# Popular colorectal cancer drug may cause permanent nerve damage

Oxaliplatin, a platinum-based anticancer drug that's made enormous headway in recent years against colorectal cancer, appears to cause nerve damage that may be permanent and worsens even months after treatment ends. The chemotherapy side effect, described by Johns Hopkins researchers in the September issue of *Neurology*, was discovered in what is believed to be the first effort to track oxaliplatin-based nerve damage through relatively cheap and easy punch skin biopsies.

The Johns Hopkins investigators emphasize that the drug therapy clearly improves length of survival in advanced cancer by months to years, and that the goal of their new study is to find ways of preventing or slowing the damage through nerve-protective therapies identfied through simple skin testing.

Many patients who take oxaliplatin report bothersome neurological side effects, including pain in the hands and feet and a numbness or tingling in the throat that affects swallowing, according to study leader Michael Polydefkis, MD, MHS, associate professor of neurology at the Johns Hopkins University School of Medicine and director of the EMG Laboratory and Cutaneous Nerve Laboratory at Johns Hopkins Bayview Medical Center. Though these symptoms develop over time in the majority of patients, some report neuropathies as early as when the drug is first infused.

To get a better sense of how oxaliplatin affects nerve cells, Polydefkis and his colleagues recruited eight cancer patients about to begin oxaliplatin treatment at The Johns Hopkins Hospital. All had been diagnosed with advanced colon cancer.

Before their first oxaliplatin infusion, each patient underwent a comprehensive neurological examination, including nerve conduction testing, a clinical exam to look for signs of nerve damage, and a punch biopsy that removed tiny (3-mm diameter) portions of skin near their knees and ankles. Once oxaliplatin treatment began, consisting of infusions over two days once every two weeks for 12 cycles, the researchers performed the same tests after 30, 90 and 180 days. Another 180 days after they finished with treatment, the patients received one final exam.

Test results showed that each of the patients' nerve function and neuropathy symptoms worsened over time and that results from the punch skin biopsies neatly mirrored the side effect arc. Using a microscope, the researchers saw that nerve cells' long extensions, called axons, degenerated over the course of oxaliplatin therapy. This progression persisted after treatment stopped. Even 180 days after their last doses, seven out of the eight patients' axons continued to wither.

"This drug has rapidly become the standard of care for people with advanced colon cancer, but we really knew little about how oxaliplatin affects nerves over time," he says. "With people living longer lives on oxaliplatin, it's important to know more about these neurological side effects so patients and their physicians can make educated choices on how this drug is

used, and perhaps suggest ways to limit the damage."

The new study strongly suggests that punch skin biopsies could be an easy and inexpensive way to follow nerve cell degeneration, a crucial prerequisite for testing the effectiveness of drugs currently in development to trace, prevent or slow nerve damage.

"Skin biopsies can be done pretty easily, uniformly and cheaply anywhere, including hospitals, doctors' offices and clinics, and those places can have the tissue sent to Hopkins for analysis," Polydefkis says. "High-quality neurological testing isn't nearly as easy or economical to do, so it's possible that the biopsies could play a pivotal role in bringing neuroprotective drugs to fruition."

Other Johns Hopkins researchers who participated in this study include Ahmet Z. Burakgazi, MD, Wells Messersmith, MD, Dhananjay Vaidya, MD, PhD, Peter Hauer, BS, and Ahmet Hoke, MD, PhD.