Oxaliplatin-Associated Neuropathy

Oxaliplatin (Eloxin®) is a chemotherapy agent used in conjunction with 5-FU (fluorouracil) and leucovorin in the treatment of advanced colorectal cancer. Oxaliplatin is fairly well tolerated by patients, but can cause neuropathy that is of great concern to patients and healthcare providers. Studies have estimated that some level of neuropathy occurs in over 90% of patients receiving oxaliplatin. The drug causes 2 types of neuropathies: acute and chronic. Acute neuropathy (AN) tends to start during the infusion and resolves within a few days. Patients describe AN as "pins and needles", numbness, tingling, or burning. It can occur in the hands, feet, mouth, and throat. Some patients will experience difficulty swallowing or shortness of breath, although these are typically self-limiting and do not require treatment. Some other sensations reported include unusual sensations in the tongue, eye pain, jaw or other muscle spasms, cramps or stiffness. Many of the symptoms are triggered or aggravated by exposure to cold. For example, drinking a cold drink can trigger a feeling of spasm in the throat, or touching a cold steering wheel could cause numbness or tingling of the hands. Although symptoms diminish over the days following treatment, they usually return with the next dose.

The second type of neuropathy is known as chronic neuropathy and has similar symptoms to AN, but the symptoms persist between cycles of chemotherapy, without resolution. In addition, patients may have changes in proprioception, which is the ability of the body to be aware of its position. For instance, you can button a shirt without looking because your fingers know how they are bending and moving to perform the task -- this is called proprioception. Without proprioception, your body would not be able to tell the position of the fingers without looking at them. This means a simple task like tying a shoelace becomes much more difficult, requiring patience and visual attention in order to complete the task. All of these symptoms are caused by damage to the peripheral nerves, or the nerves in the hands and feet. You can imagine that if you cannot sense your toes, safety becomes an issue. Chronic neuropathy usually resolves gradually over the months following the discontinuation of treatment.

Medications for the Treatment of Neuropathies

Although several researchers have proposed possible causes of oxaliplatin-associated neuropathy (ON), the exact cause remains unknown. Exposure to cold is problematic for most patients, so they should be advised to avoid it or to protect themselves from the exposure (for example, wear gloves when driving or reaching into the freezer). It has also been determined that neuropathy can be decreased by extending the infusion from 2 hours to 6 hours. For information on practical suggestions for the patient with neuropathy see: Managing Symptoms: Peripheral Neuropathy (Nerve Damage)

There have been a few small studies looking at a variety of agents to prevent ON, so let's look at some of these studies. Although many of the agents were found to have promising results, larger controlled trials are needed to confirm the results.

One small study gave patients infusions of calcium gluconate and magnesium chloride prior to administering oxaliplatin. Although the authors of the study did not statistically analyze the results, they were promising. Twenty seven percent of patients who received the calcium and magnesium had neuropathies, as compared to 75% in the non-treatment group. Another study gave patients with acute neuropathy IV magnesium and calcium, which resolved the symptoms in all patients treated.

Two anti-seizure medications have been studied, gabapentin and carbamazepine. Gabapentin was

given to a group of patients as soon as they had signs of neuropathy. All of the patients treated (seven patients) had resolution of their symptoms. Interestingly, 2 patients stopped taking the medication and the neuropathy symptoms returned, but resolved again when they restarted the gabapentin.

Two studies looked at carbamazepine: one study started the medication 1 week before starting oxaliplatin, while the other study waited to start the drug before the second dose of oxaliplatin, when some patients may have already had symptoms. The first study also continued the carbamazepine until any symptoms resolved. This group reported that they had no instances of the more severe grade 2 or 3 neuropathies. The second study began carbamazepine 5 days before dose 2 of oxaliplatin and continued the drug for 2 days after. Only one of nine patients reported any improvement in their neuropathy. These 2 studies are obviously very different in how they administered the carbamazepine and are also quite small. In addition, only one study reported the side effects of the carbamazepine, which included: memory loss, dizziness, fatigue, unsteady gait. Further investigation may be warranted.

Amifostine is a medication used to prevent loss of salivary function in patients receiving radiation for head and neck cancers. This medication was given in one study prior to oxaliplatin in order to prevent neuropathy with good results. There were significantly less days with symptoms (the measurement they used) of neuropathy in patients who received the Amifostine. In a second study, patients were started on the drug after symptoms began, but also had good results. Sixty-seven percent had less neuropathy, and the drug was well tolerated with only mild nausea and vomiting reported.

Glutathione is an enzyme that occurs naturally in the body and has been used to treat neuropathy associated with other chemotherapy agents. After 8 cycles of oxaliplatin, the researchers report grade 1 and 2 neuropathy in 43% of patients on glutathione vs. 79% on placebo. After 12 cycles of oxaliplatin, 9 out of 10 patients receiving glutathione had some level of neuropathy, and all 8 patients on placebo had neuropathy. The glutathione treatment group did have less severe neuropathy. Again, this was a small study, but further study is warranted based on the results.

The issue of oxaliplatin-associated neuropathy is not one in which we are going to see improvements unless we have a good treatment or preventative agent. Larger, controlled trials are needed to find the best agent to treat this unusual toxicity.

Other resources

Patient teaching sheet on oxaliplatin

Managing Symptoms: Peripheral Neuropathy (Nerve Damage)

References

- Cascinu, S., V. Catalano, et al. (2002). "Neuroprotective effect of reduced glutathione on oxaliplatin-based chemotherapy in advanced colorectal cancer: a randomized, double-blind, placebo-controlled trial." Journal of Clinical Oncology 20 (16): 3478-83.
- Cersosimo, R. J. (2005). "Oxaliplatin-associated neuropathy: a review." Annals of Pharmacotherapy 39 (1): 128-35.
- Gamelin, L., M. Boisdron-Celle, et al. (2004). "Prevention of oxaliplatin-related neurotoxicity by calcium and magnesium infusions: a retrospective study of 161 patients receiving oxaliplatin combined with 5-Fluorouracil and leucovorin for advanced colorectal cancer." Clinical Cancer Research 10 (12 Pt 1): 4055-61.

- Lersch, C., R. Schmelz, et al. (2002). "Prevention of oxaliplatin-induced peripheral sensory neuropathy by carbamazepine in patients with advanced colorectal cancer." Clinics in Colorectal Cancer 2 (1): 54-8.
- Mariani, G et al. "Oxaliplatin induced neuropathy: Could gabapentin be the answer?" Abstract #624, American Society of Clinical Oncology proceedings 2002.
- Rudolph, S et al. "Randomised trial with or without amifostine to reduce neurotoxicity side effects under chemotherapy with oxaliplatin." Abstract #708P, Annals of Oncology 2001; 12:421-2.
- Wilson, R. H., T. Lehky, et al. (2002). "Acute oxaliplatin-induced peripheral nerve hyperexcitability." Journal of Clinical Oncology 20 (7): 1767-74.