ABSTRACT

The pharmacist has a considerable role to play in the treatment of patients with metastatic breast cancer. Many treatments for the disease carry a significant risk for potentially serious toxicities, such as neuropathy, neutropenia, nausea, emesis, and pain. It is important that pharmacists educate patients about the potential for such toxicities as well as possible treatments. They should also continually assess patients for signs of the 2 most common toxicities, neutropenia and sensory neuropathy. With more chemotherapeutic agents becoming available in oral formulations, the issue of adherence to these therapies becomes more significant. The World Health Organization defines 5 primary dimensions of adherence: social, health-system related, condition related, therapy related, and patient related. The pharmacist can play a role in overcoming barriers in all these dimensions through counseling and recommending methods for patients to remain adherent with their treatment regimen. (Adv Stud Pharm. 2007;4(13):397-401)

BREAST CANCER TREATMENT TOXICITIES

Most treatments for metastatic breast cancer, however beneficial, result in toxicities, primarily anemia, neutropenia, neurotoxicities, nausea, emesis, osteoporosis, and pain.1

Neutropenia is defined as an absolute neutrophil count lower than 0.5 x 10^9 cells. The normal white blood cell count is 4.8 to 10.8 x 10^9/L, whereas the normal lifespan of neutrophils is 6 to 12 hours. The bone marrow can produce 600 million to 4 billion neutrophils daily. However, given their short lifespan, they are particularly sensitive to the effects of chemotherapy.

Although a reserve of neutrophils within the bone marrow provides some protection from neutropenia, this protection generally ends 7 to 14 days following the start of chemotherapy when neutrophils reach their lowest point. Recovery requires between 3 and 4 weeks. A decline in absolute neutrophil levels significantly increases the risk of infection.2 Risk factors for neutropenia include the patient’s baseline level of immune system health, nutritional history (certain vitamin deficiencies predispose one to impaired immunity), and physical barrier breaches in the skin or mucosa.3

When assessing for neutropenia in patients with cancer, pharmacists should be aware of gastrointestinal conditions, such as mucositis or diarrhea; respiratory tract symptoms, such as cough and dyspnea; and dysuria frequency, urgency, or color changes. All are potential indicators of infection.4

Indwelling devices, particularly central venous catheters for patients receiving intravenous chemotherapy, as well as breaks in the skin or mucous membrane, provide potential sites for infection. Symptoms of infection in this population include side redness, edema, tenderness, and warmth. Although fever, chills, myalgia, malaise, and fatigue may present in the presence of infection, some patients with

THE PHARMACIST’S ROLE IN THE CARE OF TREATMENT-EXPERIENCED PATIENTS WITH BREAST CANCER* —

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metastatic breast cancer do not exhibit these classic symptoms, not even fever. Thus, it is important that pharmacists educate patients on the various signs and symptoms of infection. This includes advice to monitor their temperature on a daily basis (insure they have a thermometer at home) and reminders to call the physician’s office at the first sign of fever (>100.4°F or 85°C). Patients should also be advised to practice meticulous hygiene.

In the metastatic setting, neutropenia prevention typically relies on dose modification, treatment delays, or, more rarely, the administration of growth factors.

**Neurotoxicities**

Peripheral neuropathy is the injury, inflammation, or degeneration of the peripheral nerve fibers. It can be hereditary or acquired and is often difficult to diagnose.

There are 3 main types of neuropathy in patients with cancer: sensory, motor, and autonomic. Sensory neuropathy manifests with pain, changes in touch, temperature, position, and vibration sense. Patients experiencing motor neuropathy may exhibit involuntary movements, changes in muscle tone and coordination, decreased reflexes, and weakness. Those experiencing autonomic neuropathy may present with decreased blood pressure, orthostatic changes, sexual dysfunction, and intestinal dysmotility.

Patients with cancer primarily experience sensory peripheral neuropathy, believed to affect 90% to 100% of patients with breast cancer undergoing chemotherapy. Patients describe feeling as if a “stocking glove” were on their fingers or toes. Current thinking attributes the mechanism to chemotherapeutic damage to sensory nerves, leading to degeneration and death of nerve axons and myelin sheaths. Symptoms include numbness, reduced sensation, paresthesia, dysesthesia, causalgia, and allodynia. Some patients experience decreased deep tendon reflexes and vibratory sense, ataxia, abnormal position sense, signs of large sensory nerve damage, and Lhermitte’s sign, often described as a “barber chair” phenomenon in which flexion forward of the head causes an electrical sensation that runs down the spine into the limbs.

