Animal Models of Chemotherapy-Evoked Painful Peripheral Neuropathies

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Summary: This review examines recent preclinical research on toxic peripheral neuropathy and potential therapeutic developments. Chemotherapy-induced peripheral neurotoxicity is a major clinical problem because it represents the dose-limiting side effects of a significant number of antineoplastic drugs. Patients are unable to complete full or optimal treatment schedules. The incidence of chemotherapy-induced peripheral neuropathy varies depending on the drugs and schedules used, and this can be quite high, particularly when neurophysiological methods are used to make a diagnosis. However, even when chemotherapy-induced peripheral neuropathy is not a dose-limiting side effect, its onset may severely affect the quality of life of cancer patients and cause chronic discomfort. As such, improved understanding of the pathophysiology of chemotherapy-induced neurotoxicity need for animal models is clinically relevant and will assist in the development of future neuroprotective strategies and also in the design of novel chemotherapies with improved toxicity profiles. In this review, the features of animal models of chemotherapy-induced painful neuropathy developed for 20 years, due to the administration of the most widely used drugs, such as platinum drugs, taxanes, and vinca alkaloids, will be discussed. In a second part, data available on neuroprotectants and treatment strategies, evaluated using these previous animal models in the attempt to prevent neuropathic pain, will be summarized. **Key Words:** Pain, anti-cancer agents, neurotoxicity, prevention, neuropathy.

INTRODUCTION

Recent advances in the development and administration of chemotherapy for malignant diseases have led to prolonged survival of patients and the promise of a return to normal lives. The cost of progress comes with a price, however, and the nervous system is frequently the target of therapy-induced toxicity. Chemotherapy-induced neurotoxicity is a significant complication in the successful treatment of many cancers. These neurotoxic side effects are second in frequency to hematological toxicity. Unlike heamotological side effects that can be treated with hematopoietic growth factors, neurotoxicity can not be effectively treated or prevented.[1,2] Neurotoxicity may develop as a consequence of treatment with platinum analogues (cisplatin, oxaliplatin, carboplatin), taxanes (paclitaxel, docetaxel), vinca alkaloids (vincristine), and more recently, thalidomide and bortezomib.[3] Despite the blood-brain barrier, central nervous system toxicity, mainly encephalopathy with or without seizures, occurs occasionally, even when conventional doses are used.[4] In the peripheral nervous system, the major brunt of the toxic attack is directed against the peripheral nerve, targeting the neuronal cell body, the axonal transport system, the myelin sheath, and glial support structures, resulting in chemotherapy-induced peripheral neuropathy.[5] The prevalence of chemotherapy-induced sensory neuropathies vary from 10% to 80% according to the drug, and this is sometimes associated with motor (suramin, bortezomid) or autonomic dysfunctions (vincristine). It appears that onset and severity depends on a variety of factors, including concomitant medical conditions such as diabetes, alcoholism, and paraneoplasic sensory neuropathy.[1,6] Typically, the clinical presentation reflects an axonal peripheral neuropathy with glove-and-stocking

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distribution sensory loss, combined with features suggestive of nerve hyperexcitability, including paresthesia, dysesthesia, and pain. Pain is a prominent and important side effect for many patients. It may occur early in treatment, but it is as common as a late and chronic consequence, especially for patients who experienced nociceptive sensory loss during treatment. Finally, proprioception loss may result in pseudoathetosis or ataxia with several functional impairment.[1,7,8] These symptoms may be disabling, adversely affecting activities of daily living and thereby quality of life, even after several months or years after treatment discontinuation.[3] The recovery from symptoms is often incomplete and a long period of regeneration is sometimes required to restore function. Little is known about the mechanisms responsible for the development of neuropathy. Depending on the substance used, a pure sensory and painful neuropathy (with cisplatin, oxaliplatin, carboplatin) or a mixed sensorimotor neuropathy with or without involvement of the autonomic nervous system (with vincristine, taxol, suramin) can ensue. This kind of neurotoxicity depends on the total cumulative dose and the type of drug used. Sometimes neuropathy can evolve even after a single-drug application (oxaliplatin). Finally, up to now, no drug is available to reliably prevent or cure chemotherapy-induced neuropathy, and expected final recommendations await prospective confirmatory studies.[5]

In this review, we will discuss animal models of chemotherapy-induced painful neuropathy developed for 20 years with the most widely used drugs, such as platinum drugs, taxanes, and vinca alkaloids. Second, data available on neuroprotectants and treatment strategies, evaluated by using these previous animal models in the attempt to cure or prevent neuropathic pain, will be summarized.

