Pain Ther (2022) 11:1113–1136
https://doi.org/10.1007/s40122-022-00431-8

REVIEW

Emerging Approaches for the Management of Chemotherapy-Induced Peripheral Neuropathy (CIPN): Therapeutic Potential of the C5a/C5aR Axis

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Received: July 11, 2022 / Accepted: August 30, 2022 / Published online: September 13, 2022

ABSTRACT

Chemotherapy-induced peripheral neuropathy (CIPN) is the most common neurologic complication of chemotherapy, resulting in symptoms like pain, sensory loss, and numbness in the hands and feet that cause lots of uneasiness in patients with cancer. They often suffer from pain so severe that it interrupts the treatment, thus invalidating the entire chemotherapy-based healing process, and significantly reducing their quality of life. In this paper, we underline the role of the complement system in CIPN, highlighting the relevance of the C5a fragment and its receptor C5aR1, whose activation is thought to be involved in triggering a cascade of events that can lead to CIPN onset. Recent experimental data showed the ability of docetaxel and paclitaxel to specifically bind and activate C5aR1, thus shining light on one of the molecular mechanisms by which taxanes may activate a cascade of events leading to neuropathy. According to these new evidence, it was possible to suggest new mechanisms underlying the pathophysiology of CIPN. Hence, the C5a/C5aR1 axis may represent a new target for CIPN treatment, and the use of C5aR1 inhibitors can be proposed as a potential new therapeutic option to manage this high unmet medical need.

Keywords: CIPN; Chemotherapeutic drugs; C5a/C5aR axis; C5aR inhibitors; Peripheral neuropathy

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Key Summary Points

CIPN is a major dose-limiting side effect of chemotherapy that leads to neuropathic pain.

Several chemotherapeutic agents are commonly associated with the pathophysiology of CIPN, such as platinum-based compounds, vinca alkaloids, and taxanes.

Current therapeutic strategies for the management of CIPN leave a high unmet medical need; in fact, although there are drugs for treating CIPN, they have displayed only a moderate effect. The comprehension of the underlying molecular mechanisms could support the development of tailored new therapeutic approaches.

Evidence that taxanes can bind and activate the complement receptor C5aR1 highlights a potential role of the C5a/C5aR1 axis in the development of taxane-induced CIPN and provides indications on the design of a specific pharmacological approach.

Selective C5aR1 inhibitors may represent a novel and promising approach to develop new drugs to treat CIPN.

INTRODUCTION

Chemotherapy-induced peripheral neuropathy (CIPN) is the most common neurologic complication of chemotherapy that causes pain, sensory loss, and numbness in the hands and feet [1]. All these symptoms can impair activities of daily life, such as walking, dressing themselves, and writing, and course cause deficits in sensory, motor, and autonomic functions. It is estimated that 30–40% of patients with cancer treated with chemotherapeutic drugs suffer from neuropathies [1]. In many cases, acute CIPN leads to stopping of the chemotherapeutic treatment and the condition may last for months or years until it becomes chronic. The incidence of CIPN varies from 10% to 100% [2], depending on the type and the dosing regimen of the treatment. Changes in chemotherapy regimen or treatment dismission are necessary when pain is too severe, thus resulting in the risk of reducing the therapeutic efficacy.

Chemotherapeutic drugs are used to block the progression of cancer owing to their ability to kill cancer cells. However, these drugs also affect healthy cells, causing side effects such as anemia, diarrhea, nausea, and also leading to serious complications, such as infertility, infections, and pain [3]. At the same time, chemotherapeutic agents may impact nervous system structures and, depending on the compound and its mechanism of action, they are responsible for a variety of neuropathies, such as peripheral neuropathy [3, 4]. Alterations in immune signaling and ion channel expression, neurotoxicity, mitochondrial dysfunction, and axonal degeneration are considered among the most relevant mechanisms involved in CIPN [5, 6], and several studies highlight immune system and immune-mediated neuroinflammation as key events in its development [6, 7]. Various risk factors for CIPN have been identified, some of them treatment-related, such as drug pharmacological class, number and duration of treatment cycles, and others related to patient's age, health conditions, pre-existing damage to the nervous system, and prolonged consumption of alcohol [8, 9]. The balance between chemotherapy efficacy and safety is a highly debated challenge of cancer pharmacological treatment. Starting from recent experimental data that shed new light on possible new mechanisms of the onset of CIPN, the purpose of this review is to discuss the role of the C5a/C5aR1 axis in peripheral neuropathies, particularly in CIPN, and the therapeutic potential of C5aR1 inhibitors in the treatment of CIPN.

METHODS

In this review, we conducted a literature analysis on CIPN focusing on the main classes of

antineoplastic drugs associated with its development and on available protective therapies. A specific goal of the current analysis was to unravel available knowledge on the involvement of the C5a/C5aR1 axis in the pathophysiology of CIPN. The literature review was conducted using the PubMed database, through the analysis of the most relevant papers that emerged using the following keywords: "CIPN", "chemotherapy-induced peripheral neuropathy", "pathophysiology of CIPN", "preventive and protective strategies to manage CIPN", "complement and CIPN", "C5a and peripheral neuropathies", "C5a and CIPN". We collected 180 relevant articles.

Furthermore, to complete the search, we also used other databases like Cortellis™, CDDI, and ClinicalTrials.gov, to get and manage information on drugs, targets, and clinical trials in indications of interest.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

DISCUSSION

Antineoplastic Drugs Associated with CIPN Development

Six main classes of chemotherapeutic drugs are responsible for damage to the peripheral sensory, motor, and autonomic neurons, resulting in CIPN development: taxanes (paclitaxel, docetaxel), platinum-based antineoplastics (particularly oxaliplatin and cisplatin), vinca alkaloids (particularly vincristine and vinblastine), proteasome inhibitors (bortezomib), epothilones (ixabepilone), and immunomodulatory drugs (thalidomide) [3, 10] (Table 1). Among them, taxanes, platinum compounds, ixabepilone, thalidomide and analogues are the most neurotoxic; other commonly used drugs are bortezomib and vinca alkaloids [3] (Fig. 1).