Risk factors include the use of vinca alkaloids, taxanes (more common with paclitaxel than docetaxel), or platinum analog chemotherapies, or preexisting conditions, such as diabetes, vitamin deficiencies, myasthenia gravis, hypothyroidism, and Guillain-Barre syndrome. Neuropathy related to the taxanes may be cumulative in doses greater than 200 mg/m².

A commonly used neuropathic grading scale is the Common Terminology Criteria for Adverse Events, shown in Figure 1. Even with such a scale, neuropathy grading still tends to be subjective. The primary consideration in grading neuropathy should be its effect on activities of daily living, including such things as being able to button a shirt or pick up a dime. Because many patients with metastatic breast cancer are older than 60 years, being able to open medication bottles or pick up tablets or capsules are also important considerations. In addition, patients with diabetes may exhibit difficulty manipulating syringes or insulin pens.

It is important that the pharmacist establish a baseline neurologic function before the initiation of chemotherapy because patients with baseline neurologic deficits are more likely to exhibit chemotherapy-related neurotoxicities. If these baseline deficits exist, pharmacists should alert the medical team about the possibility of increased neurologic complications and suggest altering the treatment regimen.

Assessments for sensory neurologic damage include the pinprick test to assess pain; temperature change evaluation through the application of cold or warm items; proprioception testing by moving a patient’s digits and assessing the ability to identify where the digit is in space with closed eyes; and the vibration test, by tapping a tuning fork, placing it on the farthest

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**Figure 1. Grading: CTCAE V3.0**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade</th>
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<tbody>
<tr>
<td>Neuropathy: sensory</td>
<td></td>
</tr>
<tr>
<td>Asymptomatic; loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function</td>
<td>1</td>
</tr>
<tr>
<td>Sensory alteration or paresthesia (including tingling) interfering with function but not interfering with ADL</td>
<td>2</td>
</tr>
<tr>
<td>Sensory alteration or paresthesia interfering with ADL</td>
<td>3</td>
</tr>
<tr>
<td>Sensory Disabling alteration or paresthesia interfering with ADL</td>
<td>4</td>
</tr>
</tbody>
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bony prominence, and measuring the point at which the vibratory sensation is no longer felt.\textsuperscript{6,9,10}

Interventions for neurologic damage include tricyclic antidepressants, the antiseizure medication gabapentin, glutamine (which may need to be titrated to a relatively high dose), and opioids for pain. However, there is little evidence as to the efficacy of these agents in chemotherapy-related neuropathy. Nonsteroidal anti-inflammatory drugs are not effective in managing neuropathic pain.\textsuperscript{10}

**Oral Therapy in Metastatic Breast Cancer Treatment**

Six oral agents are currently available in the metastatic breast cancer setting: cyclophosphamide, capecitabine, tamoxifen, letrozole, anastrozole, and lapatinib. With the advent of oral agents for cancer treatment, pharmacists and other healthcare professionals need to be concerned with issues regarding adherence. Adherence, previously called “compliance,” is the extent to which a patient’s behavior (including pharmaceutical adherence) corresponds with agreed-upon recommendations from a healthcare provider as directed.\textsuperscript{11}

Patient nonadherence to oral cancer medications ranges from 20% to 100%, with rates declining with the duration of the therapy. Partridge et al found 77% of patients with breast cancer on adjuvant tamoxifen therapy were adherent for the first year.\textsuperscript{12} By year 4, adherence had dropped to 50%.\textsuperscript{12,13}

The World Health Organization defines 5 primary dimensions of adherence (Figure 2):\textsuperscript{11}

- **Social/economic factors**, including poor socioeconomic factors, illiteracy, unemployment, lack of social support, unstable living conditions, and cultural beliefs about taking medication;
- **Health-system related factors**, including issues related to the patient/provider relationship;
- **Condition-related factors**, such as disabilities from the disease that may prevent patients from adhering to the medication;
- **Therapy-related factors**, including side effects and the complexity of the treatment regimen; and
- **Patient-related factors**, such as patients’ knowledge and beliefs about their illness, their motivation to manage their illness, self-efficacy, and their expectations regarding treatment outcomes.

