Neurotherapeutics (2018) 15:176–177
https://doi.org/10.1007/s13311-017-0584-1

COMMENTARY

Selective Blockade of the Sigma 1 Receptor Has Beneficial Effects on Both Acute and Chronic Oxaliplatin-Induced Peripheral Neuropathy

Susan G. Dorsey [1,2]

Published online: 6 November 2017

Chemotherapy-induced peripheral neuropathy (CIPN) is one of the main dose-limiting adverse effects of a number of first-line cancer treatment regimens that include neurotoxic chemotherapeutic agents (e.g., taxanes, platinum compounds, vinca alkaloids, and proteasome inhibitors) [1, 2]. Causing significant reductions in quality of life and functional status, CIPN typically presents in a symmetrical "glove-and-stocking" distribution [3]. Patients suffer from a variety of sensory symptoms, including dysesthesias, paresthesia, numbness, tingling, hypersensitivity to heat or cold stimuli, as well as lancing, burning, and neuropathic pain [4]. The chemotherapeutic agents do not appear to target motor axons. Although conventional treatments for neuropathic pain have been used in patients with CIPN (e.g., tricyclic antidepressants, lidocaine patches, gabapentin, duloxetine, others), they have been largely ineffective. Only duloxetine has been shown to provide clinically meaningful neuropathy relief in patients with chronic CIPN [5]. Most often, when symptoms of CIPN emerge, dose reduction or cessation of the chemotherapeutic agent is frequently the only solution. However, ending lifesaving cancer treatment is suboptimal [6].

In patients with colorectal cancer, the third leading cause of death among both men and women in the USA [7], the chemotherapeutic drug oxaliplatin is widely used in combination with several other agents [8]. Oxaliplatin produces 2 distinct clinical CIPN syndromes: the first is an acute, transient, and reversible hypersensitivity to touching or swallowing cold liquids, which affects up to 85% of patients [9, 10], and resolves within a few days. Mechanistically, this acute neurotoxicity is thought to arise from actions of oxalate, one of the main metabolites of oxaliplatin, on voltage-gated ion channels [11]. Despite this mechanistic insight, pretreatments with Ca/Mg infusions to prevent chelation of intracellular calcium by oxalate have failed to demonstrate a significant improvement *versus* placebo in a phase III randomized controlled clinical trial [12]. Thus, patients continue to suffer with acute neurotoxicity due to colorectal cancer treatment. The second CIPN syndrome associated with oxaliplatin is a cumulative, chronic sensory neuropathy, with features similar to CIPN arising from other platinum agents (e.g., cisplatin, carboplatin) [10]. Unlike the acute form, chronic oxaliplatin-induced peripheral neuropathy (OIPN) can last long after treatment has ended, and, for decades, can have long-lasting negative consequences on quality of life and functional status. Mechanistically, chronic oxaliplatin neuropathy has been attributed to oxidative stress, mitochondrial dysfunction, and axonal degeneration from drug accumulation in dorsal root ganglion neurons [13]. As with the acute neurotoxicity, there are currently no effective prevention or treatment strategies.

With such a dire need for new therapeutic strategies to treat both acute and chronic OIPN, the study by Bruna et al. [14] in this issue of *Neurotherapeutics* is both timely and important. In this clinical trial, the authors tested the efficacy of MR309, a novel selective sigma-1 receptor antagonist. The sigma-1 receptor has been shown to modulate several types of receptors and ion channels [15], and the sigma-1 receptor on the mitochondrion-associated endoplasmic reticulum member

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s13311-017-0584-1) contains supplementary material, which is available to authorized users.

✉ Susan G. Dorsey
sdorsey@umaryland.edu

[1] Department of Pain and Translational Symptom Science, Baltimore School of Nursing, University of Maryland, Baltimore, MD, USA

[2] Center to Advance Chronic Pain Research, University of Maryland, Baltimore, MD, USA

can modulate intramitochondrial calcium and control calcium homeostasis [16]. In addition, these receptors modulate nociception and regulate neuritogenesis [17, 18]. In a rodent model of CIPN, MR309 reduced allodynia and hyperalgesia [19], although the chemotherapeutic agent was a taxane, not a platinum compound.

In this study by Bruna et al. [14], 124 chemotherapy-naïve patients with colorectal cancer scheduled to receive oxaliplatin as one component of their chemotherapy regimen were randomized to either 1 daily oral dose of 400 mg of the study drug (MR309) or placebo for the first 5 days of each chemotherapy cycle, up to a maximum of 12 cycles. The trial was carried out at 5 major European hospital centers, and baseline demographic variables were similar across the 2 treatment groups. Outcome measures included changes in thermal sensitivity, the Total Neuropathy Score, nerve-conduction velocity parameters, and health-related quality of life. The results were encouraging. Compared with placebo, MR309 significantly reduced cold hypersensitivity, implying decreased acute OIPN, and the proportion of patients who developed severe chronic neuropathy was lower. In addition, patients randomized to the active treatment arm were able to receive significantly more oxaliplatin than placebo-treated patients, although this is based on raw dose and not body surface area-adjusted dose. In terms of the safety profile of MR309, the proportion of patients with at least 1 adverse event related to the study drug was higher in the treatment group compared with placebo.

