Review

Clinical Cancer Research

Recent Developments of Novel Pharmacologic Therapeutics for Prevention of Chemotherapy-Induced Peripheral Neuropathy

Shuiying Hu[1], Kevin M. Huang[1], Elizabeth J. Adams[2], Charles L. Loprinzi[3], and Maryam B. Lustberg[2]

Abstract

Chemotherapy-induced peripheral neuropathy (CIPN) is a common and dose-limiting toxicity, negatively affecting both quality of life and disease outcomes. To date, there is no proven preventative strategy for CIPN. Although multiple randomized trials have evaluated a variety of pharmacologic interventions for the treatment of CIPN, only duloxetine has shown clear efficacy in a phase III study. The National Cancer Institute's Symptom Management and Health-Related Quality of Life Steering Committee has identified CIPN as a priority for translational research in cancer care. Promising advances in preclinical research have identified several novel preventative and therapeutic targets, which have the potential to transform the care of patients with this debilitating neurotoxicity. Here, we provide an overarching view of emerging strategies and therapeutic targets that are currently being evaluated in CIPN.

Introduction

Many chemotherapeutic agents, including tubulin poisons and platinum-based agents, can induce acute and/or chronic, dose-dependent sensory peripheral neuropathy that is characterized by paresthesia, allodynia, and ataxia. The incidence of chemotherapy-induced peripheral neuropathy (CIPN) is particularly high with agents such as paclitaxel and oxaliplatin, occurring in up to 80% of patients receiving such agents (1). With continued dosing, these symptoms increase in severity and can persist for years (2), causing long-term functional impairment that affects quality of life (3). The mechanistic basis of this side effect is not entirely clear (4). Prior studies have demonstrated that these agents induce morphologic and biochemical alterations in dorsal root ganglion (DRG) satellite glial cells, which can lead to hyperplasia and hypertrophy of macrophages in the peripheral nervous system, and also increase microglial and astrocyte activation within the spinal cord (5). In addition, these agents also inflict direct damage to Schwann cells (6) and neurons (7).

Efforts over the last 30 years have yielded a multitude of methods to predict, prevent, or manage CIPN (8). There are two overarching approaches in CIPN management: to target the underlying pathologic mechanism responsible for CIPN or to address the CIPN symptoms themselves. Many strategies to combat CIPN originate from other patient populations who experience neuropathy, such as those with diabetes. In fact, it is important to control comorbid conditions which could contribute to peripheral neuropathy, including diabetes, inflammatory conditions, and nutritional disorders (9, 10). The predictive approaches have primarily concentrated on discovering hereditary biomarkers which could recognize patients at an increased risk for CIPN using candidate gene (11–14) or genome-wide association studies (15, 16).To date, however, these studies have found nonoverlapping single or pathway biomarker associations that prevent prompt clinical application (5, 15, 17, 18). Furthermore, the shortage in available alternative therapies that could supplant standard-of-care treatments and possibly the need for patient-mediated chemotherapy treatment dose reduction may deter patients from taking action when a toxicity biomarker is detected. Because of the current state of the field and the presumed negative ramifications of treatment dose reduction on disease management, the development of preventative techniques, to efficaciously impart neuroprotection during chemotherapy treatment, is imperative.

Although many prophylactic interventions have been proposed, many of these have not been evaluated in animal models or humans. Although more than 40 randomized controlled clinical trials of preventative or therapeutic agents for CIPN have been investigated, none of these trials have provided conclusive evidence for a clinically beneficial agent (19), with the exception of the serotonin and norepinephrine reuptake inhibitor, duloxetine, in a phase III study (20). The magnitude of benefit from this agent is small. Furthermore, the translational exploration of many of the proposed intervention strategies has been hampered by the recognition that (i) most drugs causing CIPN have multiple intracellular targets and, hence, blocking a single injurious event may only have partial protective effects; (ii) the protective approach may diminish the antitumor properties of drugs given the potential overlap in cell death signaling pathways between

[1]Division of Pharmaceutics and Pharmaceutical Chemistry, College of Pharmacy and Comprehensive Cancer Center, The Ohio State University, Columbus, Ohio. [2]Department of Medical Oncology, The Ohio State University, Comprehensive Cancer Center, Columbus, Ohio. [3]Department of Medical Oncology, Mayo Clinic, Rochester, Minnesota.

Corresponding Author: Maryam B. Lustberg, The Ohio State University Wexner Medical Center, B421 Starling Loving Hall, 320 W. 10th Avenue, Columbus, OH 43210. Phone: 614-366-8541; Fax: 614-293-7264; E-mail: Maryam.Lustberg@osumc.edu

Clin Cancer Res 2019;25:6295–301

doi: 10.1158/1078-0432.CCR-18-2152

normal cells and tumor cells; and (iii) heavy reliance on patient-reported outcomes as study endpoints introduce variability and measurement noise. In total, a desirable approach is to simultaneously protect the peripheral nerves against drugs without antagonizing the therapeutic effects in tumors.

The National Cancer Institute's Symptom Management and Health Related Quality of Life Steering Committee has identified CIPN as a priority for translational research in cancer care (21), and recent advances in preclinical research have identified several novel preventative and therapeutic targets, which have the potential to be translated into clinic for improved management of this debilitating neurotoxicity. Here, we provide an overarching view of emerging strategies and therapeutic targets (Fig. 1) that are currently being evaluated for CIPN.

