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Mini Review

Chemotherapy-induced Peripheral Neuropathy: A Mini-review of Current & Developmental Treatments

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Abstract

Chemotherapy-Induced Peripheral Neuropathy (CIPN) is a major limiting side effect of many common chemotherapeutics often leading patients to terminate their chemotherapy treatment regimen early. The development of CIPN differs by chemotherapeutic class, with platinum- and taxane-based treatments demonstrating the highest incidence rates. Despite its relatively high prevalence, there are currently no FDA-approved treatments for CIPN, and clinicians must rely on the off-label use of several analgesics and various non-pharmacological approaches to treat CIPN symptoms in patients. Novel insights on the development of CIPN have identified new drug targets leading to several Phase II clinical trials to be initiated. Here, we describe recent advances in drug development for CIPN.

More Information

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Introduction

Chemotherapy-Induced Peripheral Neuropathy (CIPN) [1] is a common and debilitating side effect of certain neurotoxic cancer drugs such as platinum-based compounds, taxanes, vinca alkaloids, and bortezomib [2]. CIPN can cause pain, numbness, tingling, and loss of function in the hands and feet, affecting the quality of life and survival rates of cancer patients [3]. In 2023, there were approximately 2.0 million new cases of cancer reported within the US, and it has been reported that approximately 58% of patients require some form of chemotherapy [4,5]. Of these, neurotoxic chemotherapies such as platinum- and taxane-based drugs are commonly used, and it has been estimated that 50% - 70% of cancer patients receive platinum-based therapy as part of their treatment regimen [6]. In a 2014 study, researchers examined a cohort of 4,179 cancer patients across 30 clinical studies who were treated with various neurotoxic chemotherapies, their findings of which revealed a combined CIPN prevalence of 48% among these patients [7]. Prevalence varied based on the timeframe post-treatment where approximately 68% of patients experienced CIPN after 1 month, 60% after 3 months, and 30% after 6 months following treatment [7]. However, CIPN prevalence differs based on chemotherapy type, with oxaliplatin exhibiting the highest CIPN rate at around 71% and paclitaxel at 63% measured at 6 months post-treatment [8]. Another review describes agent-dependent CIPN prevalence of 70% - 100% for platinum-based drugs, 11% - 87% for taxanes, and 20% - 60% for thalidomide and its analogues. The rate of CIPN in bortezomib-treated patients is approximately 27% [9,10].

There is no definitive or approved prevention or treatment for CIPN, but some strategies that have been studied include dose modification, pharmacological agents, and non-pharmacological interventions [11-13]. The only pharmacological agent recommended for treating CIPN pain to date is the Serotonin and Norepinephrine Reuptake Inhibitor (SNRI) antidepressant, duloxetine, however even its benefit is limited [11,14,15]. For example, one study comparing duloxetine to placebo for both the prevention and treatment of CIPN showed duloxetine's effect to be statistically similar to placebo. An alternative study suggested that duloxetine's highest approved dose of 60 mg was actually inferior to pregabalin's approved mid-dose of 150 mg in taxane-induced peripheral neuropathy [16-20]. Other drugs that may provide CIPN analgesia include opioids, steroids, topical anesthetics, and anticonvulsants [15]. Non-pharmacological interventions that may improve CIPN symptoms include physical therapy, occupational therapy, acupuncture, electrical nerve stimulation, and biofeedback [14]. However, the evidence for these modalities is limited, and more clinical data is needed to establish their efficacy and safety.

Novel, non-opioid therapeutic targets for CIPN

Despite the advances in understanding the pathophysiology

of CIPN, there is still a lack of effective and safe therapies that are specifically approved for this condition. Therefore, there is a need to explore new mechanisms of action and developmental products that target both the prevention and treatment of CIPN. Emerging approaches span a variety of mechanisms of action, the most developed of which include, IL-6 antagonists, Schwann cell differentiation enhancers, glutamate signaling modulators, Histone Deacetylase 6 (HDAC6) inhibitors, muscarinic M1 receptor antagonists, apoptosis stimulants, and SNRIs (Figure 1). Among these are both small molecules formulated as either orals or topicals, as well as injectable biologics. Here, and summarized in Table 1, we describe some select recent advances in CIPN-targeted therapeutics and their current developmental status.

