compared to approximately 1% of patients receiving panitumumab (with no fatalities reported to date).13,16 Approximately 90% of reactions occur with the first infusion. Anaphylactoid reactions characterized by lightheadedness, shortness of breath, and/or bronchospasm require immediate attention from a physician or other healthcare professionals.

Mild to moderate infusion reactions can be managed by slowing the infusion rate and continuing antihistamine use prior to subsequent infusions. Immediate and permanent discontinuation of cetuximab and treatment with epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and/or oxygen are recommended for the management of severe reactions. However, there have been some anecdotal reports of successful rechallenge with cetuximab in patients who have had severe infusion reactions.

Given the frequency of infusion reactions to cetuximab, it is very important for each institution to have its own set of guidelines for administering the drug and managing infusion reactions. The monitoring and treatment plan currently in use at the University of North Carolina Hospitals and Clinics is shown in Figure 3.

**Bevacizumab**

Unlike mAbs that inhibit EGFR, bevacizumab, a humanized mAb, inhibits vascular endothelial growth factor (VEGF) and is associated with VEGF inhibitor-induced hypertension.

A recent meta-analysis of 7 clinical trials involving 1850 patients with CRC, renal cell cancer, or breast cancer found a significantly increased risk of both hypertension and proteinuria with bevacizumab versus historical controls.17 The incidence of hypertension ranged from 2.7% to 32% with low-dose bevacizumab (relative risk of 3.0 for all grades; \( P < .001 \)) and from 17.6% to 36% with high-dose bevacizumab (relative risk of 7.5 for all grades; \( P < .001 \)). Relative risk of proteinuria was 1.4 with low-dose bevacizumab and 2.2 with high-dose bevacizumab.

The management of VEGF inhibitor-induced hypertension and proteinuria raises several questions for which there are presently no answers. For example, what are the long-term implications of anti-VEGF

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**Figure 3. Monitoring and Treatment Plan for Cetuximab Infusions and Infusion Reactions**

<table>
<thead>
<tr>
<th>A. ANTINEOPLASTIC AGENTS</th>
<th>Begin Therapy On: (Day 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antineoplastic Generic Name</strong></td>
<td><strong>Protocol Dosage</strong></td>
</tr>
<tr>
<td>Cetuximab</td>
<td>400 mg/m²</td>
</tr>
<tr>
<td>Fluid/Volume: As prepared</td>
<td>Dose reduced by ____% due to:</td>
</tr>
<tr>
<td>2 Cetuximab</td>
<td>250 mg/m²</td>
</tr>
<tr>
<td>Fluid/Volume or Standard: As prepared</td>
<td>Dose reduced by ____% due to:</td>
</tr>
</tbody>
</table>

Instructions:

1. Please note loading dose of 400 mg/m² is only given on Cycle ONE, day one.
2. Patient to be observed one-on-one with first treatment. Physician, PA, or NP must be present at initiation and 10 minutes of first infusion.
3. Discontinue cetuximab for bronchospasm and/or anaphylaxis.
4. Have available at bedside: O₂, epinephrine for subcutaneous administration (1:1000), and methylprednisolone 125 mg IV. Administer epinephrine SQ IMMEDIATELY at the first sign of possible anaphylaxis as physician is being notified. Administer methylprednisolone 125 mg IV for symptomatic abaplyactoid reactions (rash, hives, wheezing, and lightheadedness) with hypotension.
5. Cetuximab should be administered with the use of a low protein binding 0.2-micrometer in-line filter.

Standard order form from the University of North Carolina Hospitals and Clinics; updated January 2006. IV = intravenous.
therapy on hypertension? Is the prolonged survival now seen in metastatic CRC and the adjuvant setting long enough to observe the long-term complications of hypertension? Are currently used blood pressure monitoring strategies sufficient for patients receiving anti-VEGF agents? Should these patients be monitored more closely? Are currently used antihypertensive agents appropriate for the treatment of hypertension induced by anti-VEGF therapy? Should angiotensin-converting enzyme inhibitors be used instead in patients who develop proteinuria? Clearly, well-designed studies are needed to answer these questions and improve outcomes.