ANIMAL MODELS

Tubulin-binding agents

Vinka alcaloids (vincristine). The most used model is that developed by Aley et al.,[9] and its adaptation by Weng et al.[10] They described a mechanical allodynia/hyperalgesia and a heat hyperalgesia. To investigate physiopathology of this model, Tanner et al.[11,12] reported abnormal microtubule assemblies and axonal swelling in myelinated and unmyelinated fibers, and described that vincristine caused half the C-fiber nociceptors to become markedly hyper-responsive to mechanical stimulation.[13] Studying the role of transient receptor potential vaniloid 4, Alessandri et al.[14] revealed that mechanical hyperalgesia is markedly impaired in the absence of transient receptor potential vaniloid 4 function. At last, Thibault et al.[15] provided data, which support that 5-HT2A receptor is involved in vincristine mechanical hypersensitivity. Others models reported pain-related behavior. Thus, Authier et al.[16,17] described mechanical allodynia/hyperal-

Table 1. *Animal Models of Vincristine/Paclitaxel/Docetaxel Painful Neuropathy*

Animals	Schedule	Time	Injection	CD	Ref No.
Tubulin-Stabilizing Agents: Vincristine					
Rat male, SD, 250–300 g	0.1 mg/kg/d, 5 d/wk	12 d	IV	1	1
Rat male, SD, 180–200 g	0.075 mg/kg/d	10 d	IV	0.75	16
Rat male, SD, 300–400 g	0.1 mg/kg/d	14 d	IV infusion	1.4	18
Rat male, SD, 160–180 g	0.15 mg/kg/2 d	10 d	IV	0.75	17
Rat male, SD, 250–300 g	0.1 mg/kg/d, 5 d/wk	12 d	IP	1	10
Rat male, SD, 200–300 g	0.05 mg/kg/d	10 d	IP	0.5	20
Mice male, CD-1, 30–35 g	1.7 mg/kg, 2/wk	10 w	IP	34	23
Mice male, ICR, 20 g	0.125 mg/kg, 2/wk	6 wk	IP	1.5	24
Mice male, ICR, 22–30 g	0.1 mg/kg/d	14 d	IP	1.4	25
Mice male, C57BL/6, 6 wk	0.1 mg/kg × 1	14 d	IP	0.1	26
Tubulin-Stabilizing Agents: Paclitaxel					
Rat female, Wistar, 250 g	8 mg/kg/wk	5 wk	IP	40	27
	16 mg/kg/wk			80	
Rat female, SD, 320–450 g	18 mg/kg/d 0 and d 3	4 d	IV	36	30
Rat male, SD, 180–200 g	16 mg/kg/wk	5 wk	IP	80	31
	32 mg/kg × 1			32	
Rat male, SD, Adult	2 mg/kg/2 d	7 d	IP	8	33
Rat male, SD, 280–300 g	1 mg/kg/d, 5 d/wk	2 wk	IP	10	32
Mice female, C57BL/6, 8 wk	60 mg/kg/2 d	7 d	IV	180	36
Mice	10 mg/kg × 1	1 d	IP	10	37
Mice male, C57BL/6, 6 wk	5 mg/kg × 1	14 d	IP	5	26
Tubulin-Stabilizing Agents: Docetaxel					
Rat male Fisher, adult	10 mg/kg, 1/wk	4 wk	IV	40	39

CD = cumulative dose (mg/kg/animal); d = day; hr = hour ; IP = intraperitoneal; IV = intravenous; Ref No. = reference number; SC = subcutaneous; wk = week.

gesia, cold allodynia/hyperalgesia, and heat hypoalgesia, associated with a decrease in nerve conduction velocity (NCV) and pathological damages, such as degenerated myelinated axons in the fine nerve fibers of the subcutaneous paw tissue. A convenient alternative to repetitive daily injection was developed by Nozaki-Taguchi et al.[18] using continuous intravenous vincristine infusion with a mini-osmotic pump, which was adapted by Lynch et al.[19] These models displayed a mechanical allodynia and a cold allodynia, respectively. More recently, Siau et al.[20] adapted the model developed by Authier et al.[16] using intraperitoneal administration instead of intravenous, and displaying a mechanical hypersensitivity. Two other animal models were developed, but were not extensively studied. First, Boyle et al.[21] observed gait disturbance, heat hypoalgesia, and impaired proprioception. More recently, Bordet et al.[22] described a new model in the rat displaying a tactile allodynia.

