

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Strategies to Manage Chemotherapy-Induced Peripheral Neuropathy



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H&O How common is chemotherapy-induced peripheral neuropathy?

MS Chemotherapy-induced peripheral neuropathy (CIPN) is almost universal with certain neurotoxic drugs. Two types of therapies are classically associated with CIPN: platinum agents and drugs that interact with microtubules. The platinum therapies work by causing DNA damage. An example is oxaliplatin (Eloxatin, Sanofi-Aventis), which is approved for colon cancer. The microtubule agents include taxanes, such as paclitaxel, which is approved for breast cancer, lung cancer, and other malignancies.

The proteasome inhibitor bortezomib (Velcade, Takeda) is also associated with CIPN. Bortezomib was often used in multiple myeloma, but will potentially be replaced by second-generation and third-generation proteasome inhibitors, which are associated with less neurotoxicity.

Vincristine is used in both children and adults with certain types of leukemia. The neurotoxicity of vincristine is dose-limiting.

H&O What are the symptoms of CIPN?

MS The severity of CIPN can range from very mild, to moderate, to severe. The symptoms vary according to the therapy causing them. The classic symptoms are numbness and tingling in the fingers and toes, which is referred to as the stocking/glove distribution. Symptoms can evolve from numbness and tingling into discomfort or pain.

There is also temperature sensitivity. Patients may feel an electric shock when touching something cold. Touching something warm can also be uncomfortable.

In more severe cases of CIPN, patients develop functional deficits. For example, patients may have trouble buttoning a shirt, picking up small objects, tying shoelaces, sewing, or playing a musical instrument.

H&O What is the impact of CIPN?

MS CIPN is a major quality-of-life issue for cancer patients. I primarily treat patients with gastrointestinal cancer, and I see CIPN in those who receive oxaliplatin for colon cancer. These patients may need to wear warm socks and shoes in the summer. Patients also report difficulties in tasks they had previously performed with ease. A good example is a patient who had to stop driving because he could no longer feel the brake pedal and the accelerator with enough confidence to move between them. The inability to drive had a major impact on his quality of life because his wife did not drive, either.

There is an obvious impact on quality of life when neuropathy prevents patients from doing things they were formerly able to do. However, quality of life can be decreased even if the symptoms are numbness, tingling, or a feeling that something is not quite right. Patients describe feeling like there are pebbles in their shoes, which is something they notice with every step. That would have a significant impact on quality of life. The impact of CIPN is so severe that there need to be ways to alleviate it.

H&O Are there risk factors for the development of CIPN?

MS Neuropathy can be caused by conditions such as diabetes mellitus or heavy alcohol use over the course of a lifetime. Patients with these characteristics at baseline may be at higher risk of developing CIPN when treated with chemotherapy. However, there are few empirical data concerning risk factors. The dose is very important, with higher doses linked to increased risk and greater severity. As mentioned, CIPN is more closely associated with

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certain therapies. Oxaliplatin is more neurotoxic than cisplatin, although they are both platinum drugs.

The patient's age does not appear to be a risk factor. Some preliminary data suggest that the risk of neuropathy may be higher among patients of African descent compared with patients of European descent. There are no patient factors that strongly correlate with severe CIPN.

H&O What is the etiology of peripheral neuropathy?

MS Some interesting basic science research has explored this question. Overall, the mechanism is not well-understood. Most of the research shows that axon degeneration causes the neuropathy. However, different drugs may affect the axon via different mechanisms. There are uncertainties regarding the roles of ion channels and synthesis of proteins. Much-needed research is necessary to determine the mechanisms of CIPN. These mechanisms may be specific to each drug, and therefore the treatments may be different.

H&O Could you please describe the kinetic pharmacodynamic model of CIPN?