Taxanes

Paclitaxel, docetaxel, and cabazitaxel are among the most widely used anticancer drugs for first-line treatments of several solid tumors [11, 12]. The incidence of CIPN due to taxane varies from 11% to 87% [13]. Generally, neuropathy

Table 1 Summary of the main chemotherapeutic agents that cause CIPN, their incidence (%), and their mechanism of action in CIPN

Chemotherapeutic agents	Incidence (%)	Mechanism of action in CIPN	References
Paclitaxel	11–87	Increase of ROS production and oxidative stress. Decrease of membrane potential and antioxidant bioavailability	Shim et al. [20], McCormick et al. [21]
Oxaliplatin	65–98	Targeting dorsal root ganglion. DNA cross-linking interference. Decrease of mitochondrial respiration	Scuteri et al. [38]
Vincristine	20	Activity on microtubules assembly and mitotic spindle formation	Topp et al. [44]
Bortezomib	34	Increase of sphingolipids metabolism in astrocytes and release of presynaptic glutamate in the dorsal horn	Stockstill et al. [50]
Ixabepilone	67	Disruption of microtubules, impairment of axonal transport to Wallerian degeneration and altered activity of ion channels	Vahdat et al. [51]
Thalidomide	25–75	Block of TNFα production and NFκB activation	Fernyhough et al. [54]

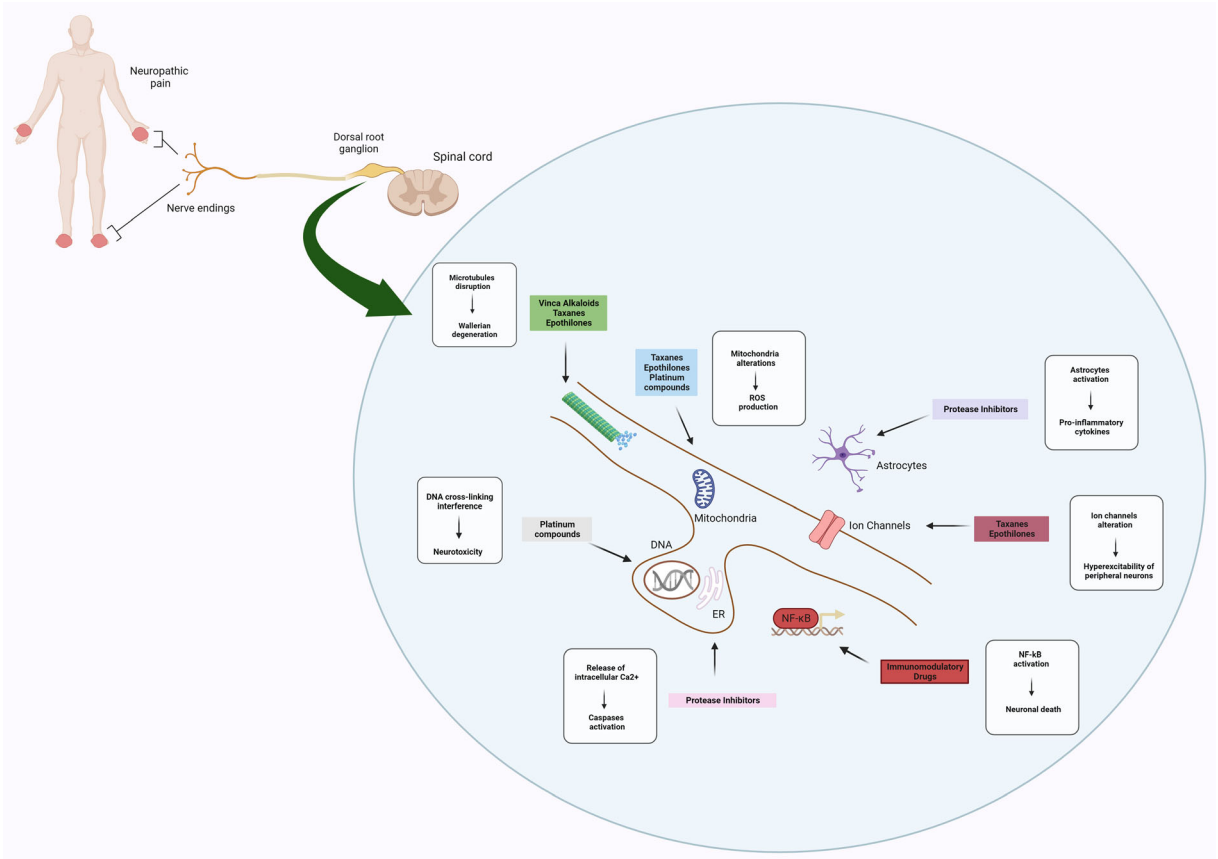

Fig. 1 Main classes of chemotherapeutic agents involved in the pathogenesis of CIPN at the dorsal root ganglia level, their targets, and main side effects

induced by taxanes is a sensory disorder which mainly affects sensory fibers, thus causing paresthesia, dysesthesia, and numbness in the fingers, although it can manifest itself also in motor fibers or the autonomic nervous system [14]. Symptoms of CIPN due to taxanes may begin a few days after the first dose and often stop at the end of the treatment, although some patients continue to suffer from CIPN for years or even for life [15]. Paclitaxel, one of the most used taxanes, causes microtubule disruption [16] which produces axon damage, impairing axonal transport and leading to Wallerian degeneration [17]. In severe cases, paclitaxel-induced impairment occurs along with secondary demyelination [18]. In addition, it also modifies expression and function of sodium, potassium, and transient receptor potential (TRP) ion channels [19], causing a hyperexcitability of peripheral neurons. Paclitaxel treatment impairs not only the axonal transport of mitochondria but also their morphology and function [18], contributing to increased production of reactive oxygen species (ROS) [20] responsible for mitochondrial activity, membrane potential and antioxidant bioavailability decrease [21], often leading to enzyme, protein, and lipid damage, dysregulation of calcium homeostasis within neurons, and finally inducing apoptotic changes and peripheral nerve demyelination [22]. Once microglia and astrocytes are activated by taxanes, both activation of immune cells and release of pro-inflammatory cytokines (interleukins and chemokines) occur, which result in nociceptor sensitization and hyperexcitability of peripheral neurons [23]. In fact, exposure to taxanes induces the production and release of pro-inflammatory cytokines such as tumor necrosis factor-α (TNFα), interleukin-1β (IL-1β), IL-6, and

chemokines such as IL-8, as well the decrease of anti-inflammatory cytokine expression, such as IL-10 and IL-4 [23]. Among the chemokines, IL-8 and its cognate receptors CXCR1 and CXCR2 are upregulated in several animal models following nerve injury [24, 25]. Furthermore, they are involved in development and maintenance of neuropathic and inflammatory hypernociception [26]. Another commercially available taxane is a protein-bound paclitaxel, nab-paclitaxel (Abraxane®). It is a nanoparticle formulation with paclitaxel bound to albumin, created as a "solvent-free" paclitaxel to avoid the observed toxic effects [27]. This formulation solved most of the problems related to hypersensitivity reactions [28, 29] associated with paclitaxel but therapy is still burdened by an increased risk of all-grade and high-grade peripheral neuropathy compared to other taxanes [30–32].