Concerning mice models, Contreras et al.[23] reported the first model of vincristine-induced nociceptive neuropathy, revealing a heat hypoalgesia and a decrease in NCV associated with significant mortality (73%). On the contrary, Kamei et al.,[24] using a different behavioral test, observed a heat hyperalgesia. Therefore, a tactile allodynia was reported by Kiguchi et al.,[25] associated with a significant increase in the number of macrophages in the sciatic nerve and lumbar dorsal root ganglia (DRG), and a concomitant increase in interleukin-6 (IL-6) expression. Finally, Gauchan et al.[26] recently published a murin model and observed a mechanical allodynia with a tendency to a decrease of peripheral blood flow.

Taxanes (paclitaxel & docetaxel). This first animal model displayed predominant damages to the largest myelinated fibers and axonal atrophy associated with NCV reduction and thermal hypoalgesia.[27,28] Campana et al.[29] also observed a paclitaxel-induced thermal hypoalgesia that was not accompanied by morphological or electrophysiological changes. Cliffer et al.[30] produced a model with a decrease in sensory nerve conduction velocities (SNCV), proprioceptive deficits, and a mechanical allodynia and cold hyperalgesia without a change in thermal nociception. Authier et al.[31] described a new animal model displaying an important and rapid mechanical hyperalgesia and a thermal hypoalgesia associated with a decrease in sciatic NCV and axonal changes. Dina et al.[32] also developed a short-term model showing a mechanical hyperalgesia and allodynia, and a thermal hyperalgesia. This mechanical hyperalgesia has been abolished by a spinal administration of antisens oligodeoxynucleotides to transient receptor potential vaniloid 4.[14] After this time, Polomano et al.[33] described a new experimental model, showing heat hyperalgesia, mechanical allodynia and hyperalgesia, and cold allodynia without any dose-response relationship. Using this model, Flatters et al.[34] observed that nociceptive signs were not accompanied, neither by peripheral nerve degeneration nor microtubules alterations in myelinated axons and C-fibers.

Concerning paclitaxel-induced neuropathy in mice, four models have been developed. First, Apfel et al.[35] observed a profound sensory neuropathy characterized by a decrease of substance P in DRG associated with heat hypoalgesia. A second model published by Wang et al.[36] reported sensory-motor dysfunction, significant reduction of SNCV, and a reduction of the mean axonal diameter. More recently, Hidaka et al.[37] developed a new model in mice after a single injection, showing a reversible mechanical allodynia and hyperalgesia. This mechanical allodynia has also been demonstrated by Gauchan et al.[26]

Furthermore, an animal model using docetaxel, displayed a dose-dependent reduction in the tail NCV, an axonal degeneration of largest myelinated fibers without axonal atrophy, a heat hypoalgesia, and lower calcitonin gene-related peptide levels in the spinal cord (Table 1).[38,39]

Platinum compounds

Oxaliplatin. The first pain behavioral assessment in rats was recently done by Ling et al.[40] who have reported cold and heat hypersensitivity with allodynia and hyperalgesia associated with mechanical allodynia, remaining after a 3-week follow-up. Moreover, so as to be clinically relevant and to mimic the effects observed in humans, especially hypersensitivity to cold, they also studied the effects of a single oxaliplatin injection showing a significant cold allodynia and hyperalgesia associated with a mechanical allodynia. An immunohistochemical study in the superficial layers of the spinal dorsal horn revealed a marked increase in substance P immunoreactivity.[41] Another acute model has been published by Joseph et al.,[42] also displaying a dose-dependent heat and cold allodynia with a mechanical hyperalgesia. They also assessed different inhibitors of several second messengers (protein kinase A, protein kinase C, NO, Ca^{2+}, Caspase), which failed to attenuate the acute mechanical hyperalgesia, whereas antioxydants (acetyl-L-carnitine, α-lipoic acid, vitamin C) and inhibitors of the mitochondrial electron transport chain (rotenone, 3-nitropropionic acid, antimycin, sodium cyanide, oligomycin) produced significant attenuation.[43]

Very recently, mice models have also been published, using single[26,44] or repeated administrations,[44] respectively, showing significant mechanical and cold allodynia and hyperalgesia. Gauchan et al.[44] also demonstrated that oxaliplatin-induced cold allodynia could be partly explained by an increase in the expression level of TRPM8 mRNA at day 3 after a single injection.

