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Review

Current status and future prospects for the treatment of chemotherapy-induced peripheral neurotoxicity

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1. Introduction

Chemotherapy-induced peripheral neurotoxicity (CIPN) is a major clinical problem because it represents the dose-limiting side-effect of a significant number of antineoplastic drugs [1]. The incidence of CIPN varies depending on the conditions. Severe neuropathy can occur in the range of 3–7% of treated cases with single agents, but can rise up to 38% with polichemotherapy regimens [2–4].

However, 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 clinical signs and symptoms of CIPN, and thus a major advance in the treatment of cancer patients would be an effective prevention and/or treatment of CIPN. In this paper, we will review the 'state-of-the-art' of CIPN prevention and treatment and we will focus particularly on the future prospects opened up by the most recent preclinical and clinical studies. The most promising neuroprotective drugs, characterised by their stronger pharmacological rationale, as well as by the wider range of preclinical and clinical data, will be discussed.

2. The past and present of neuroprotection in a clinical setting

Currently, CIPN is treated in clinical practice with different approaches usually restricted to symptomatic treatment of paraesthesia and pain. These approaches, including the use of ion channel blockers and tricyclic antidepressants, have shown limited success and produced little in the way of clinical evidence. In fact, the number of putative neuroprotective drugs evaluated in the context of large clinical trials is rather limited and, moreover, the methods used to assess the effectiveness of the treatment are not always comparable. Despite this limitation, clinically-relevant conclusions can be drawn at least for the following three drugs.

2.1. $ACTH_{4–9}$ (Org2766)

This adrenocorticotropic hormone (ACTH) analogue has been extensively evaluated in pre-clinical *in vitro* studies and in animal models of cisplatin- and paclitaxel-induced neuropathy [5,6]. Conflicting results have been obtained in double-blind placebo-controlled clinical trials. In fact, a first study showed a significant neuroprotection by $ACTH_{4–9}$ and no reduction in the chemotherapy response rate [7], but a second study performed on a series of patients with similar clinical features receiving a higher dose of ACTH $_{4–9}$ failed to confirm these results [8].

2.2. Amifostine (WR-2771)

Amifostine is an organic thiophosphate that has undergone extensive preclinical evaluation for protection against radiation, cisplatin and alkylating agents toxicity. WR-2771 is a pro-drug which is dephosphorylated to a more active metabolite (WR-1065) by a membrane-bound alkaline phosphatase, which is present mainly in normal tissues. Amifostine reduced the severity of CIPN in cisplatin-treated patients, although

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the differences between the groups was limited [9]. Small studies have been performed in carboplatin and paclitaxel-treated patients, but in this case the neuroprotective effect of amifostine has not been clearly demonstrated [10]. The use of amifostine is frequently associated with the onset of vomiting and transient, but potentially severe, systemic hypotension.

2.3. Reduced glutathione (GSH)

GSH is the major intracellular tripeptide thiol. *In vivo* animal studies have evidenced that GSH reduces the neurotoxicity of cisplatin [11] and *in vitro* experiments have demonstrated that GSH has no effect on its anticancer activity [12]. The use of GSH as a neuroprotectant against CIPN has been evaluated in ovarian cancer patients and it has been demonstrated that the coadministration of GSH reduced the neurotoxicity of cisplatin, without affecting its activity [13,14]. Moreover, GSH's neuroprotective action against chronic oxaliplatin neurotoxicity has also recently been demonstrated [15].

3. The future of neuroprotection: from preclinical results to clinical application

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 preclinical 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 preclinical and clinical applications.

3.1. Leukaemia inhibiting factor (LIF, AM424)

The neuroprotective effect of LIF, a 180 amino acids cytokine, has been explored in an animal model of paclitaxel-induced neuropathy in rats [16,17], as well as in phase I and II clinical trials. Despite proof of protection from paclitaxel-induced axonal atrophy in animal models, recent phase II data did not show any clinical improvement suggesting a role for LIF in CIPN treatment and development has been recently discontinued (press release).