Platinum Compounds

Oxaliplatin, cisplatin, and carboplatin are currently used to treat various solid tumors [33]. The incidence of peripheral neuropathies caused by platinum compounds varies depending on the chemotherapeutic agent used. It is 49–100% for cisplatin [34], 13–42% for carboplatin [35], and 65–98% for oxaliplatin [36]. These drugs mainly target the dorsal root ganglia (DRG), susceptible to chemotherapeutic treatments, as they are not protected by the blood–brain barrier, and platinum-induced neuropathy manifests itself as sensory neuropathy, with concomitant pain, muscle cramps, and cold-induced allodynia [37]. By interfering with DNA cross-linking, platinum compounds cause neurotoxicity, early p38 and ERK1/2 activation [13], reduced mitochondrial respiration, increased oxidative stress, and dose-dependent apoptosis of DRG neurons [38]. They also increase expression of pro-inflammatory cytokines including TNFα and IL-1β and decrease expression of the neuroprotective cytokines IL-10 and IL-4 [39]. In this sense, peripheral sensory DRG neurons and their axons are particularly susceptible to collateral damage due to chemotherapy. Indeed, inflammatory mediators act on DRG neurons, which are pseudounipolar neurons responsible for pain transmission, whose nociceptor cell bodies are in the DRG and communicate with neuronal elements of the spinal cord dorsal horn, such as neurons, microglia, and astrocytes [40], actively participating in the signaling process. After nerve injury, sensory neurons produce chemokines and their receptors within the DRG, and the upregulation of chemokines was found to be involved in the development of neuropathic and inflammatory hypernociception [41].

Vinca Alkaloids

Vincristine and vinblastine, both derived from the periwinkle plant, are used either alone or in combination therapy to treat hematological and solid malignancies [42]. Vinca alkaloid-induced neuropathy can be sensory or motor, with an incidence of about 20% [8]. Similarly to taxanes, all vinca alkaloids may induce dose-dependent sensorimotor neuropathy with symptoms like pain in the hands and feet, muscle weakness, and cramping that usually appear within the first 3 months of treatment [43]. These compounds interfere with the assembly and stability of microtubules and also with mitotic spindle formation [44], showing a negative impact on organelle transport and signaling molecules, and dynamically altering the cytoskeletal structure [45]. Notably, structural alterations of sensory neurons and their peripheral myelinated axons caused by vinca alkaloids may contribute to the onset of neuropathy [44].

Protease Inhibitors

Bortezomib, ixazomib, and carfilzomib are used in the treatment of progressive multiple myeloma and mantle cell lymphoma [46]. The incidence of neuropathy induced by protease inhibitors is approximately 34% [47]. Patients develop chronic, distal, and symmetrical sensory peripheral neuropathy often accompanied by neuropathic pain syndrome that may last for weeks, months, or even years after drug termination [48]. Bortezomib was reported to initiate apoptosis in a model of myeloma cell lines, through the release of intracellular Ca^{2+} in the endoplasmic reticulum (ER), leading to

activation of caspase, a protease enzyme essential for programmed cell death [49]. In astrocytes protease inhibitors also increase sphingolipid metabolism that leads to the formation of different lipid molecules whose binding to astrocyte receptors may increase the release of presynaptic glutamate at the level of the dorsal horn, a main cause of neuropathic pain development [50].

Epothilones

These drugs, mainly represented by ixabepilone and sagopilone, are relatively new antineoplastic drugs. The incidence of severe CIPN due to ixabepilone ranges from 1% in previously untreated patients to 24% for patients previously treated with other chemotherapeutics, with prevalence estimated at about 67% [3]. Clinically, neuropathy caused by epothilones presents as mild or moderate dominant sensory neuropathy that mainly affects the sensory fibers of small diameter, and usually manifests itself as paresthesia, numbness, and pain mainly affecting feet and hands [51]. Since epothilones are a new class of antineoplastic drugs, the studies regarding epothilone-induced CIPN are limited. Epothilones and taxanes share some pathological mechanisms as a result of a similar primary mechanism of action targeting microtubule disruption.

Immunomodulatory Drugs

Thalidomide is a glutamic acid derivative and an immunomodulatory drug used for multiple myeloma treatment [3, 52]. This drug induces peripheral neuropathy in 25–75% of patients, with dose-dependent prevalence and severity [53]. The anticancer mechanism of immunomodulatory drugs is still poorly understood but may include blocking of TNFα production, of NFκB activation, and the subsequent acceleration of neuronal death [54]. The second key anticancer mechanism of thalidomide is its angiogenic effect by blocking the inhibition of basic fibroblast growth factor (b-FGF) and vascular endothelial growth factor (VEGF).

Mechanisms of CIPN

Understanding the mechanisms underlying CIPN is crucial to designing pharmacological and non-pharmacological strategies to mitigate this upsetting secondary effect of anticancer treatments. Chemotherapy causes changes to cellular structure and function, alterations to membrane receptors and ion channels, intracellular signaling, and neurotransmission, and all these changes can have a role in the onset of CIPN [55]. Alterations in sodium, potassium, and calcium channels may contribute to its development, and also TRP channels, of which several members are expressed in neurons and microglia, are known to be important in pain processing [56, 57]; TRP channels are also part of cellular pathways related to the synthesis of many inflammatory mediators associated with neuroprotection/neurotoxicity [58]. Chemotherapeutic drugs also alter mitochondrial function, negatively impacting on neuronal cells [59]. Inflammatory processes may contribute to CIPN development because chemotherapeutic agents, particularly taxanes and platinum-based compounds, were found to induce activation and release of pro-inflammatory cytokine and chemokines (TNFα, Il-1β, IL-6, IL-8), and reduction of anti-inflammatory cytokines (IL-10, IL-4) [22, 60], potentially triggering the nociceptive process in CIPN [61]. To date, it is believed that pro-inflammatory cytokines can act directly on receptors expressed by neurons and other cells of the nervous system [62]. For example, after 36 days of paclitaxel treatment, expression of IL-1β and TNFα in DRG in an animal model was elevated [23]. Furthermore, oxaliplatin treatment in rats caused an increase of IL-1 and TNFα levels, and a decrease of IL-10 and IL-4 levels in the spinal cord [63]. Chemokines also play a critical role in neuropathic pain conditions [64]. Chemotherapy induces an upregulation of the expression of chemokines, including CCL2 and CX3CL1, in sensory neurons [65]. IL-8 (CXCL8) and its receptors CXCR1 and CXCR2 are emerging promising targets for the management of CIPN as a result of their involvement in the development and maintenance of neuropathic pain and inflammatory hypernociception [26, 66].