MS My colleagues and I recently developed a kinetic pharmacodynamic model of CIPN. This model drew

on data from the large, randomized, phase 3 Cancer and Leukemia Group B (CALGB) trial 40502. This trial was conducted by the Alliance for Clinical Trials in Oncology and evaluated bevacizumab in combination with paclitaxel, nanoparticle albumin-bound paclitaxel (Abraxane, Celgene), or ixabepilone (Ixempra, R-Pharm US) in patients with chemotherapy-naïve advanced breast cancer. We evaluated dosing data, as well as data about patient-reported outcomes with respect to CIPN. On day 1 of each cycle of therapy, patients completed surveys about their symptoms. We developed a score based on this symptom report and then created a model to describe the change in score over time across the population of patients. We found that dose drove the severity of CIPN. We did not have any pharmacokinetic data, so we did not know the amount of drug each patient had in her blood. We used the dose as a surrogate for exposure.

This model is the first to use patient-reported outcomes to predict who will develop more-severe vs less-severe CIPN. It was also able to predict how dose adjustments impact neuropathy. Dose adjustments have traditionally been the approach to the management of CIPN. The schedule is also potentially relevant. Sometimes adjusting the schedule also adjusts the dose. For example, if patients are receiving paclitaxel on days 1, 8, and 15 every 28 days, dropping the day 8 dose will lead to a 33% dose reduction over the course of that cycle of therapy. Our kinetic pharmacodynamic model showed that this change decreases neuropathy. For example, if a patient was developing neuropathy over the course of the first 3 cycles of therapy, a dose adjustment could reduce the severity of the neuropathy going forward.

The advantage of using a model to guide dose adjustments is that it provides a quantitative recommendation about the extent of the adjustment and can predict the impact on the patient's neuropathy. Without the model, it is just guesswork.

H&O Can pharmacologic therapy reduce CIPN?

MS Several pharmacologic therapies, such as duloxetine, gabapentin, and pregabalin, have been studied. Duloxetine is the only agent with randomized data showing that it reduced symptoms of CIPN once they developed. A blinded study from the CALGB showed reductions in the CIPN score among patients treated with duloxetine compared with those who received a placebo control. Duloxetine is included in guidelines from the American Society of Clinical Oncology. Although it does not eliminate neuropathy, it does reduce the symptoms. The lack of effective drugs to treat neuropathy once it develops highlights the need to identify at-risk patients and enact preventive measures.

H&O How are clinical trials set up to test therapies for CIPN?

MS The CALGB trial of duloxetine is an example of a well-conducted trial. The study should be randomized, placebo-controlled, and blinded to avoid a placebo effect if CIPN is assessed via patient reports. The studies should include a large number of patients, so they are best conducted by cooperative groups and other organizations.

H&O How can trials of anticancer therapies improve assessment of CIPN?

MS When a neurotoxic therapy is studied in a clinical trial, the usual primary endpoint is efficacy. It is also important, however, to collect good data regarding CIPN. Ideally, those data would be collected through investigator assessment of CIPN, which is the classic approach, and also through patient reports. Incorporating these measurement tools into clinical trials will help develop models and identify the impact of a certain drug on the development of CIPN.

H&O Are there any novel approaches to the management of CIPN?

MS There are some novel approaches. There is research focused on understanding the mechanism of CIPN, which might lead to druggable targets.

From my perspective, however, it is necessary to focus more on minimizing the development of CIPN in the first place by not giving patients too much of a drug that causes these symptoms. There is a balance between the need to give patients enough drug to see anticancer effects, but not so much that they develop neurotoxicity. Prevention is likely a key to success going forward.

H&O Are there any other promising areas of research?

MS I have been involved in research evaluating potential pharmacogenetic markers of CIPN. We are studying

patients' germline DNA to determine whether there may be polymorphisms at the genetic level that predispose patients to the development of CIPN. This knowledge could be incorporated into models to predict which patients are at higher risk, so we can watch them more carefully or even reduce drug doses to avoid severe CIPN.

There have been some minor successes in this area in the past 5 years. There are some published data on certain polymorphisms and genes that are thought to be associated with the development of CIPN. It is still early in terms of translating the science into clinical action, but it is an area of growing interest.

Disclosure

Dr Sharma has no real or apparent conflicts of interest to report.

Suggested Readings

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