Cisplatin. Tredici et al.,[46] after repeated cisplatin injection in rats, observed a heat hypoalgesia associated with a reduction of NCV and size of the somatic, nuclear,

Table 2. *Animal Models of Cisplatin/Oxaliplatin-Induced Painful Neuropathy*

Animals	Schedule	Time	Injection	CD	Ref No.
Platinum Compounds: Cisplatin					
Rat female, Swiss, 10 wk	2 mg/kg, 2/wk	4.5 wk	IP	18	46
Rat male, SD, 150–175 g	2 or 1 mg/kg/3 d	4 wk	IP	15	47
Rat male, SD, 150–175 g	3 mg/kg, 1/wk	5 wk	IP	15	48
Rat male Wistar, 280 g	2 mg/kg, 1/wk	5 wk	IP	10	84
Rat male, SD, 175–225 g	0.5 mg/kg/d	3 d	IP	1.5	49
Rat male, SD, 220–250 g	2 mg/kg × 1	5 d	IV	2	42
Mice female, Swiss, 10 wk	5 mg/kg, 1/wk	8 wk	IP	40	51
Mice male CD1, adult	6 mg/kg, every 3 wk	15	SC	30	52
Mice male, C57BL/6, 14 wk	2.3 mg/kg, 5 d/5 d rest/5 d	2 wk	IP	23	45
Platinum Compounds: Oxaliplatin					
Rat male SD, 175–200 g	2 mg/kg, 2/wk	4 wk	IV	16	40
Rat male SD, 175–200 g	6 mg/kg × 1	30 hr	IP	6	41
Rat male SD, 220–250 g	2 mg/kg × 1	5 d	IV	2	42
Mice male, C57BL/6, 6 wk	3 mg/kg × 1	10 d	IP	3	44
Mice male, C57BL/6, 14 wk	3 mg/kg, 5d/5d rest/5 d	2 wk	IP	30	45

and nucleolar area of DRG. Moreover, Authier et al.[47,48] reported mechanical and cold thermal hyperalgesia and allodynia, but also a heat thermal hypoalgesia as previously described, associated with a decrease in peripheral NCV and pathological changes in the subcutis. To elucidate cisplatin neurotoxic mechanisms, Joseph et al.,[42] using an acute model, displayed a mechanical hyperalgesia and allodynia, but also heat allodynia. This mechanical hyperalgesia was attenuated by inhibitors of caspase signaling, but not by antioxydants and inhibitors of the mitochondrial electron transport chain, findings opposite to those observed with oxaliplatin, and suggesting differents neurotoxic mechanisms. Also using a short induction period, Cata et al.[49] showed a heat thermal hypoalgesia for high doses, whereas lower doses produced mechanical hyperalgesia.

In regard to the murin model, Apfel et al.[50] established a cisplatin-induced neuropathy in mice displaying an impaired proprioception with reduced levels of calcitonin gene-related peptide in DRG and slowed NCV. Another model demonstrated that cisplatin causes a decrease in SNCV progressing in parallel with a decrease of neuropeptide expression in the terminal nerve fibers (calcitonin gene-related peptide, vasoactive intestinal peptide), associated to a lesser degree with a mechanical hypoalgesia.[51] After this, Aloe et al.[52] also reported a heat hypoalgesia with a decrease in catecholaminergic nerve fibers density and an increase in substance P levels. More recently, Ta et al.[45] have developed a model with a reported mechanical allodynia and a heat hyperalgesia (Table 2).

PHARMACOLOGICAL STUDIES

Treatment strategies

Vincristine. Seven preclinical studies investigated the analgesic effects of single or repeated injections of many drugs in vincristine-induced mechanical hypersensitivity (allodynia or hyperalgesia). Single injection of morphine, anticonvulsant drugs (lamotrigine, ethosuximide, carbamazepin, pregabalin), but also venlafaxine (antidepressant), mexiletine and lidocaine (Na channel blockers), clonidine (α_1 agonist), dextrometorphan (glutamate receptor blockers), and acetaminophen totally reversed vincristine-induced tactile allodynia.[18,19,53–55] On the other hand, some nonsteroidal anti-inflammatory drugs (NSAIDs) (e.g., aspirin, ibuprofen, celecoxib) and also desipramine (tricyclic antidepressant) did not present a curative effect on this nociceptive symptom after a single injection.[19] According to specific studies on gabapentin,[56] it seems to be effective only after repeated injection on vincristine-induced mechanical allodynia/hyperalgesia.