IL-8/CXCR1/2 signaling was demonstrated to be able to modulate cellular biomarkers of pain in sensory neurons: in fact, following treatment with paclitaxel, DRG-derived neurons express high levels of p-JAK2 which in turn activates p-STAT3, involved in neuropathic pain and whose role is critical in all cell types, including neurons [67]. In a recent study in patients with peripheral neuropathy, IL-6 and IL-8 expression appeared to be sharply increased in skin biopsies [68], drawing attention to IL-8 and IL-6 as novel potential pharmacological targets for pain management [65].

The benefits of blocking pro-inflammatory signaling emphasize the potential role of this pathway in the initiation and worsening of CIPN [69], and some CXCR1/2 inhibitors were investigated in relevant animal models [70], because the comprehension of the molecular mechanisms underlying the chemotherapy-induced IL-8 upregulation could pave the way to targeted pharmacological approaches. In fact, IL-8 emerged as a key player of paclitaxel-induced neuronal toxicity that can be reduced by CXCR1/2 inhibitors [71]. These findings prompted new studies to investigate IL-8 upstream events potentially involved in paclitaxel-induced CIPN, with the final goal to find new therapeutic approaches for CIPN treatment. Based on this rationale, and as better reported below, both the link found between the activation of the C5a/C5aR1 axis and neuropathic pain [72], and the recent demonstration of the binding of paclitaxel to C5aR1 as a crucial event for CIPN occurrence, constitute the first strong demonstration that C5aR1 may be regarded as a new potential target for the prevention and the treatment of CIPN [73], with this receptor having been identified as an upstream mediator of IL-8, capable of binding paclitaxel with high affinity.

Current Therapeutic Strategies

CIPN is a painful and debilitating side effect of cancer chemotherapy with unclear pathogenesis. Currently available therapies are inadequate, and this often leads to a significantly reduced quality of life associated with a high degree of suffering, not only because of the intensity of the pain but also its lengthy duration [74, 75]. Accumulated evidence indicates that the initiation and progression of CIPN are tightly related to oxidative stress [76], abnormal spontaneous discharge, ion channel activation [77], upregulation of various pro-inflammatory cytokines, and activation of the neuroimmune system [78]. On the basis of these findings, multiple drugs, compounds, and non-pharmacological treatments have been developed as preventive and protective strategies against peripheral neuropathies induced by chemotherapeutics. Many compounds have been investigated as both preventive and protective treatments, and here we present a short discussion on the most relevant ones.

Pain Management

Opioid Therapy

According to the German Society for Neurology, opioid therapy can be considered to treat and alleviate neuropathic pain, although several limitations have been reported as a result of side effects, development of tolerance, and misuse [79]. Neuropathic pain generally shows a moderate response to opioid therapy [80]. A lowered incidence of CIPN was associated with oxycodone administration during chemotherapy [81]. In a multicenter, phase IV study (NCT01675531), the combined use of oxycodone and naloxone with gabapentin or pregabalin improved pain relief and symptom control in patients with CIPN, pushing further investigations on opioid therapy combined with adjuvant analgesics, such as gabapentin, for the treatment of neuropathic pain. However, additional research is needed to explore efficacy and safety of oxycodone/naloxone for managing CIPN symptoms [82].

Anticonvulsant Agents

The antiepileptic agent gabapentin was studied to determine its use in improving pain and symptoms due to CIPN. In pilot studies, gabapentin was identified as a potential treatment with improved self-reported measures of CIPN [83, 84]. However, in a randomized, double-

blind, placebo-controlled, phase III trial (NCT00027963), gabapentin did not show a significant change in pain score in patients with peripheral neuropathies [85], thus leading to the assumption that the administration of gabapentin is not able to significantly improve the primary endpoints of pain intensity or sensory neuropathy.

Anti-inflammatory Therapies

One of the best approaches to treat symptomatic neuropathic pain is to start with broad-spectrum analgesic medications, e.g., non-steroidal anti-inflammatory drugs (NSAIDs) [86]. If treatment with NSAIDs fails, second-line agents like opioids are the alternative. The use of NSAIDs underlines the link between inflammation and neuropathic pain, but studies involving these compounds in the treatment of CIPN are limited and require further research.

Ion Channel-Targeted Therapies

Chemotherapy results in electrophysiological changes of peripheral nociceptors such as enhanced excitability and reduced threshold [77], associated with ion concentration alteration. The activation of sodium, potassium, and calcium ion channels, and of TRPs, plays a critical role in CIPN pathophysiology [87]. In rodent models, lidocaine and mexiletine were able to block ion channels [88], thus significantly reverting both mechanical and cold allodynia induced by oxaliplatin and vincristine [89, 90], but further efficacy studies are required. Lidocaine was investigated also in a randomized double-blind phase I/II clinical trial (NCT03254394) but, despite its analgesic effect in CIPN with a moderate long-term effect, additional studies are needed [88].

Neurotransmitter-Based Therapy

There is mounting evidence that serotonin and norepinephrine dual reuptake inhibitors (SNRIs) are effective in treating neuropathy-related pain [91]. These compounds are key neurotransmitters that suppress transmission of painful peripheral stimuli by inhibiting input to the spinal dorsal horn neurons [92]. Duloxetine, a well-known SNRI, is administered in patients with CIPN owing to its established efficacy. Studies on this compound are ongoing: indeed, in a single-center, single-arm phase II clinical trial (NCT04970121), efficacy and safety of duloxetine in patients with taxane-induced painful neuropathy are being evaluated. In a recent study aimed at comparing safety of duloxetine and pregabalin, duloxetine was demonstrated to be well tolerated and efficacious in relieving neuropathic pain in patients treated with taxanes [93]. A phase III, randomized, double-blind, placebo-controlled, crossover clinical trial (NCT00489411) found that patients treated with duloxetine experienced a great reduction of CIPN-associated pain, particularly when induced by platinum derivatives, compared to placebo-treated patients [94]. On the basis of these results, duloxetine is now recommended for CIPN therapy, but potential drug interactions, particularly regarding the hepatic metabolism of duloxetine, should be considered for each individual patient and still limit its use.