CONCLUSIONS

Colorectal cancer therapies are associated with several significant complications, including diarrhea, stomatitis, hand-foot syndrome, leukopenia, peripheral neuropathies, infusion-related reactions, rash, and hypertension and proteinuria. Other complications associated with the newer agents (but not addressed in this article) include, but are not limited to, bleeding, clotting, and bowel perforation (bevacizumab), nausea and vomiting (oxaliplatin), and hair and nail changes (EGFR inhibitors).

Increased attention to toxicities in patients receiving CRC therapy, early identification of patients at risk for toxicities, and implementation of preventive and management strategies to improve patient outcomes are essential. In addition, more research needs to be done to determine the most appropriate management strategy for each toxicity.

DISCUSSION HIGHLIGHTS

UGT1A1 TESTING

Dr Ignoffo: Has UGT1A1 ever been tested in the courts? Are there any lawsuits claiming unnecessary toxicity because the test was never done?

Dr Valgus: I haven’t heard of any cases to date, but the question of liability has been raised.

Dr Iacovelli: There’s another issue. If you use irinotecan in a patient with metastatic disease and there’s an inordinate amount of toxicity, you’re going to reduce the dose anyway, aren’t you?

Dr Valgus: That’s my argument against using the test. I said that 50% of patients who are homozygous are going to have severe toxicity. However, are you impairing drug efficacy by empiric dose reductions in the other 50%? Is that why some trials showed decreased efficacy in this patient population? Maybe so, maybe not. Should you adjust the dose for everyone just because of the 50% who are at risk? Or, would you simply monitor more frequently if toxicities occurred and then reduce the dose in the second cycle or switch to something else?

Dr Ignoffo: That sounds like a nice pharmacy resident project—a randomized trial comparing close monitoring versus UGT1A1 testing.

Mr Rutledge: Our doctors use a consent form up front for any kind of therapy. If you’re addressing those side effects up front, is there still a legal need to get the test?

Dr Ignoffo: I think the courts will be telling us the answer down the road.

Dr Valgus: I’m afraid of what the initial decision will be, and what the implications will be retrospectively if patients say, “Oh, I had significant toxicity and I was hospitalized, but I never got that test.” It will be interesting to see how this pans out.

Dr Waddell: Another issue with genetic testing for irinotecan toxicity is the effect of dose reduction on survival benefit. As Bonadonna and Valagussa noted in their reports of the classic breast cancer regimen in the late 1970s and early 1980s, patients did not obtain the maximum survival benefit unless they received at least 85% of the planned dose. Patients receiving less than 65% of the planned dose had no survival benefit at all.

Clearly, dose reduction is a consideration if we discover a genetic abnormality that causes 100% toxicity, but only 50% of the people with the UGT1A1 genotype developed severe toxicity to irinotecan. How concerned should we be about adjusting the dose and not giving our patients the dose they need for survival?

Dr Valgus: That’s one of the biggest concerns voiced by our prescribers—that they would be impairing the potential effectiveness of irinotecan by preemptively reducing the dose in those patients, even if half of them wouldn’t have needed that dose reduction. The real issue is whether you need to reduce the dose in all of those patients just because a certain percentage of them will develop toxicity. Even without using the genetic information, we know that those patients do a little worse. Is it because they needed dose reductions over time anyway? The information is still being teased out as to why they don’t do as well.

Dr Ignoffo: Are you saying that UGT-positive patients have a worse prognosis or a worse response?

Dr Valgus: Yes. Patients who are homozygous for
that variation have worse outcomes than patients who are not homozygous. We don't know why.

Dr Waddell: The possibility is that it's not a response problem; it's a toxicity problem.

Dr Valgus: That's one of the possibilities. Another is that it may be something inherent in the disease state.

Dr Ignoffo: Toxicities that lead to dose reduction, which theoretically leads to lower response, would argue against the fact that the genomic problem is having less of an impact on the kinetics.