Therapeutic approaches currently in phase 2 clinical development

Schwann Cell Differentiation Enhancement. Ono Pharmaceuticals (Japan) is developing small molecule ONO-2910 outside of the US as an orally bioavailable treatment for CIPN pain [21]. ONO-2910 accelerates the repair process of nerve fibers by enhancing Schwann cell differentiation into myelin-forming cells and suppressing the de-differentiation into injury-responsive cells [22]. By doing so, ONO-2910 may prevent or reduce the onset and severity of CIPN symptoms. ONO-2910 is currently recruiting for a Phase 2 clinical trial to investigate its use as a prevention of CIPN in breast cancer patients receiving weekly paclitaxel [23].

Glutamate Signaling Modulation. MP-101 is a small molecule, orally administered glutamate signaling modulator that acts as an NMDA receptor antagonist and contains racemic dimiracetam and its R-enantiomer as active ingredients. Excessive glutamate signaling can lead to neuronal damage and pain sensitization, and MP-101 works by blocking the release of glutamate from nerve terminals and reducing the activity of NMDA receptors, which are key mediators of glutamate signaling [24]. MP-101 is being developed by Novaremed (Switzerland) for the prevention of CIPN pain [25].

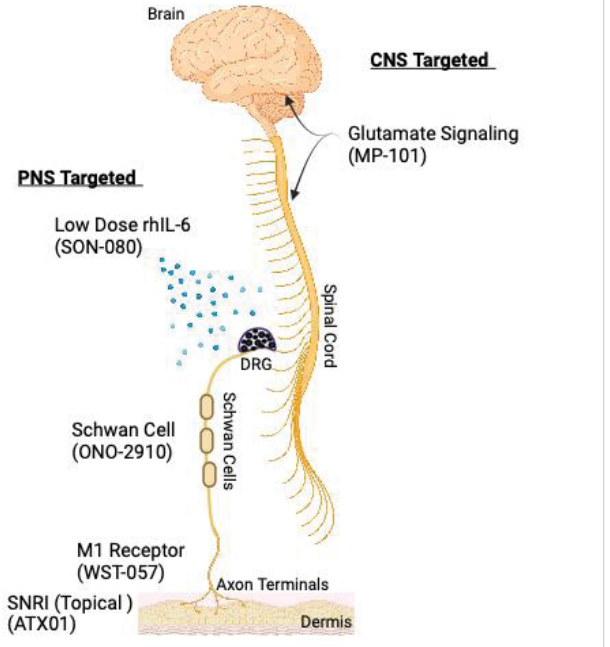

Figure 1: Peripheral and central nervous system targets of Phase II CIPN treatments. Peripheral Nervous System (PNS) targeted therapies include, SON-080 a low-dose recombinant human IL-6 (rhIL-6), ONO-2910 which enhances Schwan cell myelination, WST-057 which increases axon terminal density and ATX01 a topical SNRI. Central Nervous System (CNS) therapy includes MP-101 an NMDA receptor antagonist. DRG = Dorsal Root Ganglia.

Serotonin and Norepinephrine Reuptake Inhibition. As an SNRI, ATX01 aims to improve upon fellow SNRI duloxetine's effectiveness, which is currently used off-label to treat CIPN, but as an approved drug. AlgoTherapeutix (France) is developing ATX01 as a topical formulation of amitriptyline to target nerve fibers in the skin and avoid potential systemic toxicities and has received Fast-Track designation from the U.S. Food and Drug Administration (FDA) [26]. AlgoTherapeutic is currently enrolling for a global Phase II study of ATX01 in CIPN patients [27].

Muscarinic M1 Receptors Antagonization. WST-057 is a muscarinic M1 receptor antagonist being developed as a treatment for CIPN. WST-057 is being developed by WinSanTor (US) as a topical formulation of pirenzepine, which was originally approved for use in Europe and Asia to treat gastric ulcers but has yet to be approved by the FDA for CIPN pain. WST-057 acts to block the action of acetylcholine to prevent or reduce nerve damage and pain caused by CIPN and may have neuroprotective effects by enhancing nerve growth factor signaling and increasing nerve fiber density [28]. WST-057 is currently recruiting for a Phase 2 clinical trial in patients with CIPN [29].