Preventive Treatments

Calcium and Magnesium Infusion

Calcium and magnesium (Ca/Mg) infusion may be a promising strategy to prevent CIPN. Some ongoing clinical trials aim to test Ca/Mg infusion, immediately before and after each dose of chemotherapeutic drug, as a preventive strategy for peripheral neuropathies induced by taxanes (NCT01682499) and ixabepilone (NCT00998738). In a phase III, randomized, placebo-controlled, double-blind study (NCT00316914) involving 104 patients with colorectal cancer, it was shown that Ca/Mg infusion is an effective neuroprotectant against oxaliplatin-induced cumulative sensory neurotoxicity [95]. However, in a phase III study (NCT01099449) involving 362 patients with colon cancer, intravenous administration of Ca/Mg showed no benefits regarding the incidence of oxaliplatin-induced acute neurotoxicity symptoms [96]. Thus, the results obtained so far are contradictory and further studies are needed to reach a definitive conclusion on the efficacy of Ca/Mg infusion.

Targeting Glutathione and Glutamine Pathway

Most chemotherapeutic agents do not permeate the blood–brain barrier (BBB), but they penetrate the less efficient blood–nerve barrier and can accumulate in DRG neurons and nerve terminals [97]. Glutathione is an antioxidant involved in many detoxification reactions to protect the body from intracellular oxidants [98] and it is able to reduce the accumulation of platinum adducts in DRG [99]. Despite several positive pilot studies, a randomized phase III trial (NCT02311907) to investigate the potential role of glutathione in preventing peripheral neuropathy caused by paclitaxel and carboplatin in patients with ovarian cancer, fallopian tube cancer, and/or primary peritoneal cancer was inconclusive because it did not support the use of glutathione and did not show a higher efficacy of glutathione versus placebo in preventing peripheral neuropathy [100]. Glutamine is a non-essential amino acid stored primarily in skeletal muscle and the liver, with many biological functions including the ability to drive glutathione synthesis [101]. Some data suggest that peripheral neuropathy in patients receiving paclitaxel may be reduced with the addition of glutamine, which appeared to reduce the incidence and severity of symptoms caused by chemotherapy, such as dysesthesias, nerve conduction impairment, and interference with daily functioning [102, 103]. To date, glutamine is under development to evaluate its potential in the treatment of CIPN (NCT02215083).

Amifostine

As a result of the ability of some chemotherapeutic agents to increase ROS production [20], antioxidants have been proposed as a preventive strategy against chemotherapy-induced neurotoxicity, given that oxidative stress-mediated neurodegeneration is believed to be closely linked with CIPN [69]. In particular, amifostine, a cytoprotective antioxidant agent that accelerates DNA repair, is known for its protective effect against nephrotoxicity, neurotoxicity, and ototoxicity [104]. A phase II trial (NCT00003624) was designed to determine whether this drug prevents or ameliorates neurotoxicity associated with cisplatin and paclitaxel, but amifostine's level of activity in this trial was insufficient to warrant further study in a phase III trial [105]. In patients subjected to chemotherapy, premedication with amifostine was able to protect against sensory neuropathy [106]. However, its side effects such as hypocalcemia, hypotension, vomiting, sneezing, and nausea [107] limit a wider use of the drug.

Nutraceuticals

Several nutraceuticals/phytochemicals are used to alleviate CIPN, even with quite poor results. For instance, α-lipoic acid is a physiologic antioxidant studied in some clinical trials (NCT01313117, NCT00112996) as a preventive strategy for peripheral neuropathies in patients undergoing chemotherapy, especially when treated with taxanes, oxaliplatin, and cisplatin, but its use against CIPN has not been exhaustively investigated. Furthermore, oral α-lipoic acid administration was found to be ineffective in preventing neurotoxicity caused by oxaliplatin or cisplatin [108]. The approved nutraceutical Opera®, a combination of α-lipoic acid, *Boswellia serrata*, methylsulfonylmethane, and bromelain, was shown to be able to improve CIPN symptoms in a prospective series of patients treated with neurotoxic chemotherapeutics, with no significant toxicity or interaction [109]. Neuronorm®, a nutritional supplement containing docosahexaenoic acid, α-lipoic acid, vitamin C, and vitamin E, was studied with the aim to evaluate the prevention of the onset or the worsening of peripheral neuropathy in patients treated with bortezomib, and data seem to indicate that it may have some potential to be considered for future trials [110]. Despite positive findings in preclinical studies [111], to date the use of α-lipoic acid did not show clear benefits, and further confirmatory research is needed.

Non-pharmacological Treatments

Acupuncture has been studied in the management of peripheral neuropathy [112]. Various studies (NCT04739631, NCT03582423,

NCT02553863, NCT04770402, NCT02309164, NCT04067544, NCT02129686) suggested an interesting effect, but to date the clinical significance remains unclear and must be further investigated [113]. There has been little research on exercise therapy in the treatment of peripheral neuropathy (NCT04652609, NCT04621721, NCT03515356, NCT04888988), which in certain circumstances is thought to reduce symptoms of CIPN [114], but there are currently no evidence-based interventions that address the functional declined associated with CIPN [115].

A non-exhaustive overview of ongoing or completed clinical trials using protective and preventive treatments for CIPN is reported in Tables 2 and 3, respectively.

To date, no drugs have been approved to effectively manage CIPN; in fact, most of the drugs tested for treating CIPN aim at symptoms relief, including pain and paresthesia, but are not very efficacious [116, 117]. Clinical guidelines for CIPN treatment highlight the paucity of preventive strategies and symptoms management. This is the reason why novel therapeutic strategies are highly desirable, and research and development efforts aiming to better understand the general and specific mechanisms underlying CIPN are urgently needed.

The Complement System and the C5a/C5aR1 Axis

The complement system, which is a part of the immune system, is made up of more than 40 plasma proteins, and increases the ability of antibodies and phagocytes both to eliminate damaged or pathogenic cells from organisms and to promote inflammatory processes [118]. The proteins of the complement are synthesized by the liver and circulate in the blood as inactive precursors, activated by specific proteases to release cytokines and to initiate a cascade of events [119, 120]. The complement system has not only the function of first defense against pathogens but also it is a direct link between innate and adaptative immune systems, owing to its ability to interact with different cell types, such as dendritic cells, macrophages, and T and B cells [121]. The complement system is also involved in homeostasis, clearance of necrotic and apoptotic cells, cell debris, and immunocomplexes [122], in neurodevelopment [123], homing of hematopoietic stem and progenitor cells to bone marrow [124], tissue regeneration

Table 2 Overview of ongoing or completed clinical trials relating to treatments to manage CIPN symptoms

