

# The Role of Growth Factors in the Prevention and Treatment of Chemotherapy-Induced Peripheral Neurotoxicity

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**Abstract:** Chemotherapy-induced peripheral neurotoxicity (CIPN) is a major clinical problem since it is the dose-limiting side effect of a significant number of antineoplastic drugs. The incidence of CIPN varies depending on the conditions, but severe neuropathy can occur in up to 40% of patients undergoing a polichemotherapy regimen.

Moreover, even when CIPN is not a dose-limiting side effect, its onset may severely affect the quality of life of cancer patients and cause chronic discomfort. Currently, no treatment is available which can significantly improve the clinical signs and symptoms of CIPN. In recent years, new agents have been proposed as neuroprotectants, and some of them have been more specifically studied for CIPN. So far, the most interesting results for future applications have been obtained in the pre-clinical studies involving cytokines and growth factors. For several of these drugs, in fact, sound hypotheses have been formulated to support the idea of a protective role on selected neuronal targets. However, this theoretical basis has frequently failed to lead to consistent results in pre-clinical and clinical applications. We will review the state-of-the-art of CIPN treatment with growth factors and focus on the future prospects opened up by the most recent pre-clinical and clinical studies.

**Keywords:** Chemotherapy, peripheral neuropathy, neurotoxicity, neuroprotection, growth factors.

## INTRODUCTION

The effectiveness of antineoplastic treatment for solid and hematological malignancies has changed considerably over the last few years. One of the reasons for this positive result is the significant improvement in the management of several severe side effects. This is the case, for instance, when cell growth stimulating factors are used to manage hematological side effects or hyperhydration to minimize nephrotoxicity. However, with the clinical use of these strategies which allow the administration of more effective but also more aggressive antineoplastic schedules, other dose-limiting side effects have emerged. Neurological complications of antineoplastic chemotherapy are rather common and, in the vast majority of cases, they involve the peripheral nervous system [1-8] (Table 1). The reasons why drugs specifically designed to act against rapidly replicating cells are so frequently toxic against the nervous system (where neurons never replicate in adults and glial cells have a very low rate of replication) are not clear. On the contrary, the absence of an effective blood-nerve barrier under physiological conditions in the dorsal root ganglia (DRG) and at the nerve terminal may explain the elective localization in the peripheral nervous system of the neurotoxic action, while only in cases where there is a barrier injury (either due to pathology or to pharmacological intervention) can antineoplastic drugs enter and damage the central nervous system.

Several classes of old and new antineoplastic drugs are neurotoxic: in the case of platinum-derived agents, vinca alkaloids, taxanes, thalidomide, proteasome-inhibitors and

epothilones chemotherapy-induced peripheral neurotoxicity (CIPN) is, in most cases, the main limiting toxicity. Some millions of patients are treated every year with antineoplastic agents around the world and, although some differences exist regarding the estimate of the real incidence of CIPN (depending on the schedules used and the methods of neurological assessment, which can demonstrate a subclinical involvement in more than 40-50% of the patients treated with the most neurotoxic drugs) there is absolutely no doubt that it represents a major clinical problem. In fact, even in the cases in which CIPN is not dose-limiting, it can induce the onset of disabling symptoms and signs which may significantly impair the quality of life of otherwise successfully treated patients. In most cases, CIPN presents as an exclusively or predominantly sensory, length-dependent neuropathy with ataxia and gait difficulties, but dysesthesias/paresthesias with or without pain may also be a major problem. Motor impairment is rarer and, particularly with vinca alkaloids, autonomic damage can be severe.