Targeting Neuronal Uptake Transporters

CIPN commonly originates from substantial accumulation of chemotherapeutic drugs into DRGs as evidenced by the observed levels of these agents in the sciatic nerve and spinal cord; the centrifugal and centripetal branches of the neural axons in DRGs appear to be the location of this transport. Preceding investigations have found that facilitated transport mechanisms are responsible for the cellular uptake of platinum drugs associated with CIPN (22). Conversely, the typical dissemination patterns and pathologic transformations that occur after administering these platinum agents are confined only to cells in tissues able to deliver paclitaxel from blood to these cells. Indeed, transmembrane transport of taxanes and platinum-based chemotherapeutics is now hypothesized to be mediated by specific organic anion transporting polypeptides (OATP) and organic cation transporters (OCT), respectively. Preclinical studies have demonstrated that transporter-mediated uptake of these agents into DRGs is an initiating event to trigger the pathophysiologic changes to sensory neurons (5, 23, 24). In particular, recent studies have demonstrated that genetic or pharmacologic knockout of transporters localized to the DRG in mice, such as OATP1B2 (OATP1B1 in humans), organic cation transporter novel type (OCTN2), and OCT2, protects against CIPN associated with paclitaxel (25), vincristine (26), and oxaliplatin (23, 27). Small-molecule library screens have identified the class of FDA-approved tyrosine kinase inhibitors (TKI) as being exquisitely sensitive blockers of these uptake transporters, *in vitro* and *in vivo*, through a mechanism involving the inhibition of regulatory kinases that activate

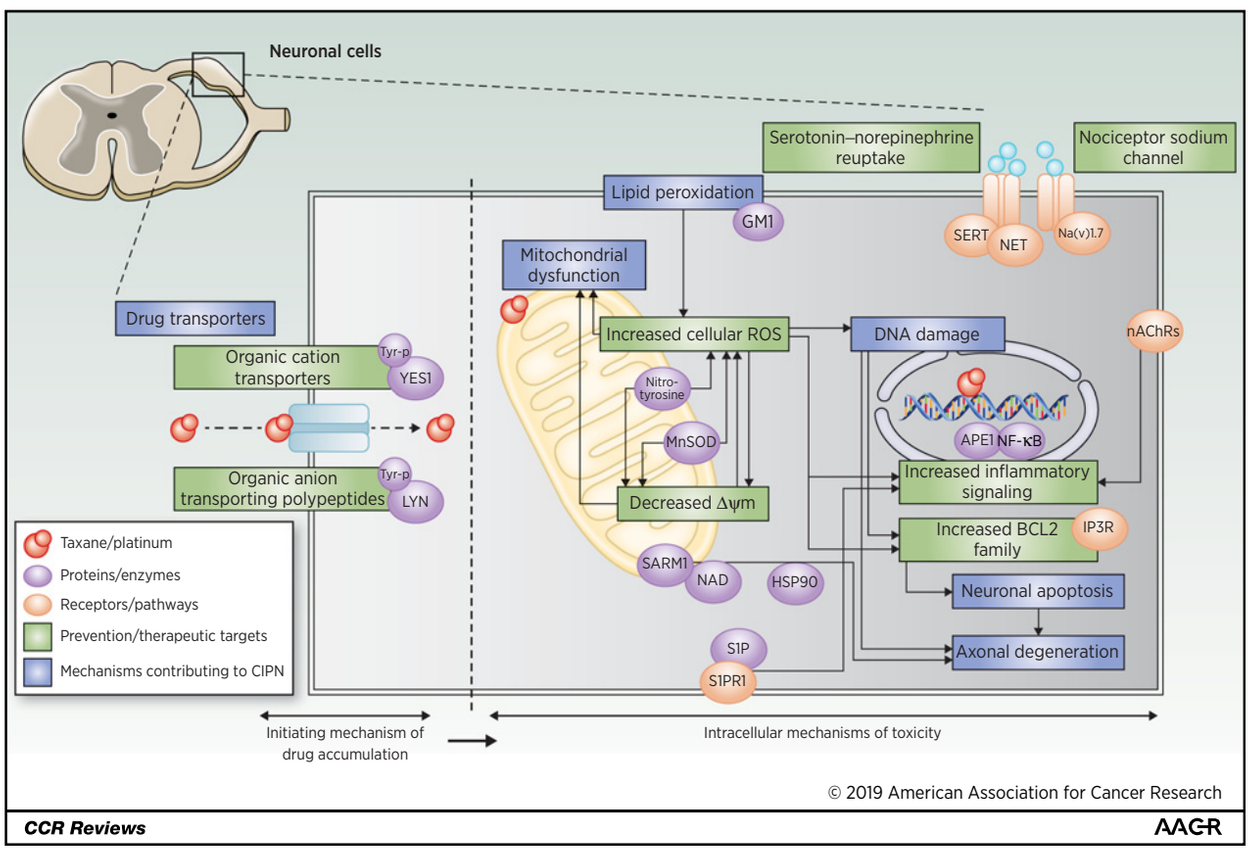

Figure 1.

Schematic depicting mechanisms of CIPN in neuronal cells. Purple/orange demonstrate proteins/enzymes/receptors involved in CIPN. Green indicates targetable preventative/treatment strategies, whereas blue indicates interconnected mechanisms of CIPN. APE1, apyrimidinic endonuclease/redox effector factor; BCL2, B-cell lymphoma 2; HSP90, heat shock protein 90; IP3R, inositol 1,4,5-triphosphate receptor; LYN, Lck/Yes novel tyrosine kinase; MnSOD, manganese superoxide dismutase; nAChR, nicotinic acetylcholine receptor; NAD, nicotinamide adenine dinucleotide; Na(v)1.7, sodium channel subtype; NET, norepinephrine transporter; ROS, reactive oxygen species; SERT or 5-HTT, serotonin transporter; Tyr-p, tyrosine phosphorylation; YES1, proto-oncogene tyrosine-protein kinase; Δψm, mitochondrial membrane potential.