Treatment	Trial code	Drug	Phase	Status	Conditions	Key results
Opioids	NCT01675531	–	IV	Completed	CIPN	Reduction of pain score with oxycodone and naloxone taken together with pregabalin [82]
Gabapentin	NCT00027963	Vinca alkaloids, taxanes, platinum compounds	III	Completed	Neurotoxicity, pain	No significant changes in pain score [85]
Lidocaine	NCT03254394	Oxaliplatin	I/II	Completed	Painful neuropathy	Analgesic effects in CIPN but additional research needed [88]
Duloxetine	NCT04970121	Taxanes	II	Recruiting	CIPN, pain	Ongoing
	NCT00489411	Taxanes, platinum compounds	III	Recruiting	Neurotoxicity, pain	Greater reduction of pain [94]

Table 3 Overview of ongoing or completed clinical trials relating to strategies to prevent CIPN

Treatment	Trial code	Drug	Phase	Status	Conditions	Key results
Calcium gluconate/magnesium sulfate	NCT00316914	Oxaliplatin	III	Completed	Oxaliplatin-induced neurotoxicity	Neuroprotection against oxaliplatin-induced sensory neurotoxicity [95]
	NCT01099449	Oxaliplatin	III	Completed	Oxaliplatin-induced neurotoxicity	No benefits [96]
Glutathione	NCT02311907	Carboplatin, paclitaxel	III	Completed	Paclitaxel and carboplatin-induced neuropathy	No benefits [100]
Glutamine	NCT02215083	Taxanes	I	Withdrawn	Peripheral neuropathy	Currently ongoing
Amifostine	NCT00003624	Cisplatin, paclitaxel	II	Terminated	Neurotoxicity	Insufficient results to warrant further studies [105]
α-Lipoic acid	NCT00112996	Cisplatin, oxaliplatin	III	Completed	Neurotoxicity	No clear benefits [108–110]
	NCT01313117	Paclitaxel	I/II	Completed	Peripheral neuropathy	

[125], and metabolism [126]. There are three distinct pathways through which the complement system can be activated. They depend on different molecules and lead to the generation of the same set of effector molecules: the classical pathway, the alternative pathway, and the lectin pathway [121]. Recently, the role of the complement system, especially of the C5a fragment in pain processes, has been gaining attention [127]. The component C5a, also known as anaphylatoxin, is common for all the pathways of complement activation and it is now considered the most powerful inflammatory mediator produced by the cascade [128]. Indeed, it is responsible for the production of inflammatory mediators in immune cells [129], for the release of pro-inflammatory chemokines and cytokines, and for the decrease of anti-inflammatory cytokines [72]. It also increases the production of ROS by phagocytes [130], and calcium influx, and activates the NFκB pathway in several cell types, including neurons [131]. C5 is enzymatically cleaved by serine protease C5 convertase to produce two fragments, known as C5a and C5b. Besides its relevant action on clearance of pathogens and host defense, inappropriate activation of C5a contributes to various disorders [132]. In fact C5a activation leads to a cascade of events involved in the pathophysiology of peripheral neuropathy and in the genesis of painful neuroinflammation [133], mainly through the binding to its two receptors, C5a receptor 1 (C5aR1, CD88) [134] and C5a receptor 2 (C5aR2, C5L2, GPR77) [134], respectively. According to the latest nomenclature, we will designate them as C5aR1 (previously C5aR) and C5aR2 (previously C5L2) [135]. In particular, the C5a/C5aR1 axis triggers recruitment of leukocytes and production of pro-inflammatory cytokines [136]. C5aR1 is

expressed in different cell types, such as immune cells (neutrophils, eosinophils, monocytes, dendritic cells, and mast cells) [137–139] and nonimmune cells, like vascular endothelium [140], astrocytes [141], microglia [142], oligodendrocytes [143], primary sensory neurons of the DRG [144], neural stem cells [145], synoviocytes [146], articular chondrocytes [147], and others. Furthermore, the role of the C5a/C5aR axis in pathological conditions [122, 148, 149] such as rheumatoid arthritis [150], sepsis [151], autoimmune disorders [152], multiple sclerosis and Alzheimer's disease [153] was investigated.

Role of the C5a/C5aR1 Axis in Neuropathic Pain

Neuropathic pain is defined by the International Association for the Study of Pain (IASP) as a chronic pain state initiated or caused by a lesion or disease of the central (CNS) or peripheral somatosensory nervous system [133]. The triggering causes of neuropathic pain are many and of different origin, such as physical trauma, inflammatory or infectious conditions, metabolic or vascular alterations, treatments involving surgery or use of radiation, autoimmune disorders, and of course neurotoxins, among which chemotherapeutic agents [154]. Recent evidence and scientific data suggest the key role of the C5a/C5aR axis in neuroimmune and inflammatory interactions involved in the initiation and development of neuropathic pain hypersensitivity [72, 155]. While the C5a/C5aR1 pathway has always been considered a key mediator of the inflammatory response with potential involvement in inflammatory pain, recent data have highlighted its involvement in the pathophysiological mechanism responsible for the genesis of acute and chronic pain states [5]. A local inflammatory process establishes immediately after nerve injury, aiming to restore the damaged tissue, and this involves the recruitment of neutrophils, macrophages, and T cells which act in conjunction with other mechanisms for the production and release of inflammatory mediators at the site of injury [156]. It can be speculated that local C5a may be involved in the recruitment of neutrophils to the site of nerve injury [157]. The nerve damage, together with infiltrating cells, contributes to a functional plasticity of the nociceptive system [133], responsible for changes in the expression of receptors, ion channels, neurotransmitters, and enzymes, that leads to sensitization of nerve fibers at the site of damage. In this scenario the complement system seems to play a role in the immune response to nerve damage, as demonstrated by the observation that the reduction of complement components inhibits the recruitment of macrophages and their activation at the level of injured sciatic nerves [158], as macrophage infiltration contributes to neuropathic pain [159]. In particular, recent evidence suggest that C5a/C5aR1 signaling takes part in neuroimmunological processes in the damaged nerve, and consequently in the onset of neuropathic pain [5] (Fig. 2). In agreement with this, data reported increased C5a and C5aR1 levels at the site of injured sciatic nerve [133]. Evidence for a role of C5aR1 expressed on peripheral neurons came from recent studies, in which C5a and C5aR1 were shown to have a nociceptive activity: indeed, using animals subjected to spared nerve injury (SNI), a classical model of neuropathic pain, upregulated levels of C5a and C5aR1 were found in spinal cord microglia [72]. Furthermore, neuroimmune interaction in the periphery and spinal cord through activation of the complement cascade and the production of the anaphylatoxin C5a contributes to the genesis of neuropathic pain [160], thus leaving room for the hypothesis that blocking the signal induced by the activation of the C5a/ C5aR1 axis could represent an interesting target for pain control. Consequently, the emerging evidence suggests that inhibition of C5a activity by C5aR antagonists could represent a potential therapeutic approach for the control and/or treatment of acute and chronic neuropathic and neuroinflammatory pain [5], supported also by the reduction of paclitaxel-induced mechanical allodynia observed in a C3 knockout (KO) rat model that demonstrated a pivotal role of complement in CIPN, and stimulated research programs to explore this intriguing hypothesis [74]. Interestingly, a potentially striking confirmation of the role of the C5a/C5aR1 axis in neuropathic pain, and specifically in CIPN,