Dr Iacovelli: However, if you're not using irinotecan in the adjuvant setting, you're not worried about cure, and dose reduction is completely appropriate. The reports of Bonadonna and Valagussa involved adjuvant therapy, in which you have to maintain relative dose intensity to derive the best treatment effect. With metastatic disease, the convention is to first do no harm, so you're going to reduce the dose in patients who have bad toxicity. Then, it falls back to the issue of whether you are going to spend $1000 on a test to see if they have this genetic polymorphism that really doesn't mean anything in the grand scheme of things.

Mr Solimando: It also goes back to whether we are going to see conflicting court cases. You're guilty if you didn't do the test up front and the patient develops toxicity. However, you're also guilty if you did do the test and reduced the dose, and the patient has a poor outcome anyway. I can see the potential for getting sued whether I do the test or not, whether I reduce the dose or not.

Dr Valgus: In the second case, you now have the package insert to back you up so that you can say, "This is what the US FDA recommended." In the opposite scenario, you don't have that authority backing you up. However, I believe that the cost of this test is reimbursed.

Dr Heaton: We cover the test.

HAND-FOOT SYNDROME

Dr Waddell: Besides dose adjustment or discontinuation of infusional 5-FU, what strategies might you use to treat or prevent hand-foot syndrome?

Dr Valgus: There is not a lot of good information in the literature. One agent that has shown some effectiveness in prevention is vitamin B₆. There are some initial data, but not enough to recommend that it be used routinely. Hand-foot syndrome is one of the oldest toxicities, but there's still no good way of preventing it or treating it.

Dr Iacovelli: There was a case report of a patient whose doctor prescribed a nicotine patch. It caused peripheral vasoconstriction, kept FU out of the periphery, and actually helped reduce hand-foot syndrome in that patient.

Dr Waddell: How about other topical treatments? Everyone I know in Texas swears by Udder Cream.

Mr Rutledge: Roche has a sample kit for patients and Udder Cream is one of the samples. A local favorite in our area is Bag Balm, which is similar.

RASH

Mr Rutledge: A patient we treated with cetuximab developed a horrible looking rash on his nose and face that was exacerbated by exposure to sunlight. Are there any recommendations regarding the use of sunscreens, or are you aware of particular types or brands of sunscreen that are more likely to exacerbate the rash?

Dr Iacovelli: The recommendation is to stay out of the sun if you're taking cetuximab or another EGFR inhibitor.

Dr Valgus: The patient information for cetuximab recommends limiting exposure to the sun. I don't know if there's a recommendation for sunscreen use because putting something else on the skin might exacerbate the rash.

Mr Bullard: Do you foresee titration to a grade 3 or grade 4 rash in treatment?

Dr Valgus: In my opinion, that will not happen until a clinical trial demonstrates a benefit.

Dr Ignoffo: Grade 4 is horrific. The most I think you would titrate to is a grade 2 rash, which itself produces significant symptomology.

Dr Waddell: All cancer drug toxicities are graded and defined. A doctor doesn't look at something and say, "That's bad. That's grade 4."

You can go to the Web site for the Cancer Therapy Evaluation Program (CTEP), which is part of the National Cancer Institute, and find every single drug toxicity you could ever imagine graded 1, 2, 3, and 4 (http://ctep.cancer.gov/). Oncologists generally watch patients with grade 1 and 2 toxicities. For grade 3 and 4 toxicities, they either reduce the dose or change to another therapy. Of course, there's also grade 0 and grade 5, but those are easy. With grade 0, you have no toxicity; with grade 5, you die of toxicity. Therefore, we always talk about grades 1 through 4.

Dr Ignoffo: The toxicities graded by the CTEP are generally common toxicities. The product information
Mr Solimando: We may need to adjust the CTEP common toxicities for the drug-induced rashes we see with the EGFR inhibitors because they’re a little different from the standard skin rashes listed in the common toxicity table.

Diarrhea

Dr Waddell: Dr Valgus, please explain the acute versus the delayed diarrhea associated with irinotecan and how they are treated.