The clinical aspects of CIPN are strictly dependent on the site of the neurotoxic action of each compound (i.e. DRG, axons, myelin sheath) but, unfortunately, in most cases the detailed mechanisms of this action are still rather unclear. On the one hand, this incomplete knowledge prevents an understanding of the real interaction occurring between drugs and neural targets and, on the other hand, is a severe limitation in attempting to prevent or treat CIPN. In fact, schedule modifications have been performed in an attempt to optimize the treatment with an acceptable neurological toxicity [9], but in most cases this has been only partially successful. For this reason, several pharmacological strategies have been attempted. In some cases (particularly some years ago) the selection of these neuroprotective agents was based on weak evidence regarding their mechanism of action or it was found that they interfered with the antineoplastic action of the neurotoxic substance. However,

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**Table 1. Summary of the Main Features of CIPN Due the Most Commonly Used Antineoplastic Drugs**

Substance	Target of toxicity	Main clinical features	Pre-clinical models available
Platinum derived drugs	DRG neurons with secondary axonopathy (cisplatin, carboplatin, oxaliplatin)	Sensory impairment (predominantly ataxia)	Yes
	Voltage-gated sodium channels (oxaliplatin)	Cold-related perioral and pharyngeal paresthesias	Yes
Taxanes	Axons (DRG?)	Distal symmetrical polyneuropathy (sensory>motor)	Yes
Vinca alkaloids	Axons	Distal symmetrical polyneuropathy (sensory+motor)	Yes
		Autonomic neuropathy	No
Suramin	DRG Axons	Distal symmetrical polyneuropathy (sensory>motor)	Yes
	Myelin	Acute motor polyradiculoneuropathy	No
Thalidomide	Axons Rarely DRG neurons	Distal symmetrical polyneuropathy (sensory>>motor)	No
Epothilones	Unknown *	Distal symmetrical polyneuropathy (sensory>motor)*	No
Proteasome inhibitors	Unknown *	Distal symmetrical polyneuropathy (sensory>motor)*	No

DRG = dorsal root ganglia; \* only preliminary data available so far.

most of the drugs used more recently as pharmacological neuroprotectants have a reasonable theoretical background for their putative action and, in most cases, antineoplastic activity interference has been researched and excluded. The main classes of drugs tested in this setting include chelating, antioxidant or antiapoptotic agents [10-23] and neurotrophic factors [24-29], although only a few of these compounds have been evaluated in clinical trials (Table 2).

Among these classes of neuroprotective substances, neurotrophic factors are of particular interest [30]. In fact, it has been well-established that several neurotrophic factors are crucial not only in the developmental stage of the central and peripheral nervous system, but also during injury and repair. Moreover, neurotrophic factors act on the nervous

system cells by means of specific receptors, which can be up- and down-regulated during the course of a neurological disease, and these receptors (despite, in most cases, not being restricted to the nervous system) are differentially expressed in other normal and pathological tissues. Interestingly, these modifications in the receptors' expression have been demonstrated also after antineoplastic drug exposure [31, 32]. Finally, the development of new delivery systems and more effective production methods mean that a large number of patients can be treated.

We will review the data which are currently available regarding the use of established neurotrophic factors in the prevention and treatment of CIPN and, moreover, we will examine the results obtained with other drugs which can

**Table 2. Summary of Other Neuroprotectants Clinically Tested to Prevent or Treat CIPN in Recent Years**

Drug	Clinical data on CIPN	Notes
ACTH <sub>4-9</sub> (Org.2766)	Conflicting results with cisplatin (negative in the most recent trials) [17, 101] and negative with vincristine [13]	
Amifostine (WR2721)	Conflicting results with cisplatin, other platinum drugs and taxanes [15, 102, 103]	Tolerability problems (possible severe arterial hypotension)
Reduced glutathione (GSH)	Reduces cisplatin and oxaliplatin toxicity [74, 76]	Although no reduction in antineoplastic activity was ever demonstrated, elevated intracellular GSH level have been associated with platinum drug resistance
Glutamine	Reduction in symptoms induced by paclitaxel treatment [104]	
Vitamin E	Reduces cisplatin and paclitaxel toxicity [19, 22]	Possible reduction in antineoplastic activity [105]
Gabapentin	No effect in the attempt to treat CIPN symptoms induced by platinum drugs and taxanes	
Dimesna (BNP2778)	Data not yet available	Phase II trial ongoing

enhance the effect of physiologically-produced neurotrophic factors.