Table 1. List of emerging clinical trials for the prevention and treatment of CIPN

Intervention	Target/pathway	*N*	Patient population (NCT # if available)	References
Nilotinib	OATP1B1-3 uptake transporter inhibitor	95	Breast cancer patients initiating paclitaxel	(25, 71)
Dasatinib	OCT2 uptake transporter inhibitor	20	Stage 4 colorectal patients initiating oxaliplatin-based therapy	(22, 72)
Calmangafodipir	Reduction of ROS	1) 420	1) Stage 4 colorectal patients initiating oxaliplatin-based therapy (POLAR M; NCT03654729)	(31, 73)
		2) 280	2) Adjuvant oxaliplatin-based therapy (POLAR A)	
APX3330	Enhance APE1 expression	30	Adjuvant oxaliplatin-based therapy	(39, 40)
Fingolimod	S1PR1 antagonism	1) 10–20	1) Breast cancer patients initiating adjuvant paclitaxel	(43, 44)
		2) 10–20	2) Patients with established, long-standing CIPN	
Duloxetine	Serotonin–norepinephrine reuptake inhibitor	248	Patients initiating oxaliplatin-based adjuvant therapy	(20, 74)
GM-1	Lipid peroxidation inhibition	188	Patients initiating oxaliplatin-based adjuvant therapy (NCT02251977)	(53, 75)

transporters by tyrosine phosphorylation (27). Subsequent proof-of-principle studies with nilotinib (an OATP1B2 inhibitor) and dasatinib (an OCT2 inhibitor) have demonstrated that targeting of specific transporters could be an effective neuroprotective strategy for regimens involving paclitaxel and oxaliplatin, without affecting systemic drug clearance or negatively influencing antitumor efficacy. The hypothesis that TKIs, such as nilotinib and dasatinib, can be repurposed as pharmacologic inhibitors of transporters that are essential to the uptake of chemotherapy drugs into peripheral neurons to ameliorate CIPN is currently being tested in ongoing phase 1b trial and double-blinded, placebo-controlled, randomized phase II studies (Table 1). Risk and benefit analysis must be performed on a patient-specific basis to determine the appropriateness of TKIs in the prevention of CIPN because of adverse effects which include corrected Q-T interval (QTc) prolongation and cytopenias (28). The findings obtained from these studies will provide future directions on the potential of inhibition of uptake transporters as a prevention strategy to reduce the onset, incidence, and severity of various forms of CIPN.

Mitochondrial Enzyme and Oxidative Stress

One of the proposed mechanisms of CIPN is neuronal mitochondrial injury, which can promote the degeneration of somatosensory neurons (29). Oxidative stress from chemotherapy is the primary inducer of mitochondrial damage, and neutralization of reactive oxygen species is a potential preventative strategy for CIPN. Calmangafodipir, derived from mangafodipir, a magnetic resonance imaging contrast agent, mimics the mitochondrial enzyme manganese superoxide dismutase and reduces reactive oxygen species and subsequent nerve injury (30). Preclinical data, regarding this agent, are strongest with platinum agents; however, neuroprotection from calmangafodipir may also be possible with other chemotherapeutic classes as well. In a placebo-controlled, double-blinded randomized phase II study in patients with metastatic colorectal cancer, calmangafodipir reduced cold allodynia and other sensory symptoms during and after treatment (31). Progression-free and overall survival outcomes were not adversely affected in this study. Two international trials, POLAR A and POLAR M, are currently evaluating the efficacy of calmangafodipir for the prevention of oxaliplatin-induced neuropathy in colorectal cancer patients (Polar M: NCT03654729). These phase III, multicenter, placebo-controlled trials are evaluating stage II and III patients in POLAR A using a randomized 1:1 ratio of 5 μmol/kg calmangafodipir ($n = 140$) or placebo ($n = 140$), whereas POLAR M is evaluating metastatic patients using a 1:1:1 ratio of 5 μmol/kg calmangafodipir, 2 μmol/kg calmangafodipir, or placebo (each arm, $n = 140$). Results are expected by the end of 2020.

Preclinical data also suggest promising activity associated with a commonly used antihypertensive and cardioprotectant drug, carvedilol. In rodent models, administration of carvedilol reduced levels of nitrotyrosine and subsequently increased expression of mitochondrial superoxide dismutase in both sciatic nerves and DRG tissues (32). Based on this mechanism of action, the drug has the potential for preventing an alteration in mitochondrial membrane potential in sciatic nerves and the loss of intraepidermal nerve fiber density in the foot pads (32). Although there are a number of ongoing studies evaluating carvedilol for a variety of clinical conditions, there is currently no clinical study for the prevention of CIPN. Because there are ongoing cancer trials evaluating the cardioprotective properties of carvedilol, prevention of CIPN might be considered as an exploratory endpoint.

Prevention of Axonal Degeneration

Acute axonal degeneration is another principal pathway implicated in CIPN from a variety of chemotherapeutic agents. Axonal degeneration is dependent on several pathways.

The sterile alpha and TIR motif-containing protein (SARM-1), expressed primarily in the nervous system, and its downstream cascade are key instigators of acute chemotherapy-induced axonal destruction (33). Activated SARM-1 induces the rapid destruction of the essential metabolic cofactor nicotinamide adenine dinucleotide, which leads to axonal degeneration (34). The exact location of SARM-1 is under investigation, with some evidence suggesting that it may be localized to neuronal mitochondria and may associate with other mitochondrial proteins to induce apoptosis (35). Hence, targeting of SARM-1 is an emerging strategy for the prevention of CIPN with targeted drugs currently being in development.