Likewise, a new mitochondrial-targeted neuroprotective (TRO19622), reversed tactile allodynia in vincristine-treated rats after daily repeated injection.[22] Activation of cannabinoid receptor, using a single injection of a cannabinoid (CB)1/CB2 agonist (WIN55,212-2) or a CB2-selective agonist (AM1241), also inhibited this mechanical allodynia.[55] Finally, concerning the opioid system, administration of a complete inhibitor of enkephalin-catabolizing enzymes (PL37) also induced an antinociceptive and anti-allodynic effect, but were not effective on cold allodynia.[57]

More recently, to investigate if blood flow reduction is involved in this neuropathy, Gauchan et al.[58] assessed the effect of limaprost, a prostaglandin E1 analog, on mechanical allodynia without effectiveness.

Paclitaxel. Morphine-induced analgesic affect has been assessed and only high doses elicited up to a 50% reversal of mechanical alodynia/hyperalgesia.[54] More recently, Xiao et al.[56] investigated potential analgesics on mechanical allodynia or hyperalgesia in paclitaxel evoked painful neuropathy in rats. Amitriptyline pro-

duced a significant effect after the second injection. Tramadol produced a consistent, near-complete analgesia, which did not persist to 24 hours post-injection. Topiramate displayed significant effects, evident after 6 to 8 days of dosing.

Three recent studies suggested that cannabinoid receptors may be an important therapeutic target for the treatment of paclitaxel-evoked painful neuropathy. First, Pascual et al.[59] demonstrated that WIN55,212-2 significantly reduced the heat hyperalgesia and the tactile allodynia. Second, using two CB2 agonists (AM1241 and AM1714), Rahn et al.[60] demonstrated that activation of CB2 receptors also suppresses mechanical allodynia. At last, a novel selective CB2 agonist, named MDA7, also attenuated tactile allodynia.[61]

In regard to analgesic effects of calcium channel blockers or anti-epileptic drugs, ethosuximide, elicited a near complete reversal of mechanical allodynia/hyperalgesia and also inhibited cold allodynia.[54] Therefore, Matsumoto et al.[62] observed that gabapentin completely abrogated heat hyperalgesia and mechanical allodynia. Gabapentin also displayed a significant effect on mechanical allodynia and hyperalgesia after repeating dosing.[26,63]

Repeated administration of limaprost, contrary to vincristine, significantly inhibited the late phase of mechanical allodynia induced by a single injection of paclitaxel.[58] Therefore, repeated administration of acetyl-L-carnitine (ALC) displayed a significant attenuation of established paclitaxel-induced mechanical hypersensitivity, but this analgesic effect dissipated shortly after ALC discontinuation.[64]

Oxaliplatin. Ling et al.[40] compared pharmacological sensitivity between single administered drugs on oxaliplatin-induced cold hypersensitivity. They reported an antinociceptive effect of magnesium and venlafaxine administrations, whereas gabapentin, clomipramine, and lidocaine only induced an anti-allodynic effect. According to authors, pregabalin seems to be more effective than morphine or lidocaine to treat this cold hypersensitivity.[65] Oral administration of gabapentin produced a dose-dependent inhibition of mechanical allodynia caused by oxaliplatin in mice, whereas intrathecal and intraplantar injections were ineffective.[26]

As for paclitaxel-induced neuropathy, limaprost inhibited peripheral blood flow decrease and mechanical allodynia at the late phase of oxaliplatin acute neuropathy in mice.[58]

Cisplatin. Supporting the hypothesis that altered nerve growth factor (NGF) receptor functions might be a cause of cisplatin neurotoxicity, repeated injection of exogenous NGF in a mice model have shown that this drug induced recovery of peripheral sensory response.[52] The leukemia inhibitory factor proved efficacy in reversing heat hypoalgesia, improving the reduction in SNCV induced by cisplatin, and restoring pathological changes (Table 3).[66]