### LEUKEMIA INHIBITORY FACTOR (LIF)

LIF is a cytokine belonging to the gp130 group, which also includes ciliary neurotrophic factor, interleukin-6, interleukin-11, cardiotrophin 1 and oncostatin-M. LIF has pleiotrophic activities: it is upregulated after nerve injury, it protects nerves in axotomy models and it retards the progression of motor neuron axonopathy in the wobbler mouse [33, 34]. Signaling is due to LIF interaction with a cell-surface receptor complex composed of two distinct components: LIFR and gp130. The LIF receptor is expressed on several cell types including neurons, megakaryocytes, adipocytes, macrophages, hepatocytes, osteoblasts, myoblasts, kidney and breast epithelium [35]. LIF-receptor interaction leads to changes in gene expression, cell proliferation, differentiation and regeneration, and LIF treatment does not impair the antitumor effect of several antineoplastic drugs [36].

On the basis of these observations, a preclinical study was performed in a rat paclitaxel model of chronic treatment in order to assess the neuroprotective role of LIF [37]. In this model, recombinant murine LIF (rmLIF) was administered daily by subcutaneous injection in combination with weekly intraperitoneal paclitaxel. It was able to protect from paclitaxel-induced axonal atrophy in a dose-dependent manner (with the best responses being at the lowest vs. the highest doses investigated). This inverted dose-response was interpreted as a possible effect of high doses of rmLIF reacting with monomeric receptors thereby interfering with heterodimeric formations and, possibly, with signal transduction.

The positive results of this experimental model and the preclinical studies which demonstrated that LIF does not interfere with cisplatin, carboplatin and paclitaxel antitumor activity, prompted the execution of a randomized, double-blinded, placebo controlled phase II study with recombinant human LIF (rhuLIF, Emfilermin, AM424) to prevent carboplatin/paclitaxel peripheral neurotoxicity [38]. An extended panel of neurological examinations (based on both clinical and neurophysiological endpoints) was used to assess the neurological outcome of the patients. Unfortunately, the results of the clinical trial failed to demonstrate that rhuLIF is effective. There are several possible reasons for such a discrepancy between the preclinical and the clinical results. First of all, antineoplastic schedule differences should be considered, since the preclinical model where LIF was neuroprotective investigated only paclitaxel treatment and not the carboplatin/paclitaxel combination. Moreover, the effect of rmLIF was assessed (as generally occurs) on developing animals, as evidenced by the increase in nerve conduction velocity in control rats due to maturation of the peripheral nerves, and it is possible that the effect of rhuLIF was different on the completely mature nerves of the patients enrolled in the trial. Finally, in view of the dose-dependency of the LIF effect evidenced by the preclinical study, it is uncertain whether the bioavailability of LIF is comparable in the animal model and in the clinical trial, since the dose equivalency was assessed as a constant fraction of weight

and did not take interspecies differences into consideration (thus leading to a higher dose-equivalent schedule in the clinical trial). Moreover, no data regarding the levels reached by LIF in the tissues of interest were given. However, on the basis of the negative results obtained in the clinical trial, the Authors have stated that rhuLIF will not undergo further development as an agent for the prevention of CIPN.

### NEUROTROPHINS

The first neurotrophic factor to be discovered was Nerve Growth Factor (NGF) [39], after the experimental observation of a hypertrophic response of sensory ganglia exposed to the substance. Years after this discovery, a second member of the same family of neurotrophic agents with a 50% homology in amino acid structure was discovered and named Brain-Derived Neurotrophic Factor (BDNF) and this observation led to a search for similar agents resulting in the discovery of Neurotrophin-3 (NT-3), Neurotrophin-4/5 (NT-4/5) and Neurotrophin-6, described only in fish. The neurotrophins act through a common interaction with a low-affinity receptor ( $p75^{NGFR}$ ) and a specific interaction with a family of high affinity tyrosine kinase receptors, named trkA (for NGF), trkB (for BDNF and NT-4/5) and trkC (for NT-3), which are differentially expressed in different tissues and even in different parts of the nervous system [40]. A reciprocal modulation in the activity of the different neurotrophins has also been described [41].