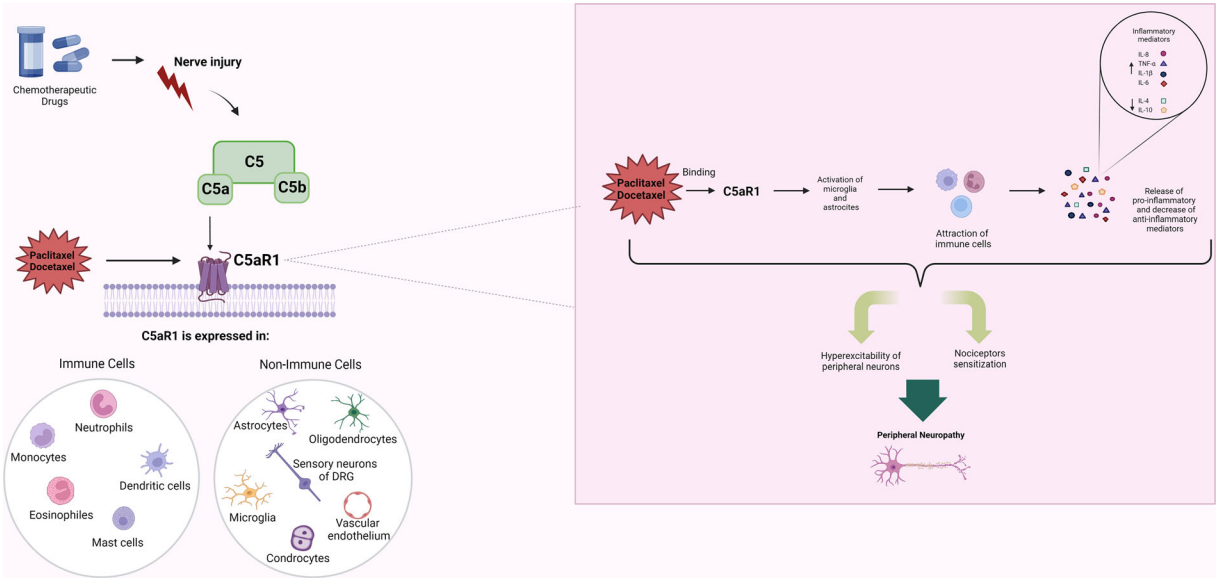

Fig. 2 Schematic representation of the C5a/C5aR1 axis and inflammatory process involved in the pathophysiology of peripheral neuropathies, and an overview of the effects of the binding of taxanes to C5aR1

recently emerged in preclinical studies addressing the molecular mechanisms underlying the undesirable effects of taxanes [73], as previously discussed, one of the most commonly used class of chemotherapeutics associated with CIPN development. Studies on activation pathways induced by taxanes in peripheral neural cells led researchers to identify and test both in vitro and in vivo that C5aR1 binding and activation by paclitaxel are crucial steps in the development and maintenance of taxane-induced CIPN, and that the blockage of C5aR1 is effective in preventing and counteracting CIPN [73]. In that study, C5aR1 was shown to be a molecular target of paclitaxel and involved in the previously reported taxane-induced IL-8 expression, and subsequent activation of CXCR1/2 signaling in neural cells, implicated in the taxane-induced neuropathic pain [73]. As a result of the urgent need for effective treatments for CIPN, a targeted pharmacological approach based on C5aR inhibition could represent an innovative and valuable approach to improve health and quality of life in patients with cancer undergoing taxane therapy [161]. Interestingly, CXCR1/2 pathway activation and IL-8 expression are common features between taxane-induced and platinum compound-induced neuropathic pain, and this observation in our opinion paves the way to additional studies aimed at clarifying the molecular mechanism of off-target effects associated with other classes of chemotherapeutics.

C5aR Inhibitors

Over the few last years, some therapeutic strategies have been proposed to inhibit C5a receptors and targeting C5aR has emerged as a novel anti-inflammatory strategy. However, the development of potent C5aR antagonists as drugs has proven to be difficult, despite the number of preclinical and clinical studies reported, mainly as a result of unclear disease mechanisms and unwanted side effects [162]. A possible alternative strategy for novel C5aR inhibitors is the allosteric approach. In fact, it is well known that allosteric modulators, owing to their structurally driven design, generally have improved drug-likeness properties [5] and ameliorated safety profile. This is an intrinsic and peculiar feature of allosteric modulation. It is due to the selective impact of modulators only on some of the intracellular transduction pathways that leaves others unaltered, without preventing the binding of the natural ligand to its receptor, in contrast with the classical

mechanism of action of orthosteric inhibitors such as peptidomimetics, which mimic the structure of C-terminal segment of C5a [163, 164].

In this context, several molecules were investigated, and new compounds selected and developed. Among them, avacopan (Vynpenta®), previously known as CCX-168, is an orally available small molecule C5aR inhibitor, launched in 2021 for the treatment of orphan and rare renal conditions, primarily as adjunctive treatment of adult patients with severe active anti-neutrophil cytoplasmic autoantibody-associated vasculitis (ANCA-associated vasculitis or ANCA vasculitis, AAV) in combination with standard therapy [165], a disorder for which avacopan is now considered a valid alternative to high-dose glucocorticoids known for their side effects [166], owing to its good safety and tolerability profile [167].

Avdoralimab, also known as IPH5401, is a human monoclonal antibody targeting C5aR expressed on neutrophils and myeloid-derived suppressor cells (MDSCs), able to reduce the release of pro-inflammatory factors and cancer cell proliferation [168, 169]. Currently, avdoralimab is under active development in phase II in the dermatological indication of bullous pemphigoid.