In addition to the SARM-1 pathway, there are other targetable molecules that may protect axonal health. In preclinical DRG cell lines and rodent models, ethoxyquin prevents paclitaxel- and cisplatin-induced distal axonal degeneration via HSP 90 modulation, without compromising antitumor efficacy (36). Clinical trial testing of this agent is currently under consideration. In addition, the Bcl2 family of proteins, including Bclw, may play a role in axonal degeneration caused by paclitaxel. The addition of the peptide Bclw prevented chemotherapy-induced nerve degeneration by interaction with IP3 receptor activity on neurons. Thus,

modulation of Bclw levels might represent another novel therapeutic strategy for prevention of CIPN (37).

Targeting Apurinic/Apyrimidinic Endonuclease Function

Another mechanism of nerve injury from chemotherapy, particularly cisplatin and oxaliplatin, is secondary to drug-induced DNA damage in sensory neurons (38). The base excision repair pathway is the primary means for repairing oxidative DNA damage; within this pathway, the enzyme apyrimidinic endonuclease/redox effector factor (APE1) is important for the removal of the damaged bases. Reduction of APE1 expression in sensory neurons increases neurotoxicity (39), and the targeting of APE1 by small-molecule APX3330 is protective against CIPN while also having *de novo* antitumor efficacy (40). APX3330 is entering human clinical trials as an antineoplastic agent as well for prevention of CIPN.

Targeting Inhibition of Neuronal Apoptosis and Astrocyte Activation

Fingolimod is commercially available as a marketed drug for multiple sclerosis. Preclinical models have suggested that this agent may also be a promising agent to prevent CIPN. In animal models, oral administration of fingolimod can both prevent and treat neuropathic pain from a variety of chemotherapeutic agents, without the development of tolerance to an analgesic effect. Importantly, fingolimod does not interfere with antitumor efficacy of chemotherapy (41, 42) and may have synergistic antitumor properties, making it an attractive agent for CIPN prevention studies during chemotherapy. The protective mechanism of action for fingolimod is based on the direct disruption on the sphingosine-1-phosphate (S1P) activation pathway, leading to an analgesic effect that is independent of the opiate pathway. Certain chemotherapy classes including taxanes (paclitaxel; ref. 41), platinum-based agents (oxaliplatin; ref. 41), and proteasome inhibitors (bortezomib; ref. 42) drive the development of CIPN by dysregulating sphingolipid metabolism, leading to increased formation of S1P, which binds and activates sphingosine-1-phosphate receptor 1 (S1PR1). Fingolimod may also promote peripheral nerve regeneration by S1P signaling (43, 44). The downstream effect of S1PR1 blockade is the inhibition of the Nuclear Factor Kappa B (NF-kB) pathway. Fingolimod's associated adverse effects which include bradycardia, atrioventricular conduction block, and hypotension must be considered when utilizing this drug for CIPN prevention and treatment (45).

Through a different mechanism, but with the ultimate downstream effect on the NF-kB pathway, nicotine is under investigation as another potential therapeutic strategy for both prevention and treatment of paclitaxel-induced CIPN (46). Associated data suggest that targeting the nicotinic acetylcholine receptor–mediated pathways may be promising for the prevention and treatment of CIPN induced by paclitaxel or oxaliplatin (47). A primary concern is that nicotine may also stimulate tumor growth, although the evidence for tumor proliferation has been inconsistent in preclinical models (47). Interestingly, smoking history has been classified as a risk factor for CIPN; however, this finding has limitations due to its determination from a secondary analysis whose primary endpoint was not related to this topic (48). Regardless, preclinical mechanistic data support further investigations through clinical trials utilizing commercially available nicotine replacement have been proposed. Other strategies include nicotinic acetylcholine agonists (49) or nicotinic receptor antagonists (50), as novel strategies for the prevention and treatment of CIPN.

Targeting the Gangliosinide-Monosialic Acid Pathway

Ganglioside-monosialic acid (GM1) is a type of glycosphingolipid, located in the outer layer of the plasma membrane, which is critical for nerve development, differentiation, and repair after injury (51). The proposed mechanisms of neuroprotection involve nerve regeneration, removal of oxygen free radicals, and inhibition of lipid peroxidation. In preclinical studies, GM1 has been effective for the prevention of CIPN (52). In the first published randomized clinical trial, 120 patients with gastrointestinal tumors received either oxaliplatin standard of care or with GM1 combination therapy (53). GM1 was associated with a reduced severity of oxaliplatin-induced neurotoxicity in this preliminary study, rendering clinically and statistically significant results and meeting the primary endpoint. The control group endured grades 2 and 3 neurotoxicity at a greater probability than the GM1 group (logistic ordinal regression), whereas the GM1 group experienced grades 0 or 1 neurotoxicity at a greater probability (logistic ordinal regression). A retrospective study was also performed to assess the efficacy of monosialotetrahexosylganglioside (GM1) for preventing oxaliplatin-induced neurotoxicity: from a total of 278 cases, 114 in GM1 group and 164 in control group, incidences of grade 1–3 and grade 3 acute and chronic neurotoxicity were lower in GM1 group (54). Additional placebo-controlled studies are needed, to better assess the utility of this agent, and a clinical trial study is currently ongoing, NCT02251977.