Despite the successes, there were several limitations associated with this study, and the authors rightly characterize the study as "proof-of-concept exploratory". First, there were a significant number of patients who withdrew prematurely from the study (27 in the MR309 group; 36 in the placebo group) largely owing to cancer progression. This limited the statistical power of the study. However patients did not withdraw from the study owing to adverse events related to the study drug, so the withdrawals were not clinically significant. Second, owing to the exploratory nature, no primary and secondary endpoints were predefined, and no adjustments for multiplicity of the various endpoints were made. Thus, the potential for type I error was not controlled for, and that could confound the study results.

Despite the limitations and the exploratory nature of the study, the results are very encouraging in a field with few successful randomized controlled trials of effective interventions. Moreover, the promising results provide clear direction for future studies of the efficacy of MR309 to treat OIPN and, perhaps, CIPN due to other neurotoxic chemotherapeutic agents.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

References

1. Cavaletti G, Marmiroli P. Chemotherapy-induced peripheral neurotoxicity. Curr Opin Neurol 2015; 28: 500-507.
2. Flatters SJL, Dougherty PM, Colvin LA. Clinical and preclinical perspectives on chemotherapy-induced peripheral neuropathy: a narrative review. Br J Anesth 2017; 119: 737-749.
3. Hershman DL, Lacchetti C, Dworkin RH, et al. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology Clinical Practice Guidelines. J Clin Oncol 2014; 32: 1941-1969.
4. Von Hehn CA, Baron R, Woolf CJ. Deconstructing the neuropathic pain phenotype to reveal neural mechanisms. Neuron 2012; 73: 638-652.
5. Smith EM, Pang H, Cirrincione C, et al. Effect of duloxetine on pain, function and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial. JAMA 2013: 309; 1359-1367.
6. Bhatnagar B, Gilmore S, Golouveva O, et al. Chemotherapy dose reduction due to chemotherapy induced peripheral neuropathy in breast cancer patients receiving chemotherapy in the neoadjuvant or adjuvant settings: a single center experience. Springerplus 2014: 2; 366.
7. American Cancer Society. Key statistics for colorectal cancer. Available at: https://www.cancer.org/cancer/colon-rectal-cancer/about/key-statistics.html. Accessed October 17, 2017.
8. Andre T, Boni C, Mounedji-Boudiaf L, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 2004: 350; 2343-2351.
9. Griffith KA, Zhu S, Johantgen M, Kessler MD, et al. Oxaliplatin-induced peripheral neuropathy and identification of unique severity groups in colorectal cancer. J Pain Symptom Manage 2017; 54: 701-706.
10. Grothey A. Oxaliplatin-safety profile: neurotoxicity. Semin Oncol 2003: 30; 5-13.
11. Gamelin L, Capitain O, Morel A, et al. Predictive factors of oxaliplatin neurotoxicity: the involvement of the oxalate outcome pathway. Clin Cancer Res 2007; 13: 6359-6368.
12. Loprinzi CL, Qin R, Dakhil SR, et al. Phase III randomized, placebo-controlled, double-blind study of intravenous calcium and magnesium to prevent oxaliplatin-induced sensory neurotoxicity (N08CB/Alliance). J Clin Oncol 2014: 32; 997-1005.
13. Renn CL, Carozzi VA, Rhee P, Gallop D, Dorsey SG, Cavaletti G. Multimodal assessment of painful peripheral neuropathy induced by chronic oxaliplatin-based chemotherapy in mice. Mol Pain 2011: 7; 29.
14. Bruna J, Videla S, Argyriou AA, et al. Efficacy of a novel sigma-1 receptor antagonist for oxaliplatin-induced neuropathy: a randomized, double-blind, placebo-controlled phase IIa clinical trial. Neurotherapeutics 2017 (this issue).
15. Cobos EJ, Entrena JM, Nieto FR, Cendan CM, Del Pozo E. Pharmacology and therapeutic potential of sigma-1 receptor ligands. Curr Neuropharmacol 2008: 6; 344-366.
16. Su TP, Hayashi T, Maurice T, Buch S, Ruoho AE. The sigma-1 receptor chaperone as an inter-organelle signaling modulator. Trends Pharmacol Sci 2010: 31; 557-566.
17. Sy TP, Su TC, Nakamura Y, Tsai SY. The sigma-1 receptor as a pluripotent modulator in living systems. Trends Pharmacol Sci 2016: 37; 262-278.
18. Vela JM, Merlos M, ALmansa C. Investigational sigma-1 receptor antagonists for the treatment of pain. Expert Opin Investig Drugs 2015: 24; 883-896.
19. Nieto FR, Cendan CM, Canizares FJ, et al. Genetic inactivation and pharmacological blockade of sigma-1 receptors prevent paclitaxel-induced sensory-nerve mitochondrial abnormalities and neuropathic pain in mice. Mol Pain 2014: 10; 11.