### BDNF

TrkB, the specific receptor for BDNF, is widely expressed in the peripheral nervous system, including the DRG and spinal motor neurons [40]. Several lines of evidence suggest a protective role for BDNF against different motor neuron types of injury, but the *in vitro* investigations performed on well-established models of cisplatin neurotoxicity have failed to evidence any clear effect.

### NT-3

The theoretical rationale for the use of NT-3 as a neuroprotectant is based mainly on the observations that most antineoplastic agents induce sensory or sensory-motor neuropathy and that that trkC expression is very high in the subpopulation of large-sized DRG neurons [40], a potential target of the toxicity of several antineoplastic drugs. *In vitro* studies suggested that NT-3 might be effective [42] and, in an experimental study in a chronic rat model of cisplatin peripheral neurotoxicity, the subcutaneous administration of NT-3 was able to completely reverse the reduction in myelinated sensory axon density, the decrease in nerve conduction velocity and the abnormal neurofilament distribution in DRG neurons induced by CDDP [43]. This very impressive result has never been replicated by other groups and, so far, no data are available as to the possible use of NT-3 in humans, despite the fact that a phase I study on healthy volunteers was performed with an extended dose range of the substance.

### NGF

The NGF specific receptor, trkA, is widely expressed on several subpopulations of DRG neurons [40] and it has been

demonstrated that *trkA* plays a role not only in their developmental stage, but also in their rescue from toxic damage [32].

Several *in vitro* studies have been performed using DRG explants or PC12 cell cultures in order to investigate the possible neuroprotective effect of NGF [32, 44-49], and in most instances NGF has shown interesting positive results. Moreover, NGF is able to modulate the expression of the other neurotrophins [50]. As regards clinical evidence, the importance of NGF in the course of CIPN has been further suggested by the findings of De Santis *et al.* [51] who reported that circulating NGF levels are markedly reduced in neuropathic cancer patients who have been treated with different neurotoxic combination chemotherapy schedules. These findings were subsequently confirmed in a prospective study on patients treated with cisplatin and paclitaxel which evidenced a significant correlation between the severity of the peripheral neurotoxicity and the circulating levels of NGF [52]. These results are in agreement with the finding that NGF circulating levels decrease during cisplatin and oxaliplatin (but not paclitaxel) administration in rats [46, 47, 53], and that the decrease is closely correlated with the onset of peripheral neuropathy [31]. The possibility that exogenous NGF may protect from CIPN, suggested by these preclinical and clinical results, has been demonstrated in *in vivo* animal models of cisplatin [32, 46, 54-56] and paclitaxel [57] intoxication. In fact, all these models consistently demonstrated that NGF reduced the severity of CIPN on neurophysiological and/or pathological grounds. The use of NGF as a neuroprotectant has recently been tested in humans: Apfel *et al.* [58] demonstrated the effectiveness of NGF in the treatment of human diabetic polyneuropathy and the feasibility of long-term treatment. However, several practical problems emerged in the diabetes trial leading to the conclusion that the direct administration of NGF (and probably other neurotrophins) to cancer patients would probably be hampered by the severity of the local and systemic side effects of the administration of the high dose of this substance needed to achieve sufficient bioavailability in the nervous system.

In order to solve this problem, different approaches can be considered including the implementation of the same gene therapy strategies which have already been successfully used in animal models [59] and also in humans [60]. This therapy might allow the production of biologically-significant amounts of NGF by the transfected tissues or NGF-modulating or NGF-mimicking drugs could be administered.

### **Neurotrophin Gene Therapy, NGF-Modulating and NGF-Mimicking Drugs**

The administration of viral vector encoding for neurotrophins or their direct gene transfer has been proposed to circumvent the problems due to the direct injection of these growth factors. Recently, very interesting results have been obtained in cisplatin *in vivo* models by electroporation-mediated nonviral NT-3 gene transfer into muscles [61] and by virus-mediated herpes simplex NGF and NT-3 gene transfer [62]. Both strategies induced a significant neuroprotection on multimodal examinations and further development is warranted in order to better ascertain the

safety and effectiveness of gene therapy in the prevention and treatment of CIPN.