Serotonin–Norepinephrine Reuptake and Nociceptor Sodium Channel Inhibition

Serotonin and norepinephrine dual reuptake inhibitors, such as duloxetine and venlafaxine, are effective antidepressants with evidence of efficacy for improving neuropathic pain (55). To date, duloxetine, a serotonin–norepinephrine reuptake inhibitor, has been the only randomized phase III intervention study in CIPN associated with a significant reduction in neuropathic pain symptoms (20). Other studies with duloxetine have similarly supported the efficacy of this drug for reducing neuropathy symptoms following chemotherapy treatment (56, 57). The mechanism of duloxetine-induced analgesia is thought to be related to the blocking of serotonin and norepinephrine transporters, as well as blocking of sodium channel currents and affecting the descending inhibitory pain neural networks (58–60). As a consequence, spontaneous nerve impulses from peripheral nerves are not transmitted to the central nervous system, diminishing pain symptoms. Although the published data on the analgesic effects of duloxetine are on treatment of neuropathic pain, emerging preclinical data suggest that duloxetine may also be effective for prevention of CIPN. A new NCI-funded clinical trial is currently undergoing protocol development to evaluate the efficacy of duloxetine for prevention of oxaliplatin neuropathy.

The GABA-analogue and the voltage-gated Ca^{+2} channel antagonist, pregabalin, is also frequently recommended for pain associated with CIPN, because of its efficacy in managing diabetic neuropathic pain (61), neuropathic cancer pain (62), and rat CIPN models (63). However, a pilot trial did not suggest that pregabalin could prevent CIPN (64). This suggests that CIPN is a distinct condition independent from other peripheral neuropathies, such as those associated with diabetes, fibromyalgia, and neuropathic cancer pain in which pregabalin is effective (65). Gabapentin is another drug frequently recommended for CIPN management and shares the same mechanism of action as pregabalin. Similarly, trials do not demonstrate gabapentin's efficacy in treating established CIPN, best illustrated in a phase III trial (66).

The voltage-gated sodium channel 1.7 (Nav1.7) plays an important role in multiple preclinical models of neuropathic pain and in inherited human pain phenotypes. In preclinical models, utilization of peripheral sodium channel blockers targeting Na(v)1.7 was able to reverse hyperalgesia and allodynia without damaging motor function (67). In humans, SCN9A gene mutations that cause Na(v)1.7 deficiency lead to an inability to sense pain, or congenital indifference to pain, whereas gain-of-function missense mutations lead to spontaneous pain characterized by inherited erythromelalgia (IEM; ref. 68). Recent work demonstrates that the expression and function of the Na(v)1.7 are increased in a preclinical model of CIPN; more interestingly, it also shows that Nav1.7 is increased in human DRG neurons only in dermatomes where patients are experiencing acquired neuropathic pain symptoms (69). Data from a randomized, double-blind placebo-controlled crossover pilot study investigating the Na(v)1.7 antagonist, XEN402, indicate that patients with IEM experience 42% less pain from Na(v)1.7 blocking than placebo ($P = 0.014$; ref. 70). Further study is warranted to investigate the utility of Na(v)1.7 blocking agents such as XEN402 in patients experiencing neuropathic pain, including chemotherapy-induced neuropathic pain.

Conclusions

There are many novel promising targets that look promising for the prevention of CIPN and/or treatment of established CIPN. Several of these are currently entering clinical trials. If multiple agents are successful in clinical investigation, future studies will need to investigate the right target for individualized patients given at the right dose. Genomic and clinical predictors of response will hopefully be developed and validated as the potential for multiple promising agents may become a reality. The identified preclinical targets of CIPN discussed in this overview may be helpful as biomarkers of CIPN toxicity and treatment efficacy.

Disclosure of Potential Conflicts of Interest

C.L. Loprinzi is a consultant/advisory board member for PledPharma, Metys, Disarm Therapeutics, and Asahi Kasei Pharma Corporation. M.B. Lustberg is a consultant/advisory board member for PledPharma. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

Any opinions, findings, and conclusions expressed in this material are those of the authors and do not necessarily reflect those of the funding agency and Pelotonia program. The funding bodies had no role in the preparation of the article.

Acknowledgments

The project was supported in part by NIH grant R01CA238946 (M.B. Lustberg and S. Hu) and by The Ohio State University Comprehensive Cancer Center using Pelotonia funds (M.B. Lustberg and S. Hu).

Received February 22, 2019; revised April 17, 2019; accepted May 17, 2019; published first May 23, 2019.