3.2. Insulin-like growth factor-I (IGF-I)

IGF-I is a growth factor with a potent effect on nerve regeneration and, possibly, on neuronal survival. IGF-I has been evaluated in clinical trials in patients affected by amyotrophic lateral sclerosis (ALS), a neurodegenerative disease affecting motoneurones, demonstrating that effective plasma levels of the drug can be achieved without inducing severe side-effects [18]. Preclinical studies in mice have evidenced a neuroprotective action against vincristine toxicity [19].

3.3. Neurotrophins

The neurotrophins are a family of growth factors including nerve growth factor (NGF) and neurotrophin-3 (NT-3). Each neuronal class seems to be dependent on a specific neurotrophic factor which exerts its action through a common low-affinity receptor and specific high-affinity tyrosine kinase receptors. The relationship between neurotrophins and sensory neurones is at the basis of the long-standing interest in the use of these factors in the prevention and treatment of sensory CIPN. Moreover, the high-affinity receptors for these substances are almost completely restricted to neurones and they are unable to induce a proliferative response in cancer cells. Although the most interesting results regarding CIPN concern NT-3 and NGF, it should be remembered that most of the details which regulate the interaction between each neurotrophin and the other members of the family are still not completely understood and it is likely that the administration of a single factor also modulates the expression of others.

3.3.1. Neurotrophin-3 (NT-3)

NT-3 is probably the most important neurotrophin for large-sized primary sensory neurones which express significant levels of the specific high-affinity receptor. The effect of the systemic administration of NT-3 has been examined *in vivo* in a rat model of cisplatin neurotoxicity and the results seemed extremely promising [20]. The results of that study have never been confirmed by others and a planned clinical trial regarding the use of NT-3 during cisplatin-treatment has not yet been performed. Very recently, a different experimental approach has been proposed and plasmid DNA encoding murine NT-3 was intramuscularly injected into cisplatin treated rats, with a reduction in the severity of the sensory neuropathy [21].

3.3.2. Nerve growth factor (NGF)

Several *in vitro* studies have been performed using DRG explants or PC12 cell cultures in order to investigate the possible neuroprotective effect of NGF [22—24]. The importance of NGF in the course of CIPN has been further suggested by the findings of Aloe and colleagues [25] who reported that circulating NGF levels are markedly reduced in neuropathic cancer patients who have been treated with different neurotoxic combination chemotherapy schedules. The possibility that exogenous NGF may protect from CIPN has been demonstrated in *in vivo* animal models of cisplatin [26–

Table 1
Summary of the preclinical and clinical results obtained with putative neuroprotectant agents for CIPN

Drug	Proposed mechanism of action	*In vivo* preclinical evidence for CIPN	Clinical data on CIPN	Clinical development for CIPN	Notes
$ACTH_{4–9}$	Neurotrophic	Cisplatin	Conflicting results with cisplatin		
		Paclitaxel			
AMIFOSTINE	Detoxicant		Conflicting results with cisplatin and other platinum drugs		Tolerability problems
GSH	Detoxicant	Cisplatin	Reduces cisplatin and oxaliplatin toxicity		
LIF	Unknown	Cisplatin	Negative	Discontinued	
IGF-1	Neurotrophic	Vinca alkaloid			Clinical trials in ALS
NT-3	Neurotrophic	Cisplatin		Controlled phase I/II study planned	
NGF	Neurotrophic	Cisplatin			Positive data in human diabetic neuropathy
		Paclitaxel			
ALCAR	NGF-enhancing	Cisplatin	Reduction of paclitaxel and cisplatin CIPN	Phase II studies in CIPN	
		Paclitaxel			
Others					
Glutamate	Unknown	Preliminary data on vincristine cisplatin and paclitaxel	Reduction in vincristine neurotoxicity [46]		
Glutamine	Upregulation of *NGF* mRNA		Reduction in symptoms induced by paclitaxel treatment [47]		
Purine analogue (AIT-082)	Unknown	Vincristine [48]			
Dimesna (BNP7787)	Reversible inhibition of tubulin polymerisation	Cisplatin and paclitaxel [49,50]		Phase II/III studies for prevention of paclitaxel neurotoxicity planned	
Lithium	Activation of microtubular system	Vincristine	Reduction in vincristine neurotoxicity [51]		Need for larger placebo-controlled, double blind clinical trials and preclinical studies
Vitamin E	Radical scavenger		Reduction in cisplatin neurotoxicity [52]		Larger clinical study completed, evaluation ongoing
Prosaptide	Neurotrophic effect	Cisplatin and paclitaxel [54]			
Xaliproden	Upregulation of *NGF* mRNA	Not available	Not available		Clinical trials in ALS [53]
Glial cell line-derived neurotrophic factor (GDNF)	Interaction with specific receptors	Negative data on cisplatin			
Ciliary neurotrophic factor (CNTF)	Interaction with specific receptors				Severe toxicity in clinical trials in ALS [53]