Low-Dose IL-6 Mimetic. Sonnet Biotherapeutics (US) is currently developing an injectable, low-dose IL-6 antagonist (SON-080) for the treatment of CIPN pain [30]. At high expression levels, IL-6 acts as a proinflammatory cytokine. However, as a recombinant human IL-6 mimetic, SON-080 works by mimicking the physiological effects of low levels of native IL-6 which can reduce inflammation, promote nerve regeneration, and improve glucose homeostasis. Sonnet is currently recruiting for a Phase 1/2 trial for SON-080 in CIPN patients [31].

Therapeutic approaches currently in phase 1 clinical development

Histone Deacetylase 6 Inhibition. Regenacy Pharmaceuticals (US) is currently developing ricolinostat, an aHDAC6 inhibitor, as an orally bioavailable treatment for CIPN pain. Ricolinostat works by inhibiting the HDAC6 enzyme, which removes acetyl groups from proteins, and HDAC6 specifically is a key regulator of various mitochondrial mechanisms, dysfunction of which can lead to peripheral neuropathy [32]. Also, by selectively inhibiting HDAC6 as

Table 1: Select Therapeutic Approaches Currently in Phase 1 & Phase 2 Clinical Development for CIPN.

Drug	MoA	Company	Phase	Molecule Type	Route of Administration	Intervention Type	Patient Population
ONO-2910	Enhancement of Schwann cell differentiation	Ono Pharmaceutical	Phase 2	Small	Oral	Prevention	Breast cancer patients
MP-101	Glutamate signaling modulator (acetylcholine receptor agonist; NMDA receptor antagonist)	Novaremed	Phase 2	Small	Oral	Prevention	CIPN patients
ATX01	Serotonin & norepinephrine reuptake inhibitor	Algo Therapeutix	Phase 2	Small	Topical	Treatment	CIPN patients
WST-057	Muscarinic M1 receptor antagonist	WinSanTor	Phase 2	Small	Topical	Treatment	CIPN patients
SON-080	IL-6 antagonist	Sonnet BioTherapeutics	Phase 1/2	Biologic	Injectable	Treatment	CIPN patients
BXQ-350	Apoptosis stimulant	Bexion Pharmaceuticals	Phase 1	Biologic	Injectable	Treatment	CIPN patients
Ricolinostat	Histone deacetylase 6 (HDAC6) inhibitor	Regenacy Pharmaceuticals	Phase 1	Small	Oral	Treatment	CIPN patients

opposed to pan-HDAC inhibition by drugs such as vorinostat and panobinostat, ricolinostat may resultingly confer a lower risk of side effects [33]. It may also have neuroprotective effects. Regenacy Pharmaceuticals is currently recruiting for a Phase 1 CIPN trial for the use of ricolinostat in breast cancer patients previously treated with docetaxel or paclitaxel [34].

Apoptosis Stimulation. BXQ-350 is an apoptosis stimulant being developed by Bexion Pharmaceuticals (US). BXQ-350 may have neuroprotective effects by reducing the levels of Sphingosine-1-Phosphate (S1P), an anti-apoptotic sphingolipid that promotes cell survival, proliferation, and migration, as well as immune suppression and inflammation [35]. S1P has also been implicated in the development and maintenance of neuropathic pain, as it selectively activates the S1P receptor subtype 1 in astrocytes to modulate neuro-immune cell interactions [36,37]. Neuroinflammation, triggered by elevated proinflammatory cytokines within the spinal cord, most notably TNFα and IL-1β, plays a pivotal role in the initiation and persistence of neuropathic pain [38]. Specifically, IL-1β enhances neuronal excitability, thereby contributing to central sensitization during neuropathic pain, partly through its inhibitory effect on IL-10 release [38].

Conclusion

Here, we describe the current efforts of several clinical-stage CIPN-targeted programs. Despite several drugs in Phase 2 clinical trials, high historical failure rates of drugs to advance from Phase 2 to approval means it is likely that many, if not most, of these drugs will never make it to market and into clinical use. In fact, the likelihood of a neuro-targeted drug in Phase 2 clinical development reaching approval is approximately 24%, which is less than the 27% average for non-oncology drugs in general [39]. Thus, there is a large need for other novel therapeutic targets to be identified which can expand our efforts to better prevent and treat CIPN as well as expand our drug armamentarium.

Conflict of interest

Robert Freeze and Scott Scarneo are both shareholders in EydisBio, Inc., which is currently developing novel treatments for CIPN.

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