Preventive strategies

Vincristine. Boyle et al.[21] observed a preventive effect of glutamate, ameliorating all manifestations of sensory neuropathy, such as heat hypoalgesia. Insulin-like growth factor-1 used for a long time (10 weeks) partially prevented this thermal hypoalgesia.[23] More recently, propentofylline, a glial-modulating agent, has been reported as preventing vincristine-evoked tactile allodynia in the rat, suggesting that central glial cells may play an important role in the development of this painful neuropathy.[67] Moreover, two clinically used drugs with significant Na^+/Ca^{2+} and Na^+/H^+ exchange inhibitory activities, pralidoxime, and amiloride, co-administered with vincristine in rat, partially attenuated mechanical hypersensitivity, cold allodynia, and heat hyperalgesia, and reduced axonal degeneration.[68] Then, using α_1 (yohimbin) and α_2 (prazosin)-adrenoreceptor antagonists, Bujalska et al.[69] demonstrated a preventive effect of both drugs on mechanical hyperalgesia. The same authors observed that co-administration of two NSAIDs (indomethacin and celecoxib) also prevent this mechanical hyperalgesia.[70] These kind of results had already been observed with two other NSAIDs (ibuprofen and rofecoxib),[71] whereas NSAIDs did not showed analgesic effects. At last, IL-6, known to be implicated both in the neural degeneration and the regeneration process, displayed in the rat as a preventive effect on heat hypoalgesia.[72]

Paclitaxel. ALC, a compound that has a role in intermediary metabolism, administered in combination with paclitaxel in repeated injection into rats, was able to significantly prevent mechanical hypersensitivity.[64] The growth factor leukemia inhibitory factor belongs to a group of cytokines that includes ciliary neurotrophic factors (IL-6, IL-11) and prevented, at low or high dose, the onset of thermal hypoalgesia.[73] Ledeboer et al.[74] investigated interleukin-10 (anti-inflammatory cytokine) gene therapy and observed a preventive effect on paclitaxel-induced mechanical allodynia. As with other neuroprotective drugs, co-administration of NGF with paclitaxel in mice prevented heat hypoalgesia.[75] More recently, two preclinical studies revealed the therapeutic efficacy of prosaposin (TX14[A]), a precursor of saposins, in preventing paclitaxel-induced thermal hypoalgesia[76] and tactile allodynia.[77] Then, repeated administration of neurotropin, a drug clinically used for its analgesic properties, displayed a curative effect on tactile allodynia and cold hyperalgesia.[78] Also, monosialic acid ganglioside (GM1) has been shown to prevent thermal hypoalgesia.[79] At last, regarding paclitaxel, Hidaka et al.[37] investigated preventive effect of Shakuyaku-kanzo-to, an herbal medicine, and loxoprofen (NSAID), and revealed a signifi-

Table 3. *Treatment Strategies in Chemotherapy-Induced Animal Models*

Treatment Strategies							
			Effect on Pain Thresholds				
Drug	Model	Dose	MA	MH	CA	HH	Ref No.
Morphine	TAX	8 mg/kg	+	+			54
	OXA	2–4 mg/kg			+		40, 65
	VCT	0.2–0.9/5 mg/kg	+				18, 19
Tramadol	TAX	20 mg/kg/d, 4d	+	+			56
Amitriptyline	TAX	30 mg/kg/d, 4d	+	+			56
Clomipramine	OXA	2.5 mg/kg × 5			+		40
Venlafaxine	OXA	7.5 mg/kg × 5			+		40
	VCT	20–40 mg/kg		+			53
Carbamazepine	VCT	3,600 μmol/kg (ED50)	+				19
Ethosuximide	TAX	100–300 mg/kg × 3	+	+	+		54
	VCT	300 mg/kg × 1	+	+			54
Gabapentin	OXA	300 mg/kg × 1			+		40
	OXA	30–100 mg/kg × 1	+				26
	TAX		+				26
	TAX	30 mg/kg × 1	+			+	62
	TAX	100 mg/kg/d, 4 d	+	+			63
	VCT	400 μmol/kg (ED50)	+				19
	VCT	100 mg/kg/d, 4 d	+	+			63
Pregabalin	OXA	10–100 mg/kg			+		65
	VCT	80 mg/kg	+				18
Lamotrigine	VCT	82 μmol/kg (ED50)	+				19
Topiramate	TAX	20 mg/kg × 2/d, 12d	+	+			56
Acetaminophen	VCT	1100 μmol/kg (ED50)	+				19
Acetyl-L-carnitine	TAX	100 mg/kg/d, 5d	+	+			34
AM 1714	TAX	10 mg/kg × 1	+				60
AM 1241							
Clonidine	VCT	0.35 μmol/kg (ED50)	+				19
Dextrometorphan	VCT	94 μmol/kg (ED50)	+				19
Lidocaine	OXA	3 mg/kg × 1			+		40, 65
	VCT	45 mg/kg × 1	+				17
LIF	CIS	2 μg/kg/d				+	66
Limaprost	OXA	0.3 mg/kg × 10 (/d)	+				58
	TAX		+				58
MDA7	TAX	10 mg/kg × 1	+				61
Magnesium	OXA	30 mg/kg × 3/1 hr			+		40
Mexiletin	TAX	30 mg/kg × 2	+	+			56
	VCT	30 mg/kg	+				17
PL37	VCT	50–100 mg/kg × 1	+	+			57
WIN 55212-2	TAX	1 mg/kg × 1	+	+			59
	VCT	2.5 mg/kg × 1	+				60