A different strategy to increase the levels of neurotrophins, and particularly of NGF, available for the injured target includes the use of drugs capable of increasing the local concentration of neurotrophins. This theory has already been tested in the central nervous system of infant and adult rats, and a significant increase in the local neurotrophin levels was obtained. 4-Methylcatechol is a low molecular weight molecule known to stimulate NGF synthesis *in vitro* and *in vivo* and its neuroprotective effect has been demonstrated in animal models of toxic neuropathy [63, 64]. Similarly, propentofylline, a xanthine derivative, acts as a potent and effective stimulant of NGF synthesis [64]. Recently, a NGF-mimicking effect has been proposed for a purine analog: the systemic injection of this substance (neotrofin, AIT-082) was able to increase both NGF and *trkA* levels in DRG without inducing any significant side effect [65].

Taking into consideration substances already available in clinical practice in several countries and with a neuroprotective action which is probably mediated at least in part through an interaction with NGF, acetyl-L-carnitine (ALC) is definitely of interest. ALC is a member of the family of carnitines, a group of natural compounds which have an essential role in intermediary metabolism. ALC has shown a protective effect in mono or polyneuropathies of different origin. Exogenous administration of ALC increases NGF levels in the central nervous system (66) and in the rate of transcription of the gene coding for the p75<sup>NGFR</sup> [67]. The relationship between NGF and ALCAR is supported by different experimental results which demonstrate that ALCAR co-administration allows PC12 cells to be differentiated with sub-optimal doses of NGF. ALCAR co-treatment reduces the severity of cisplatin and paclitaxel neurotoxicity in rat animal models [68] and does not interfere with the antitumor activity of either drug, as assessed in several *in vitro* and *in vivo* models using murine and human solid cancer cell lines [68].

This molecule is particularly interesting since preliminary clinical results have suggested that treatment with ALCAR downgrades the severity of CIPN induced by cisplatin and/or paclitaxel. Based on this pre-clinical evidence, clinical trials are currently ongoing in cisplatin-, oxaliplatin-, paclitaxel- and vincristine-treated patients.

Finally, it has been reported that reduced glutathione (GSH), one of the major endogenous antioxidants, also acts as an NGF-enhancing drug [69]. GSH is the major intracellular tripeptide thiol and *in vivo* animal studies have evidenced that GSH reduces the neurotoxicity of cisplatin [70, 71], while *in vitro* experiments have demonstrated that GSH has no effect on its anticancer activity [72]. The issue of non interference with antitumor effectiveness is particularly important in the case of GSH, since elevated intracellular GSH levels in cancer cells have been associated in several cases with an increased resistance to anticancer drug action [73]. The use of GSH as a neuroprotectant against CIPN has been evaluated in randomized clinical trials in ovarian cancer patients and it has been demonstrated that the co-administration of GSH reduced the neurotoxicity

of cisplatin without affecting its activity [74, 75]. Moreover, the neuroprotective action of GSH also against chronic oxaliplatin neurotoxicity has recently been demonstrated [76]. In both clinical studies no reduction in the anticancer response rate was found [74, 75].

### ERYTHROPOIETIN

Erythropoietin (EPO), a 165 amino acid sialoglycoprotein, is a widely used growth factor which plays a crucial role in the regulation of erythropoiesis. In clinical practice, EPO is a very effective, well-tolerated and largely used treatment for anemia in cancer patients undergoing chemotherapy. However, the bone marrow is not the only EPO target tissue, and the wide expression of functional receptors for EPO explains the non-erythropoietic functions of this hormone, including its neuroprotective action on the injured nervous system. A solid theoretical basis has been demonstrated for EPO and a wide range of effects *in vivo* as a neuroprotectant have been observed. In fact, EPO and its receptors are expressed in nerve axons, Schwann cells and DRG neurons, and their over-expression after nerve injury prevents axonal degeneration [77-79]. In primary neuronal cultures or neuronal cell lines recombinant human EPO protects from apoptosis [80]. In *in vivo* models, EPO protects neurons from cerebral ischemia and traumatic injury [81] and it reduces the severity of experimental autoimmune encephalomyelitis, spinal cord injury and sciatic nerve compression [82]. Moreover, it has recently been demonstrated that EPO both protects and reverses the severity of experimental diabetic neuropathy [83].