Dr Valgus: Atropine is the standard of care for acute diarrhea that occurs during the infusion. Delayed diarrhea is initially treated with loperamide-based therapy unless there are complicating factors, such as cramping, fever, bleeding, or dehydration. Then, you would use an octreotide-based regimen and hospitalize those patients.

Dr Waddell: Are your oncologists ordering atropine for acute irinotecan-induced diarrhea, or are they giving it as a premedication?

Mr Rutledge: We’ve done it both ways. Our oncologists recently backed off a little on using it as a standard premedication, but it seems that most patients need it. I think the pendulum is going to swing back to using it as a standard premedication.

Mr Solimando: I don’t think I’ve ever seen it used as a standard premedication for everybody from dose one. The orders I still see at Walter Reed are “if needed.” However, if patients need it with the first dose, they will often need it with every dose. For some of these patients, it becomes the standard premedication.

Dr Waddell: Is irinotecan 300 mg/m² or 350 mg/m² once every 3 weeks still being administered, or has that dose gone by the wayside?

Dr Iacovelli: There are doctors at Duke who are using 600 mg/m² in their research protocols.

Dr Waddell: What kind of toxicity are they seeing with that?

Dr Iacovelli: Bad diarrhea, nausea and vomiting, neutropenia—the whole gamut.

Dr Waddell: Could you also comment on the intense dosing of loperamide? It’s not according to the label.

Dr Valgus: The initial dose is 4 mg followed by 2 mg every 4 hours; forget about the 16-mg cap. If the diarrhea progresses, the recommendations are to give 2 mg every 2 hours. If it continues to progress, you would then move to an octreotide-based regimen for refractory but still uncomplicated diarrhea. You can also use octreotide on an outpatient basis in these patients.

Dr Waddell: What is everyone’s experience with outpatient octreotide?

Dr Ignoffo: It’s very simple to use. It’s a 1-cc subcutaneous injection, painless. Generally, our infusion nurses teach the patients. I don’t know if community pharmacists carry the drug or know a lot about it. If they did, they would have to teach the patient how to use it, but, frankly, I don’t think that would come up often.

Mr Rutledge: We recently began dispensing vials of octreotide versus ampules, which has eliminated the need to train patients in the use of a filter needle.

Dr Waddell: I switched to vials pretty quickly because I didn’t want patients manipulating ampules, breaking the glass, and dealing with filter needles. Interestingly, I’ve never tried to get anybody to inject 1 cc subcutaneously. I always get a 1000 µg/mL multidose vial and just give patients insulin syringes in which they can pull up 0.1 cc. It’s a lot less volume to inject under the skin with limited skill.

Dr Valgus: As noted in the ASCO guidelines, octreotide can be used in patients who develop severe diarrhea during the earlier chemotherapy cycles. Also mentioned is the use of depot octreotide with subsequent cycles, thus there’s no longer a need to administer it 3 times a day during subsequent cycles.

Neurotoxicity

Mr Solimando: There is some controversy in some institutions about whether calcium-magnesium infusions should be used and whether they prevent neurotoxicity.

Dr Iacovelli: The National Comprehensive Cancer Network does not recommend using them because there are no prospective randomized data demonstrating their efficacy. However, there is a science-based article by Gamelin et al, and the biology makes sense. I’d rather use something that may offer protection than see some of those bad neurotoxicities associated with oxaliplatin.

Dr Waddell: Calcium and magnesium infusions are also inexpensive, and they’re not toxic.

Dr Ignoffo: I would prefer using them based on the article by Gamelin et al, even though it’s not a big randomized trial.

Mr Solimando: If you got an order for an oxali-
platin infusion, but no order for a calcium-magnesium infusion, would you call the physician and recommend that it be ordered as well?

Dr Ignoffo: If it were a new practitioner, I'd at least call and say, “Some of the physicians here order a calcium-magnesium infusion for patients receiving oxaliplatin because it might be helpful in protecting against neuropathy.” If the doctor knows about it, but doesn't believe in it or prefers not to use it, that's fine. At least I've done my due diligence. Unless there is a protocol within the institution that says, “We're going to use this for all of our patients. Let us know if you do not want to,” the decision is up to the physician.

REFERENCES


