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Platinum-Induced Neurotoxicity and Preventive Strategies: Past, Present, and Future

Abolfazl Avan,[a] Tjeerd J. Postma,[b] Cecilia Ceresa,[c] Amir Avan,[a,d] Guido Cavaletti,[c] Elisa Giovannetti,[a] Godefridus J. Peters[a]

Departments of [a]Medical Oncology and [b]Neurology, VU University Medical Center, Amsterdam, The Netherlands; [c]Department of Surgery and Translational Medicine, University of Milano-Bicocca, Monza, Italy; [d]Department of New Sciences and Technology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

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Key Words. Neurotoxicity • Platinum • Pathogenesis • Polymorphism • Prevention • Models

Abstract

Neurotoxicity is a burdensome side effect of platinum-based chemotherapy that prevents administration of the full efficacious dosage and often leads to treatment withdrawal. Peripheral sensory neurotoxicity varies from paresthesia in fingers to ataxic gait, which might be transient or irreversible. Because the number of patients being treated with these neurotoxic agents is still increasing, the need for understanding the pathogenesis of this dramatic side effect is critical. Platinum derivatives, such as cisplatin and carboplatin, harm mainly peripheral nerves and dorsal root ganglia neurons, possibly because of progressive DNA-adduct accumulation and inhibition of DNA repair pathways (e.g., extracellular signal-regulated kinase 1/2, c-Jun N-terminal kinase/stress-activated protein kinase, and p38 mitogen-activated protein kinass), which finally mediate apoptosis. Oxaliplatin, with a completely different pharmacokinetic profile, may also alter calcium-sensitive voltage-gated sodium channel kinetics through a calcium ion immobilization by oxalate residue as a calcium chelator and cause acute neurotoxicity. Polymorphisms in several genes, such as voltage-gated sodium channel genes or genes affecting the activity of pivotal metal transporters (e.g., organic cation transporters, organic cation/carnitine transporters, and some metal transporters, such as the copper transporters, and multidrug resistance-associated proteins), can also influence drug neurotoxicity and treatment response. However, most pharmacogenetics studies need to be elucidated by robust evidence. There are supportive reports about the effectiveness of several neuroprotective agents (e.g., vitamin E, glutathione, amifostine, xaliproden, and venlafaxine), but dose adjustment and/or drug withdrawal seem to be the most frequently used methods in the management of platinum-induced peripheral neurotoxicity. To develop alternative options in the treatment of platinum-induced neuropathy, studies on in vitro models and appropriate trials planning should be integrated into the future design of neuroprotective strategies to find the best patient-oriented solution. ***The Oncologist*** 2015;20:411–432

Implications for Practice: Neurotoxicity is a burdensome side effect of platinum-based chemotherapy that prevents administration of the full efficacious dosage and often leads to treatment withdrawal. This review summarizes preclinical and clinical evidence of pathogenesis and pathophysiology of platinum-induced peripheral neurotoxicity, as well as available evidence of neuroprotective and therapeutic strategies. These data may help to develop alternative options in the treatment of platinum-induced neuropathy, studies on in vitro models, and appropriate trials planning to find the best patient-oriented solution.

Introduction

Since the discovery of cisplatin in the mid-1960s, many platinum compounds (more than 3,000 compounds) have been developed. Thirty-five of these compounds have exhibited adequate pharmacological advantages (e.g., reaching sufficiently high plasma levels not associated with common toxicities, such as renal toxicity and thrombocytopenia) [1]. Some of them have been registered or are being considered for registration for treatment of different cancers, such as the second (carboplatin, nedaplatin, tetraplatin, and iproplatin) and third (oxaliplatin, lobaplatin, heptaplatin, satraplatin, and LA-12) generation, usually with better safety profiles [2–4].