References

1. De Iuliis F, Taglieri L, Salerno G, Lanza R, Scarpa S. Taxane induced neuropathy in patients affected by breast cancer: literature review. Crit Rev Oncol Hematol 2015;96:34–45.
2. Ewertz M, Qvortrup C, Eckhoff L. Chemotherapy-induced peripheral neuropathy in patients treated with taxanes and platinum derivatives. Acta Oncol 2015;54:587–91.
3. Bonhof CS, Mols F, Vos MC, Pijnenborg JMA, Boll D, Vreugdenhil G, et al. Course of chemotherapy-induced peripheral neuropathy and its impact on health-related quality of life among ovarian cancer patients: a longitudinal study. Gynecol Oncol 2018;149:455–63.
4. Carozzi VA, Canta A, Chiorazzi A. Chemotherapy-induced peripheral neuropathy: what do we know about mechanisms? Neurosci Lett 2015; 596:90–107.
5. Brewer JR, Morrison G, Dolan ME, Fleming GF. Chemotherapy-induced peripheral neuropathy: current status and progress. Gynecol Oncol 2016; 140:176–83.
6. Imai S, Koyanagi M, Azimi Z, Nakazato Y, Matsumoto M, Ogihara T, et al. Taxanes and platinum derivatives impair Schwann cells via distinct mechanisms. Sci Rep 2017;7:5947.
7. Kroigard T, Schroder HD, Qvortrup C, Eckhoff L, Pfeiffer P, Gaist D, et al. Characterization and diagnostic evaluation of chronic polyneuropathies induced by oxaliplatin and docetaxel comparing skin biopsy to quantitative sensory testing and nerve conduction studies. Eur J Neurol 2014;21: 623–9.
8. Hou S, Huh B, Kim HK, Kim KH, Abdi S. Treatment of chemotherapy-induced peripheral neuropathy: systematic review and recommendations. Pain Physician 2018;21:571–92.
9. Brown TJ, Sedhom R, Gupta A. Chemotherapy-induced peripheral neuropathy. JAMA Oncol 2019;5:750.
10. Boyette-Davis JA, Walters ET, Dougherty PM. Mechanisms involved in the development of chemotherapy-induced neuropathy. Pain Manag 2015;5: 285–96.
11. Boora GK, Kanwar R, Kulkarni AA, Abyzov A, Sloan J, Ruddy KJ, et al. Testing of candidate single nucleotide variants associated with paclitaxel neuropathy in the trial NCCTG N08C1 (Alliance). Cancer Med 2016;5: 631–9.
12. de Graan AJ, Elens L, Sprowl JA, Sparreboom A, Friberg LE, van der Holt B, et al. CYP3A4*22 genotype and systemic exposure affect paclitaxel-induced neurotoxicity. Clin Cancer Res 2013;19:3316–24.
13. Hertz DL, Roy S, Motsinger-Reif AA, Drobish A, Clark LS, McLeod HL, et al. CYP2C8*3 increases risk of neuropathy in breast cancer patients treated with paclitaxel. Ann Oncol 2013;24:1472–8.
14. Tanabe Y, Shimizu C, Hamada A, Hashimoto K, Ikeda K, Nishizawa D, et al. Paclitaxel-induced sensory peripheral neuropathy is associated with an ABCB1 single nucleotide polymorphism and older age in Japanese. Cancer Chemother Pharmacol 2017;79:1179–86.
15. Schneider BP, Li L, Radovich M, Shen F, Miller KD, Flockhart DA, et al. Genome-wide association studies for taxane-induced peripheral neuropathy in ECOG-5103 and ECOG-1199. Clin Cancer Res 2015;21: 5082–91.
16. Sucheston-Campbell LE, Clay-Gilmour AI, Barlow WE, Budd GT, Stram DO, Haiman CA, et al. Genome-wide meta-analyses identifies novel taxane-induced peripheral neuropathy-associated loci. Pharmacogenet Genomics 2018;28:49–55.