CD = cumulative dose (mg/kg/animal); d = day; hr = hour; IV = intravenous; IP = intraperitoneal; LIF = leukemia inhibitory factor; OXA = oxaliplatin; Ref No. = reference number; SC = subcutaneous; TAX = paxlitaxel; VCT = vincristine; wk = week.

cant relief of mechanical allodynia and hyperalgesia, whereas loxoprofen was without effect.

In regard to docetaxel-induced neuropathy, Roglio et al.[39] demonstrated that progesterone, but greater than all others, dihydroprogesterone, two neuroactive steroids, exert a protective effect preventing thermal heat hypoalgesia.

Oxaliplatin. Only one preclinical study reported a preventive effect of ALC, coadministered with oxaliplatin, against behavioral changes (decreased nociceptive threshold) and electrophysiological changes (nerve conduction velocities reduction).[80] Most of the preventive studies have been involved in patients.

Cisplatin. According to Bianchi et al.,[81,82] co-administration of cisplatin and erythropoietin, or carbamylated erythropoietin, partially but significantly prevented the thermal heat hypoalgesia without affecting tumor growth. In regard to human recombinant NGF, co-administrered with cisplatin in the rat, it prevents or delays the impaired proprioception.[83] Regard to IL-6, it also showed a preventive effect on thermal heat hypoalgesia in cisplatin-induced neuropathy in rats.[72] As in paclitaxel-induced sensory neuropathy, leukemia inhibitory factor also prevented onset of thermal hypoalgesia in a chronic cisplatin-induced model in the rat, without concern for

Table 4. *Preventive Strategies in Chemotherapy-Induced Animal Models*

Preventive Strategies								
			Effect on Pain Thresholds					
Drug	Model	Dose	MA	MH	CA	CH	HH	Ref No.
Acetyl-L-carnitine	TAX	100 mg/kg/d	+	+				34, 56
Amiloride	VCT	15 mg/kg/d, 10 d	+	+	+		+	68
Indomethacin	VCT	1 mg/kg		+				70, 71
Ibuprofen		50 mg/kg						
Celecoxib		1 mg/kg						
Rofecoxib		10 mg/kg						
Erythropoietin	CIS	50 μg/kg, 3/wk					+	81, 82
Ghrelin	CIS	0.8 mg/kg, 2/d		+				85
Ganglioside GM1	TAX	30 mg/kg/d, 5 d/wk, 5 wk					+	79
Glutamate	VCT	500 mg/kg/d, 16 d					+	21
IGF-1	VCT	1 mg/kg/d, 10 wk					+	23
Interleukin-6	VCT	1–10 μg/kg/d					+	72
	CIS	1–10 μg/kg/d						
	TAX	10 μg/kg, 3/wk						
LIF	CIS	2 μg/kg/d, 7 d					+	73
	TAX							
NGF	CIS	. . .					+	35
	TAX							50
Neurotropin	TAX	200 U/kg, 3/wk, 4 wk	+			+		78
Pralidoxine	VCT	20 mg/kg/d, 10 d	+	+	+		+	68
Prazosin	VCT	0.3 mg/kg/d, 10 d		+				69
Propentofylline	VCT	10 mg/kg/d, 10 d	+					67
Prosaptide	TAX	3–10 mg/rat/d, 5 d/7, 3 wk	+				+	76, 77
Shakuyaku-Kanzo-to	TAX	1, 75 mg/mouse/d, 6 d	+	+				37
WIN 55, 212-2	CIS	1–2 mg/kg, 2/wk	+					84
Yohimbin	VCT	0.1 mg/kg/d, 10 d		+				69