Despite the efficacy of platinum analogs in cancer treatment, serious side effects, especially peripheral sensory neurotoxicity, often prevent their administration at their full efficacious doses or may considerably affect the quality of life of cancer patients being treated with them [5, 6]. Cisplatin was the first heavy metal used in several kinds of solid tumors, including lung, ovary, testis, bladder, head and neck, and

Correspondence: Godefridus J. Peters, Ph.D., Department of Medical Oncology, Cancer Center Amsterdam, VU University Medical Center, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands. Telephone: 31-20-4442633; E-Mail: gj.peters@vumc.nl Received February 5, 2014; accepted for publication December 11, 2014; published Online First on March 12, 2015. ©AlphaMed Press 1083-7159/2015/$20.00/0 http://dx.doi.org/10.1634/theoncologist.2014-0044

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endometrium [7, 8]; most patients develop a symptomatic neuropathy [9]. Second and third generations of platinum compounds have emerged in attempts to reduce the toxicity of cisplatin. Carboplatin, a second generation of platinums used to treat ovarian, non-small cell lung, and refractory testicular cancers, was thought to be associated with a lower risk of developing neurotoxicity [9]. However, the most recent Cochrane review comparing the toxicity of carboplatin versus cisplatin in combination with third-generation drugs for advanced non-small cell lung cancer reported an almost two times higher rate of neurotoxicity in the carboplatin group [10]. Oxaliplatin, as a widely used third-generation platinum analog approved for use in the treatment of metastatic colon cancer, is reported by the Food and Drug Administration to be responsible for more than 70% rate of symptomatic neurotoxicity with any severity [11] and often leads to treatment discontinuation [12–14]. In other studies, approximately 80% of colorectal cancer patients treated with oxaliplatin alone or in combination with other chemotherapeutics experienced neurotoxicity [15–17], and impairment may be permanent. Because the number of patients being treated with a neurotoxic agent is increasing, it is essential to understand the nature of such a problematic side effect. Furthermore, testing and validating available protective strategies in preclinical and clinical settings should be the next steps in overcoming platinum-induced peripheral neurotoxicity.

Clinical Features of Neurotoxicity

Platinum drugs are almost always given in combination with other chemotherapy drugs and/or radiation that may be neurotoxic in their own right. Early presentation of peripheral neurotoxicity can be with numbness, tingling, or paresthesia in fingers and/or toes, a decreased distal vibratory sensitivity, and/or loss of ankle jerks [5]. Moreover, prolonged treatment may also affect proprioception, which may result in ataxic gait.

Oxaliplatin and cisplatin are the two most commonly used neurotoxic platinum agents. Platinum-induced peripheral neurotoxicity can present as two clinically distinct syndromes. The acute transient paresthesia in the distal extremities, which is only commonly seen with oxaliplatin, usually occurs within the early phase of drug administration, whereas the chronic cumulative sensory neuropathy causes more persistent clinical impairments [5]. The latter deteriorates with cumulative doses [18], followed by "coasting," wherein symptoms worsen even months after treatment withdrawal. Furthermore, patients can develop Lhermitte's syndrome, which is a shocklike sensation of paresthesia radiating from the neck to the feet triggered by neck flexion. This phenomenon indicates the involvement of the centripetal branch of the sensory pathway within the spinal cord [19]. Neuropathy can also become irreversible. In a prospective multicenter study, Argyriou et al. [20] reported that oxaliplatin can result in an acute and chronic rate of neuropathy in 85% (169 patients of 200) and 73% (145 patients of 200) of patients, respectively.

Hearing loss or ototoxicity is another progressive and irreversible adverse effect of platinum chemotherapy [21] with a high frequency of almost 88% [22], which usually presents bilaterally and can occur during or years after treatment [23]. Nevertheless, the risk of ototoxicity may vary between cisplatin, carboplatin, and oxaliplatin treatments, and cisplatin is believed to be the most ototoxic and oxaliplatin is believed to be the least [24]. In one study, 19%–77% of patients treated with cisplatin developed bilateral sensorineural hearing loss, and 19%–42% developed permanent tinnitus [25]. Cisplatin accumulates in the cochlear tissue, forms DNA adducts, and causes inefficient and dysfunctional protein and enzyme synthesis leading to apoptosis of auditory sensory cells [26].