17. Frederiks CN, Lam SW, Guchelaar HJ, Boven E. Genetic polymorphisms and paclitaxel- or docetaxel-induced toxicities: a systematic review. Cancer Treat Rev 2015;41:935–50.
18. Schneider BP, Hershman DL, Loprinzi C. Symptoms: chemotherapy-induced peripheral neuropathy. Adv Exp Med Biol 2015;862:77–87.
19. Hershman DL, Lacchetti C, Dworkin RH, Lavoie Smith EM, Bleeker J, Cavaletti G, et al. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 2014;32: 1941–67.
20. Smith EM, Pang H, Cirrincione C, Fleishman S, Paskett ED, Ahles T, 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;309:1359–67.
21. Dorsey SG, Kleckner IR, Barton D, Mustian K, O'Mara A, St Germain D, et al. NCI Clinical Trials Planning Meeting for prevention and treatment of chemotherapy-induced peripheral neuropathy. J Natl Cancer Inst 2019 Jan 31 [Epub ahead of print].
22. Sprowl JA, Ness RA, Sparreboom A. Polymorphic transporters and platinum pharmacodynamics. Drug Metab Pharmacokinet 2013;28:19–27.
23. Fujita S, Hirota T, Sakiyama R, Baba M, Ieiri I. Identification of drug transporters contributing to oxaliplatin-induced peripheral neuropathy. J Neurochem 2019;148:373–85.
24. Liu JJ, Kim Y, Yan F, Ding Q, Ip V, Jong NN, et al. Contributions of rat Ctr1 to the uptake and toxicity of copper and platinum anticancer drugs in dorsal root ganglion neurons. Biochem Pharmacol 2013;85:207–15.
25. Leblanc AF, Sprowl JA, Alberti P, Chiorazzi A, Arnold WD, Gibson AA, et al. OATP1B2 deficiency protects against paclitaxel-induced neurotoxicity. J Clin Invest 2018;128:816–25.
26. Leblanc AF SJ, Gibson AA, Sparreboom A, Hu S. Targeting transporters to ameliorate chemotherapy-induced peripheral neuropathy. Eur J Cancer 2018;103:60.
27. Sprowl JA, Ong SS, Gibson AA, Hu S, Du G, Lin W, et al. A phosphotyrosine switch regulates organic cation transporters. Nat Commun 2016;7:10880.
28. Suh KJ, Lee JY, Shin DY, Koh Y, Bang SM, Yoon SS, et al. Analysis of adverse events associated with dasatinib and nilotinib treatments in chronic-phase chronic myeloid leukemia patients outside clinical trials. Int J Hematol 2017;106:229–39.
29. Xiao WH, Bennett GJ. Effects of mitochondrial poisons on the neuropathic pain produced by the chemotherapeutic agents, paclitaxel and oxaliplatin. Pain 2012;153:704–9.
30. Karlsson JO, Ignarro LJ, Lundstrom I, Jynge P, Almen T. Calmangafodipir [Ca4Mn(DPDP)5], mangafodipir (MnDPDP) and MnPLED with special reference to their SOD mimetic and therapeutic properties. Drug Discov Today 2015;20:411–21.
31. Glimelius B, Manojlovic N, Pfeiffer P, Mosidze B, Kurteva G, Karlberg M, et al. Persistent prevention of oxaliplatin-induced peripheral neuropathy using calmangafodipir (PledOx((R))): a placebo-controlled randomised phase II study (PLIANT). Acta Oncol 2018;57:393–402.
32. Areti A, Komirishetty P, Kumar A. Carvedilol prevents functional deficits in peripheral nerve mitochondria of rats with oxaliplatin-evoked painful peripheral neuropathy. Toxicol Appl Pharmacol 2017;322:97–103.
33. Geisler S, Doan RA, Strickland A, Huang X, Milbrandt J, DiAntonio A. Prevention of vincristine-induced peripheral neuropathy by genetic deletion of SARM1 in mice. Brain 2016;139:3092–108.
34. Gerdts J, Brace EJ, Sasaki Y, DiAntonio A, Milbrandt J. SARM1 activation triggers axon degeneration locally via NAD(+) destruction. Science 2015; 348:453–7.
35. Killackey SA, Rahman MA, Soares F, Zhang AB, Abdel-Nour M, Philpott DJ, et al. The mitochondrial Nod-like receptor NLRX1 modifies apoptosis through SARM1. Mol Cell Biochem 2019;453:187–96.
36. Zhu J, Carozzi VA, Reed N, Mi R, Marmiroli P, Cavaletti G, et al. Ethoxyquin provides neuroprotection against cisplatin-induced neurotoxicity. Sci Rep 2016;6:28861.
37. Pease-Raissi SE, Pazyra-Murphy MF, Li Y, Wachter F, Fukuda Y, Fenstermacher SJ, et al. Paclitaxel reduces axonal Bclw to initiate IP3R1-dependent axon degeneration. Neuron 2017;96:373–86e6.
38. Ta LE, Espeset L, Podratz J, Windebank AJ. Neurotoxicity of oxaliplatin and cisplatin for dorsal root ganglion neurons correlates with platinum-DNA binding. Neurotoxicology 2006;27:992–1002.
39. Kelley MR, Jiang Y, Guo C, Reed A, Meng H, Vasko MR. Role of the DNA base excision repair protein, APE1 in cisplatin, oxaliplatin, or carboplatin induced sensory neuropathy. PLoS One 2014;9:e106485.
40. Kelley MR, Wikel JH, Guo C, Pollok KE, Bailey BJ, Wireman R, et al. Identification and characterization of new chemical entities targeting apurinic/apyrimidinic endonuclease 1 for the prevention of chemotherapy-induced peripheral neuropathy. J Pharmacol Exp Ther 2016;359: 300–9.
41. Janes K, Little JW, Li C, Bryant L, Chen C, Chen Z, et al. The development and maintenance of paclitaxel-induced neuropathic pain require activation of the sphingosine 1-phosphate receptor subtype 1. J Biol Chem 2014; 289:21082–97.
42. Stockstill K, Doyle TM, Yan X, Chen Z, Janes K, Little JW, et al. Dysregulation of sphingolipid metabolism contributes to bortezomib-induced neuropathic pain. J Exp Med 2018;215:1301–13.
43. Heinen A, Beyer F, Tzekova N, Hartung HP, Kury P. Fingolimod induces the transition to a nerve regeneration promoting Schwann cell phenotype. Exp Neurol 2015;271:25–35.
44. Szepanowski F, Derksen A, Steiner I, Meyer Zu Horste G, Daldrup T, Hartung HP, et al. Fingolimod promotes peripheral nerve regeneration via modulation of lysophospholipid signaling. J Neuroinflammation 2016;13:143.
45. Kappos L, Radue EW, O'Connor P, Polman C, Hohlfeld R, Calabresi P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N Engl J Med 2010;362:387–401.
46. Kyte SL, Toma W, Bagdas D, Meade JA, Schurman LD, Lichtman AH, et al. Nicotine prevents and reverses paclitaxel-induced mechanical allodynia in a mouse model of CIPN. J Pharmacol Exp Ther 2018;364:110–9.
47. Kyte SL, Gewirtz DA. The Influence of nicotine on lung tumor growth, cancer chemotherapy, and chemotherapy-induced peripheral neuropathy. J Pharmacol Exp Ther 2018;366:303–13.
48. Kawakami K, Tunoda T, Takiguchi T, Shibata K, Ohtani T, Kizu J, et al. Factors exacerbating peripheral neuropathy induced by paclitaxel plus carboplatin in non-small cell lung cancer. Oncol Res 2012;20:179–85.
49. Lynch JJ 3rd, Wade CL, Mikusa JP, Decker MW, Honore P. ABT-594 (a nicotinic acetylcholine agonist): anti-allodynia in a rat chemotherapy-induced pain model. Eur J Pharmacol 2005;509:43–8.
50. Pacini A, Micheli L, Maresca M, Branca JJ, McIntosh JM, Ghelardini C, et al. The alpha9alpha10 nicotinic receptor antagonist alpha-conotoxin RgIA prevents neuropathic pain induced by oxaliplatin treatment. Exp Neurol 2016;282:37–48.
51. Ferrari G, Anderson BL, Stephens RM, Kaplan DR, Greene LA. Prevention of apoptotic neuronal death by GM1 ganglioside. Involvement of Trk neurotrophin receptors. J Biol Chem 1995;270:3074–80.
52. Chentanez V, Thanomsridejchai N, Duangmardphon N, Agthong S, Kaewsema A, Huanmanop T, et al. Ganglioside GM1 (porcine) ameliorates paclitaxel-induced neuropathy in rats. J Med Assoc Thai 2009;92:50–7.
53. Zhu Y, Yang J, Jiao S, Ji T. Ganglioside-monosialic acid (GM1) prevents oxaliplatin-induced peripheral neurotoxicity in patients with gastrointestinal tumors. World J Surg Oncol 2013;11:19.
54. Chen XF, Wang R, Yin YM, Roe OD, Li J, Zhu LJ, et al. The effect of monosialotetrahexosylganglioside (GM1) in prevention of oxaliplatin induced neurotoxicity: a retrospective study. Biomed Pharmacother 2012;66:279–84.
55. Lunn MP, Hughes RA, Wiffen PJ. Duloxetine for treating painful neuropathy, chronic pain or fibromyalgia. Cochrane Database Syst Rev 2014: CD007115.
56. Battaglini E, Park SB, Barnes EH, Goldstein D. A double blind, placebo controlled, phase II randomised cross-over trial investigating the use of duloxetine for the treatment of chemotherapy-induced peripheral neuropathy. Contemp Clin Trials 2018;70:135–8.
57. Yang YH, Lin JK, Chen WS, Lin TC, Yang SH, Jiang JK, et al. Duloxetine improves oxaliplatin-induced neuropathy in patients with colorectal cancer: an open-label pilot study. Support Care Cancer 2012;20: 1491–7.
58. Bymaster FP, Dreshfield-Ahmad LJ, Threlkeld PG, Shaw JL, Thompson L, Nelson DL, et al. Comparative affinity of duloxetine and venlafaxine for serotonin and norepinephrine transporters in vitro and in vivo, human serotonin receptor subtypes, and other neuronal receptors. Neuropsychopharmacol 2001;25:871–80.