The cyclic hexapeptide PMX-53, also named 3D53, is a cyclic peptidomimetic C5aR antagonist, with nanomolar affinity towards the effector site with a well-clarified binding mode to the receptor [170]. This molecule blocks C5aR at an earlier stage of the immune and inflammatory process, and was shown active by intravenous, intraperitoneal, and subcutaneous injection [171], resulting in promising safe and well-tolerated treatment of inflammatory and autoimmune diseases (rheumatoid arthritis and psoriasis) [172]; however, this molecule failed in phase II because of its short half-life and unfavorable bioavailability.

C5aR inhibitors have been found efficacious and promising in several and different indications, but currently none of them is under development for the treatment of neuropathies, despite the scientific rationale supporting their use in this area [5]. Table 4 reports the highest phase of development for the aforementioned drugs by indication.

Table 4 C5aR inhibitors and their highest development stage by indication

Drug	Indication/therapeutic group	Highest stage
Avacopan	Severe active anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis	Launched (Tavneos®)
		Phase II
	Vasculitis	Phase II
	Hidradenitis suppurativa acne inversa	Phase III
	C3 glomerulopathy	
Avdoralimab	Bullous pemphigoid	Phase II
	COVID-19, infection	Phase II
	advanced/metastatic hematological or solid tumors	Phase I
	Advanced solid tumors	
PMX-53	Anti-inflammatory dermatological agent	Phase II
	Atopic dermatitis	
W-54011	Antiarthritic drugs	Preclinical
DF3016A	Analgesic drugs	Preclinical
DF3966A	Analgesic drugs	Preclinical

In recent years, GPCR allosteric modulation has been proposed as a promising new paradigm for the design of potent and selective drugs with improved drug-like properties, finely modulating the receptor function. Dompé farmaceutici S.p.A. conducted an extensive drug discovery and medicinal chemistry program targeting GPCRs, including C5aR, aimed at selecting and characterizing new chemical classes of allosteric modulators with optimal drug-likeness properties and improved safety profile over classic orthosteric inhibitors [173]. Initially, a first class of promising C5aR non-competitive allosteric inhibitors was identified, and the lead compound DF2593A was characterized in several in vivo models, among them a SNI model [174],

in which the pathophysiological role of the C5a/C5aR axis has been well clarified. DF2593A was selected starting from a chemo- and bioinformatic drug discovery approach using a technological platform targeting GPCRs. As a result of the lack of a known crystal structure of C5aR, a homology modelling approach was followed, which combined structural and functional information of allosteric sites in homologous GPCRs. Thus, it was possible to identify and characterize novel classes of C5aR allosteric inhibitors [174]. Starting from these first results, and performing additional MedChem, in vitro, and in vivo studies, a second-generation lead compound, DF3966A, was selected owing to its high activity and selectivity, combined with an improved pharmacokinetic and safety profile, making the lead suitable for further studies [175]. Recently, and for the first time, DF3966A was characterized in paclitaxel-induced CIPN [73]. The molecule was able to inhibit several paclitaxel-related effects, such as upregulation of several pro-inflammatory mediators, and expression of ion channels TRPV1 and TRPV4, key mediators of thermal, chemical, and mechanical stimuli in nociception. DF3966A can completely restore the altered electrical activity by both short and long exposure to paclitaxel and it reduces the increase of mRNA level of TNFα, a mediator of both spinal microglial activation and hypersensitivity to neuropathic pain. Finally, starting from the observation on the comparable effects shown by paclitaxel and C5a on the electrophysiological behavior of DRG primary neurons, it was shown that C5aR1 inhibition can completely counteract DRG alterations induced by both C5a and paclitaxel, thus further confirming both the relevant role of C5aR1 inhibition in mediating paclitaxel neuropathological mechanisms and the potential of targeting the C5a/C5aR1 axis as a new therapeutic approach to treat CIPN [73].

CONCLUSIONS

CIPN is a major dose-limiting side effect of chemotherapy, associated with neuropathic pain, and its burden continues to increase with increasing cancer survivorship. Furthermore, this condition is often so severe that chemotherapeutic treatments must be interrupted, with evident consequences in terms of quality of life and life expectancy of patients. For this reason, the importance of new strategies to prevent and treat CIPN is becoming clearer every day. Nutraceuticals, drugs, and various techniques currently used to prevent or treat CIPN have so far not shown the expected benefits, as a result of the unclear pathophysiology of CIPN, the poor pharmacokinetic profiles of the tested molecules, and/or their side effects.

The complement system is known to play a crucial role in chronic pain through the C5a/C5aR axis. Its activation was found to be involved in the pathophysiology of peripheral neuropathy and several painful neuroinflammatory states, thus leading to consideration of the C5a/C5aR axis as a master mediator of inflammation. Furthermore, new experimental evidence has highlighted the role of taxanes in the pathophysiology of CIPN, underlining the ability of paclitaxel to bind and activate C5aR1. Starting from the poor availability of drugs to efficaciously treat CIPN, and from the many clinical failures in this field, the well-assessed role of the C5a/C5aR1 axis in the pathogenesis of inflammation, neuroinflammation, and neuropathic pain makes it reasonable to hypothesize that targeting the complement axis with novel C5aR1 inhibitors could represent an innovative approach to block and/or revert the onset and progression of CIPN. Further, the inhibition of C5aR1 could have a double advantage in oncology, not only that of reversing and controlling the side effects of chemotherapy, such as peripheral neuropathies, but also that of not interfering with anticancer therapy but, on the contrary, enhancing its effect, as demonstrated by several preclinical studies on the synergistic effect of anti-complement drugs in combination with immunotherapy in the treatment of different tumors [176, 177]. These observations, together with the promising results of preclinical and clinical studies of immunotherapies combined with paclitaxel that showed an improvement in the anticancer effect by paclitaxel [178–180], if confirmed by additional and necessary studies,

could really pave the way for opening an entirely new scenario in the treatment of CIPN, and potentially in obtaining through the inhibition of C5aR1 a synergistic positive effect on cancer progression, as a new strategy to manage this high unmet medical need.

ACKNOWLEDGEMENTS

Funding. This work was supported by Italian Ministry of Economic Development Grant N. F/090033/01-03-04/X36.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take the responsibility for the integrity of the work as a whole and have given their approval for this version to be published.

Author Contributions. Conceptualization and design: Marcello Allegretti, Maria C. Cesta. Drafting the manuscript: Maria C. Spera, Mara Zippoli, Maria C. Cesta. Supervision: Giustino Varrassi, Marcello Allegretti.

Disclosures. Maria C. Cesta, Mara Zippoli and Marcello Allegretti are permanent employees of Dompé Farmaceutici S.p.A. Maria C. Spera is an intern in Dompé Farmaceutici S.p.A. Giustino Varrassi declares not to have conflicts of interest to disclose.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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