Diagnosis and Evaluation

The clinical diagnosis is generally not very difficult [27]. Nerve biopsies and neurophysiologic assessments are helpful for the examination of pathological and functional nerve damage (e.g., demyelinating versus axonal pathology; abnormalities in nerve conduction studies, somatosensory evoked potentials, magnetic resonance imaging, threshold tracking techniques, and quantitative sensory testing) [27]. Objective electromyography assessment of motor nerve excitability is a sensitive and specific endpoint of acute oxaliplatin-induced motor nerve hyperexcitability, which has the advantage of being widely available [28, 29]. Additionally, the threshold tracking technique is used to assess axonal excitability [30]. This technique allows the detection of sensory axonal dysfunction before clinical symptoms [18] and can be used as a predictive marker for nerve dysfunction.

Chemotherapy-induced peripheral neurotoxicity is typically a multidisciplinary medical issue, leading to different terminology, measurement, clinical evaluation, and grading, precluding the reliability of neurological assessment. However, standardization is improving. The Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity Scale, the FACT-Taxane scales, the Patient Neurotoxicity Questionnaire, European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire [QLQ] to assess chemotherapy-induced peripheral neuropathy, and the EORTC QLQ C30 questionnaire are scoring systems that have been used for neurotoxicity assessment to quantify the impact of chemotherapy-induced neurotoxicity on patients' quality of life [31]. Among the questionnaires, the EORTC questionnaires are widely used nowadays [32]. Among different common toxicity criteria scales that are used for peripheral neurotoxicity assessment, the one developed by the Eastern Cooperative Oncology Group and National Cancer Institute (NCI-CTC) is most widely used [19, 33–35]. Although the reliability of different assessment methods has been tested in different settings, there are vast discrepancies between patient perception and objective tools, particularly in intermediate grades [32, 36], which increase the need for a more effective and standardized method [19].

Nature of Neurotoxicity

The pathophysiology of platinum-induced peripheral neurotoxicity is not completely elucidated. Based on available data, platinum compounds may actively enter the tumor and normal cells through organic cation transporters [37], organic cation/carnitine transporters [38], and some metal transporters, such as the copper transporters [39, 40]. Platinum compounds can be excreted via platinum efflux transporters (e.g., ATP7A, ATP7B, and MRP2) [41–45] (Fig. 1). The platinum adducts are formed intracellularly because of a hydrolysis process [46], resulting in interstrand cross-links, intrastrand cross-links

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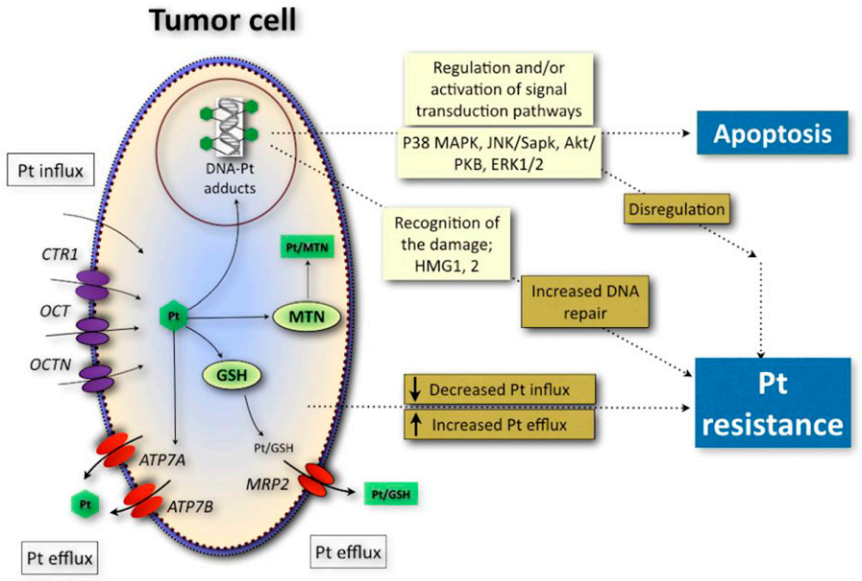

Figure 1. Effects of platinated compounds (Pt) and potential mechanisms of action. Pt may enter tumor cells (Pt influx) via copper transporter, organic cation transporters, and organic cation/carnitine transporters or by passive diffusion. DNA-platinum adducts block DNA replication, transcription, and other nuclear functions and also activate signal transduction pathways, which result in apoptosis and necrosis in tumor cells. In dividing tumor cells, the formation of DNA adducts is supposed to cause growth inhibition and cell kill, hence eliminating the tumor cells. DNA damage is recognized via high mobility group nonhistone proteins (HMG1 and HMG2) and/or various DNA repair pathways, depending on the Pt analog. GSH and MTN can neutralize Pt (e.g., by a complex that can be effluxed). MRPs (multidrug resistance-associated proteins, e.g., MRP2, also known as ABCC2) and some other efflux transporters (ATP7A and ATP7B) can excrete Pt from cells (Pt efflux). The increased repair of DNA damage and protection with GSH, as well as dysregulation in apoptosis pathways and reduced Pt influx and increased Pt efflux, can induce Pt resistance.