Assessment tools to evaluate a patient’s knowledge about their medications include the MedTake test (Figure 3), designed to assess a patient’s knowledge about the medication and their ability to take it,\textsuperscript{14} and the Drug Regimen Unassisted Grading Scale (Figure 4), in which patients bring their medication into the office and then explain what it is used for and how and when they are supposed to take it. It is also used to assess patients’ knowledge about their medication.\textsuperscript{11,15}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Figure2.png}
\caption{The 5 Dimensions of Adherence}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Figure3.png}
\caption{MedTake Test}
\end{figure}
IMPROVING ADHERENCE

Tools to improve adherence include calendar blister packs, pill organizers, having patients bring their medications to healthcare provider visits and counting the remaining pills, conducting an ability-to-pay assessment and recommending available financial resources, and providing refill information. Many pharmacies offer refill reminders via phone, e-mail, or mail. It is important that pharmacists assess adherence at each visit, because patient circumstances may change.11

Although education may help, much of the motivation for therapy adherence relies on a patient’s internal motivation. Thus, the pharmacist must work to develop skills with patients that evoke a behavioral change (Figure 5).11

There are 5 components of patient counseling contained in the acronym READS16:

- Roll with resistance and acknowledge that patients are not taking their medication in a non-combative manner.
- Express empathy over any social/personal issues that result in nonadherence.
- Avoid arguing.
- Develop discrepancy (ie, work with the patient to identify those factors required to increase adherence).
- Support self-efficacy (ie, help patients take responsibility for the management of their own disease instead of relying on the provider).

CONCLUSIONS

In conclusion, the pharmacist’s role when working with patients with metastatic breast cancer is to take a complete medication history (prescription, over-the-counter, retail, and mail order), including any issues related to adherence. The pharmacist also should review any previous cancer treatments, focusing on adverse effects and the need for supportive care, and assess the patient’s understanding of the current therapy.

In addition, pharmacists should encourage healthy behaviors and help identify resources for patients, whether financial, social, or occupational. They also should provide counseling related to the adverse-effect profile of the prescribed treatment and identify supportive care, provide a drug diary/calendar (see www.xeloda.com/pdf/your-xeloda-therapy.pdf for one example), teach patients to monitor and report on adverse effects, assess adherence, and conduct appropriate follow-up.

DISCUSSION

Mr Solimando: Gabapentin is approved for neuropathic pain. Could that work?

Dr Ignoffo: When I was working with gynecology/oncology patients, taxol/carboplatin was the therapy of choice. Thus, it was not unusual for approximately 40% of our patients to have neuropathy. My usual intervention was pyridoxine. If that did not work, then I would try some-
thing like gabapentin starting at 300 mg and working up to 900 mg; anecdotally, that helped.

**Dr Almuete:** However, the gabapentin capsules are large. And if patients have nausea, it might be difficult for them to swallow. And gabapentin is expensive. Pyridoxine is a little cheaper.

**Dr Adel:** We are seeing a lot of edema in the lower extremities with gabapentin. There are also some reports about increased blood glucose levels. And these patients might already be taking steroids. Therefore, I think gabapentin has disadvantages.

**Dr Almuete:** Plus, there is fatigue when you first start gabapentin, which might be an issue for patients with anemia.

**Dr Medina:** I think one thing to stress in this is the pharmacist’s role in improving adherence. Many retail pharmacists may think, “Well, they are getting chemotherapy. They are going to take it because it is important.” But studies show that 50% of patients taking life-improving therapies take them wrong, and that pharmacists can improve that figure. The other important thing to do is prevent overadherence.

**Dr Adel:** Instead of giving patients a bottle of 100 pills, it is better to give them the exact number of pills per cycle. Then they have to return to pick up their refill, which provides an opportunity for the pharmacist to assess the patient for side effects.

**Dr Medina:** Patient calendars also help patients follow the dosage schedule, even printing out the calendar for them and handing it to them when they leave.

**Dr Adel:** I am concerned that many patients are filling their oral chemotherapy drugs in retail pharmacies, not cancer centers. Many of the retail pharmacists may not be familiar with all the drug-drug interactions of these medications. I also know several retail pharmacists who do not feel comfortable filling chemotherapy agents.

**Dr Almuete:** Our goal should be to support our retail colleagues and encourage them to call and verify doses with us.

**REFERENCES**