59. Skljarevski V, Zhang S, Iyengar S, D'Souza D, Alaka K, Chappell A, et al. Efficacy of duloxetine in patients with chronic pain conditions. Curr Drug ther 2011;6:296–303.
60. Wang SY, Calderon J, Kuo Wang G. Block of neuronal Na+ channels by antidepressant duloxetine in a state-dependent manner. Anesthesiology 2010;113:655–65.
61. Satoh J, Yagihashi S, Baba M, Suzuki M, Arakawa A, Yoshiyama T, et al. Efficacy and safety of pregabalin for treating neuropathic pain associated with diabetic peripheral neuropathy: a 14 week, randomized, double-blind, placebo-controlled trial. Diabet Med 2011;28:109–16.
62. Mishra S, Bhatnagar S, Goyal GN, Rana SP, Upadhya SP. A comparative efficacy of amitriptyline, gabapentin, and pregabalin in neuropathic cancer pain: a prospective randomized double-blind placebo-controlled study. Am J Hosp Palliat Care 2012;29:177–82.
63. Xiao W, Boroujerdi A, Bennett GJ, Luo ZD. Chemotherapy-evoked painful peripheral neuropathy: analgesic effects of gabapentin and effects on expression of the alpha-2-delta type-1 calcium channel subunit. Neuroscience 2007;144:714–20.
64. Shinde SS, Seisler D, Soori G, Atherton PJ, Pachman DR, Lafky J, et al. Can pregabalin prevent paclitaxel-associated neuropathy?–An ACCRU pilot trial. Support Care Cancer 2016;24:547–53.
65. Verma V, Singh N, Singh Jaggi A. Pregabalin in neuropathic pain: evidences and possible mechanisms. Curr Neuropharmacol 2014;12:44–56.
66. Rao RD, Michalak JC, Sloan JA, Loprinzi CL, Soori GS, Nikcevich DA, et al. Efficacy of gabapentin in the management of chemotherapy-induced peripheral neuropathy: a phase 3 randomized, double-blind, placebo-controlled, crossover trial (N00C3). Cancer 2007;110:2110–8.
67. Bankar G, Goodchild SJ, Howard S, Nelkenbrecher K, Waldbrook M, Dourado M, et al. Selective NaV1.7 antagonists with long residence time show improved efficacy against inflammatory and neuropathic pain. Cell Rep 2018;24:3133–45.
68. Drenth JP, Waxman SG. Mutations in sodium-channel gene SCN9A cause a spectrum of human genetic pain disorders. J Clin Invest 2007; 117:3603–9.
69. Li Y, North RY, Rhines LD, Tatsui CE, Rao G, Edwards DD, et al. DRG voltage-gated sodium channel 1.7 is upregulated in paclitaxel-induced neuropathy in rats and in humans with neuropathic pain. J Neurosci 2018; 38:1124–36.
70. Goldberg YP, Price N, Namdari R, Cohen CJ, Lamers MH, Winters C, et al. Treatment of Na(v)1.7-mediated pain in inherited erythromelalgia using a novel sodium channel blocker. Pain 2012;153:80–5.
71. Lustberg MB, Hu S. Prevention of paclitaxel-induced peripheral neuropathy with nilotinib. NCI R012019.
72. Hu S, Noonan A. Prevention of oxaliplatin neuripathy with dasatanib. Pelotonia Funding The Ohio State Comprehensive Cancer Center 2019.
73. Preventive Treatment of Oxaliplatin Induced Peripheral Neuropathy in Metastatic Colorectal Cancer (POLAR M). NCT03654729 [cited 2019 Feb 13]. Available from: https://clinicaltrials.gov/ct2/show/NCT03654729.
74. Ellin S. Duloxetine for the prevention of oxaliplatin neuropathy. NCI R012019.
75. Effect of GM1 in Prevention of Oxaliplatin Induced Neurotoxicity in Stage II/III Colorectal Cancer. NCT02251977 [cited 2019 Feb 13]. Available from: https://clinicaltrials.gov/ct2/show/NCT02251977.