The protective effect of EPO against CIPN was recently suggested in an experimental model of chronic cisplatin administration [84]. However, this rat model was characterized by a motor, demyelinating neuropathy that did not reproduce the typical effects of cisplatin administration in humans (i.e. sensory impairment with axonal damage in the peripheral nerves), thus raising some concern as to the relevance of the positive results obtained for potential clinical application.

As previously observed, one of the major points of concern in the use of neuroprotectant drugs to prevent CIPN is possible interference with the antineoplastic activity of chemotherapy or a direct effect on tumor growth [85]. This is true for EPO and concern has been recently raised about the use of EPO in cancer patients, although this is a substance that is widely used in the clinical management of anemia in patients with cancer. Another major point of concern in proposing EPO as a neuroprotectant in clinical practice is the risk of a marked increase in the hematocrit value with long-term treatment. Recently different groups have identified derivatives of EPO, including carbamylated EPO [86], and asialoEPO [87] which are non-erythropoietic but which retain their neuroprotective actions in different animal models including cerebral ischemia, spinal cord injury, and diabetic neuropathy.

### OTHER NEUROTROPHIC AGENTS

#### Insulin-Like Growth Factor-1 (IGF-1)

Insulin, proinsulin and IGFs are members of a family including cytokines, hormones and growth factors. IGF-1 is

particularly interesting since it has been demonstrated that it acts on adult sensory neurons and is present in axons and Schwann cells. IGF-1 receptor (IGF-1R) is expressed within the central and peripheral nervous systems [88, 89]. Interestingly, IGF-1 can act synergistically with NGF [90] and a decrease in NGF and IGF-1 immunoreactivity levels selectively decrease in axonopathies [91]. Previous studies have demonstrated that IGF-1 can be safely administered for a period of 6 months in humans [92]. Preclinical evidence of a role of IGF-1 as a neuroprotectant for CIPN has been obtained in vincristine models both *in vitro* [93] and *in vivo* [94]. Cross-linked action on IGF-1R has been postulated also for insulin, which was proposed as a neuroprotectant in a recent *in vivo* study [95].

#### Glial Cell Line-Derived Neurotrophic Factor (GDNF)

GDNF is trophic to motor and sensory neurons (where its receptor is expressed on a selected population of small- and middle-sized neurons) in animal models and GDNF mRNA is up-regulated in Schwann cells after peripheral nerve injury in rats [96]. Moreover, also for this trophic factor, a relationship with NGF is probable [97]. However, a preliminary *in vivo* study using a chronic model of cisplatin administration failed to demonstrate any effect of GDNF (personal observation).

#### Ciliary Neurotrophic Factor (CNTF)

CNTF is a 200 amino acid protein belonging to the neurotrophic cytokine family [98] and its receptor, which is present on several neuronal populations including primary sensory neurons, consists of three subunits partially shared with other trophic factors: CNTF receptor alpha, gp130 and LIF receptor beta [99]. Most studies have so far focused on motor neuron rescue and survival, but *in vitro* experiments have also been performed to test its effectiveness against cisplatin-induced neurotoxicity [100] with negative results.

### CONCLUSIONS

The well-established clinical importance of CIPN is a major driving force in the effort to better clarify the most suitable strategies to minimize its severity. Several attempts have been made to obtain structurally modified antineoplastic drugs which might be less neurotoxic than the first-in-class molecule, but so far the results have not been completely satisfactory: this is the case, for instance, with the platinum-derived agents carboplatin and oxaliplatin and with the semi synthetic taxane docetaxel. Although this strategy should be further explored and will potentially allow the neurotoxicity of antineoplastic compounds to be reduced, the combined use of neuroprotectants should also be considered and, therefore, investigated. In fact, for all the reasons reported above, at present neurotrophic factors can definitely be considered as promising putative candidates, but the reality is that no clearly effective substances are yet available for clinical use.

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