CA = cold allodynia; CH = cold hyperalgesia; CIS = cisplatin; d = day; GF-1 = growth factor-1; HH = heat hypoalgesia; IGF = insulin-like growth factor; LIF = leukemia inhibitory factor; MA = mechanical allodynia; MH = mechanical hyperalgesia; NGF = nerve growth factor; OXA = oxaliplatin; Ref No. = reference number; TAX = paxlitaxel; VCT = vincristine; wk = week.

impairment of an antitumor effect.[73] WIN 55,212-2, a synthetic CB1/CB2 agonist that has previously showed antinociceptive effect in vincristine and paclitaxel-induced neuropathy, also prevented the development of mechanical allodynia induced by chronic cisplatin administration.[84]

Finally, the recently discovered hormone, Ghrelin, a potent GH secretagogue mainly secreted from the stomach, with neuroprotective properties, displayed an inhibition of the cisplatin-induced mechanical hyperalgesia, correlated to the decrease in insulin-like growth factor-1 levels (Table 4).[85]

CONCLUSION

For the past 20 years, several animal models have been published and used to further investigate anticancer agent-induced neuropathic pain. The most commonly used animal models have been developed in rodents. Many models were not intended to suggest an immediate translation into clinical use, but rather to illustrate a concept and to identify a possible novel mechanism that could be exploited to avoid this important side effect of certain chemotherapeutic agents. The findings distinguishing regarding the chemotherapeutic agent used, even sometimes those in a single chemical class, suggest that the underlying mechanisms of various forms of peripheral neuropathy may be different.

Concerning methods used to quantify pain in animals, all behavioral tests used in these preclinical studies assessed sensory thresholds to nociceptive or non-nociceptive stimuli, and the results, especially regarding thermal (cold or heat) sensitivity, were sometimes contradictory. Except in one study,[57] only static stimuli were applied, whereas dynamic stimuli could give us further information regarding physiopathology of this kind of neuropathic pain. Very few studies carried out a motor performance assessment in animals to evaluate the real feasibility of sensory behavioral tests. Moreover, it would be more clinically relevant to investigate spontaneous pain more than hypersensitivity, but there is a real lack of reliable tools and a lack of consensus regarding which behaviors to measure. For example, chronic pain conditions could be eval-

uated by gait disturbances, grooming behavior, nocifensive behaviors, or guarding behaviors using video-tracking systems.[86] On the other hand, many factors could influence pain behavioral outcomes, including different species, genetic strain, gender, and age, and any homogeneity that was observed in the animals used for these rodent models (Tables 1 and 2). For example, it is likely that further animal studies are needed to investigate how the effect of age, correlated with the degree of maturation of the peripheral nervous system, could affect this neurotoxicity.

Enough animal models have been developed on the microtubule-stabilizing agents and platinum compound, except for epothilones, such as ixabepilone, a promising agent in locally advanced or metastatic breast cancer that induced 72% of neuropathy in patients.[87] Now, two ideas can be considered. First, in order to always be more clinically relevant, anticancer agents could be administered in animal models of cancer.[88] However, it will be difficult to differentiate pain due to the disease and pain induced by anticancer agents, probably involving different physiopatholgical mechanisms. Then a general predisposition for developing a chemotherapy-induced neuropathy was observed in nerves previously damaged by diabetes mellitus, alcohol, or inherited neuropathy. Thus, using animal models of metabolic-induced neuropathy, for example, it would be interesting to study animals on how this predisposition can emphasize the prevalence or the clinical profile of the peripheral neurotoxic side effects. Therefore, to determine the need for selective therapy for different types of neuropathy, more comparative preclinical studies should be carried out using toxic, metabolic, and traumatic nociceptive peripheral neuropathies. Then with pharmacological approaches, especially treatment strategies, repeated administration of potential analgesic drugs would be prefered to single administration, and the number of animals significantly relieved by a treatment should be given by authors as useful information to compare with human findings.

Finally, it is likely that there are genetic factors involved in the risk of developing chemotherapy-induced neuropathy, and this field of investigation will likely result in very significant benefits for patients in the future. These animal models could be useful for increasing our knowledge of the mechanisms of chemotherapy-induced neuropathic pain and for evaluating possible strategies aimed at preventing or reducing this dose-limiting side effect through schedule modification, treatment strategies, or in combination with putative neuroprotectant drugs.

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