Abbreviations: ERK, extracellular signal-regulated kinase; GSH, reduced glutathione; HMG, high mobility group nonhistone protein; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; MTN, metallothionein protein; PKB (Akt), protein kinase B; Pt, platinated compounds; Sapk, stress-activated protein kinase.

and/or DNA-protein cross-links with platinum, affecting DNA synthesis in cancer cells [47] and mediating apoptosis [48]. Extensive DNA repair is considered as a major mechanism of chemotherapy resistance (Fig. 1), but efficient DNA repair can possibly prevent development of neurotoxicity. In dividing tumor cells, the formation of DNA adducts is supposed to cause growth inhibition and cell kills, hence eliminating the tumor cells.

Platinum products accumulate in the dorsal root ganglia (DRG), which is the main target, and in peripheral neurons (Fig. 2). Because these cells are postmitotic and not dividing, the formation of DNA adducts is not lethal, although the extent of DNA cross-links in DRG neurons at a specific cumulative dose strongly correlates with the degree of neurotoxicity [49]. Cisplatin produces approximately three times more adducts in the DRG compared with oxaliplatin [50], which is consistent with its higher neurotoxicity [12]. Platinum adducts probably cause axonal changes secondary to the neuronal damage [51], whereas brain and spinal cord are to some extent protected by the blood-brain barrier (BBB) [52]. However, there are data showing that cisplatin crosses the BBB and can accumulate when repeated dosages are given [53]. This can cause demyelination and vacuolar changes in the white matter [54]. It is believed that impaired axonal voltage-gated sodium channels kinetics can interfere with channel kinetics by oxalate (a metabolic product of oxaliplatin) [55] and can also reduce sodium ions current [56]. Sittl et al. [57] also showed that cooling in the presence of oxaliplatin induced bursts of action potentials in myelinated A but not unmyelinated C-fibers from human and mouse peripheral axons. Consequently, these alterations led to enhanced resurgent and persistent current amplitudes in large, but not small, diameter DRG neurons. Potassium channel blockade and calcium chelation are also two other etiologic possibilities [56, 58–60]. Besides, oxidative stress and mitochondrial dysfunction are regarded as another probable etiology of the apoptosis [61]. Podratz et al. [62] showed that cisplatin might inhibit mitochondrial DNA replication and cause mitochondrial vacuolization and degradation in DRG neurons in vitro and in vivo. These events can, to some extent, explain the mechanism of the neurotoxic effect of platinum compounds.

Pharmacogenetics

Single-nucleotide polymorphisms (SNPs) may play a key role in determining the induction of neurotoxicity, as well as apoptosis, because they may impair DNA repair pathways, including genes in base excision repair, nucleotide excision repair, mismatch repair, and double-strand break repair pathways [63] (Fig. 2). Moreover, SNPs can alter the drug metabolism, cell cycle control, detoxification, or excretion pathways, which finally may lead to drug toxicities, e.g., neurotoxicity. Several studies evaluated the pharmacogenetic association of SNPs with potential functional changes in the encoded protein that play a role in drug disposition, metabolism, and detoxification, DNA repair, and cancer-cell resistance and that may lead to platinum peripheral neurotoxicity [19]. However, the results are scattered and diverse with several methodological flaws, including small sample size, retrospective study design, and the implementation of a post hoc analysis of oncology-based databases of different, not preplanned sizes as well as lacking a prestudy hypothesis based on the known role of the investigated targets in the peripheral nervous system and