CIPN, chemotherapy-induced peripheral neurotoxicity; ACTH, adrenocorticotrophic hormone; GSH, glutathione; LIF, leukaemia inhibiting factor; IGF-1, insulin-like growth factor-1; NT-3, neurotrophin-3; NGF, nerve growth factor; ALCAR, acetyl-L-carnitine; ALS, amyotrophic lateral sclerosis.

29] and paclitaxel [30] intoxication. These results are in agreement with the finding that NGF circulating levels decrease during cisplatin administration in rats, and that the decrease is closely correlated with the onset of a peripheral neuropathy [31]. The use of NGF as a neuroprotectant has recently been tested in humans: Apfel and colleagues [32] demonstrated the effectiveness of NGF in the treatment of human diabetic polyneuropathy and the feasibility of long-term treatment. However, the direct administration of NGF 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 order to circumvent this problem, different approaches should be considered including the implementation also for NGF of the same gene therapy strategies which have already been successfully used in animal models [21] and in humans [33]: such gene therapy might allow the production of biologically-significant amounts of NGF by the transfected tissues.

3.3.3. Neurotrophin-enhancing drugs

A different strategy to increase the levels of neurotrophins, and particularly of NGF, available for the injured target includes the use of drugs able to increase the local concentration of neurotrophins. This theory has already been tested in the central nervous system (CNS) of infant and adult rats [34,35], and a significant increase in the local neurotrophin levels was obtained.

Another substance with a neuroprotective action which is probably mediated, at least in part, through an interaction with NGF is acetyl-L-carnitine (ALCAR). ALCAR is a member of the family of carnitines, a group of natural compounds which have an essential role in intermediary metabolism [36,37]. ALCAR has been shown to have a protective effect in mono or polyneuropathies of different origin [38–40]. Exogenous administration of ALCAR increases NGF levels in the CNS [41] and the rate of transcription of the gene coding for the $p75^{NGFR}$ (the low-affinity NGF receptor) [42]. 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 [43,44] and does not interfere with the antitumour activity of both drugs, as assessed in several *in vitro* and *in vivo* models using murine and human solid cancer cell lines.

Preliminary clinical results have suggested that treatment with ALCAR downgrades the severity of CIPN induced by cisplatin and/or paclitaxel [45]. Based on this preclinical evidence, clinical trials are currently ongoing in CIPN.

4. Others

Many other drugs have been studied for CIPN treatment either in preclinical or, more rarely, in clinical settings. This is a heterogeneous group of different compounds, most of which have failed to show a confirmed preclinical rationale. Further evidence in preclinical models and, if positive, in large controlled clinical trials is still needed to offer a proper evaluation of these therapeutic options (Table 1).

5. Conclusions

As shown, interesting results have been achieved in the attempt to overcome the clinical problem represented by CIPN. However, none of the strategies available has been fully confirmed in properly designed clinical trials and further efforts are needed in order to demonstrate a favourable impact on patient management. Moreover, a closer interaction between basic and clinical researchers is essential in order to have a more complete comprehension of CIPN and, thus, of the potentially effective drugs. This should allow appropriate clinical trials to be designed with the most promising drugs based on a sounder rationale and with the final aim of providing better treatment opportunities for cancer patients.

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