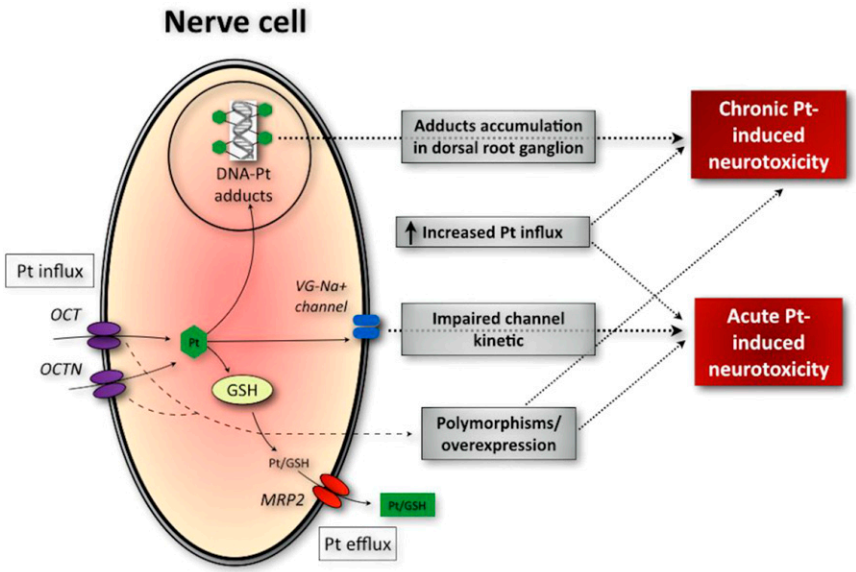

Figure 2. Mechanism of acute and chronic platinum-induced neurotoxicity. Oxaliplatin may impair normal calcium-sensitive voltage-gated sodium channels, which cause acute neurotoxicity. Platinated compound (Pt) adducts can accumulate in dorsal root ganglia and lead to chronic neurotoxicity. Because these cells are post-mitotic and not dividing, the formation of DNA adducts is not lethal to neurons. Increased Pt influx by organic cation transporters (OCTs) and organic cation/carnitine transporters (OCTNs), as well as polymorphisms and/or overexpression of some genes that play a role in Pt metabolism (e.g., in OCT, OCTN, and GSH), can contribute to Pt-induced neurotoxicity.

Abbreviations: GSH, reduced glutathione; Pt, platinated compounds; VG, voltage-gated.

the inappropriate outcome measures for neurological impairment [64] (Table 1).

There are controversial reports on the association of polymorphisms in some genes with platinum-induced neurotoxicity. These genes include ATP-binding cassette subfamily B member 1 (*ABCB1*) [65–68], ATP-binding cassette subfamily C member 1 or 2 (*ABCC1*, *C2*, or *CG2*) [69, 70], alanine-glyoxylate aminotransferase (*AGXT*) [69, 72, 73, 77, 94], cyclin H (*CCNH*) [70], catechol *O*-methyltransferase (*COMT*) [76], cytochrome P450s (CYPs; e.g., *CYP2C8*, *CYP3A5* exons 3 and 5) [65–68], excision repair cross-complementation group 1 (*ERCC1*) and *ERCC2* (alias *XPD*, xeroderma pigmentosum group D) [67, 68, 71, 74, 75, 77–87, 88], integrin β3 (*ITGB3*) [92], glutathione *S*-transferases (e.g., *GSTM1* [69, 77, 78, 85, 86, 88, 89–91], *GSTM3* [84, 75], and *GSTT1* [88, 91]), voltage-gated sodium channel genes (*SCNAs*) [20, 71, 98], thiopurine *S*-methyltransferase (*TPMT*) [76], and x-ray repair cross-complementing protein 1 (*XRCC1*) [71, 73]. Although some data support the role of the mentioned genetic variations in the presentation and severity of platinum-induced peripheral neurotoxicity, the results are scattered and diverse (Tables 1, 2), which may form leads for future research.

ABCB1, *ABCC1*, *ABCC2*, *ABCG2*, and probably several other subfamily members mediate the cellular trafficking of drugs, their metabolites, and their endogenous factors, e.g., platinum efflux [99, 100]. *CCNH* plays an important role in the cell cycle progression, the transcriptional activity of the RNA polymerase II, and the DNA repairing process [101]. Thus, it may deregulate the repair after platinum damage to the dorsal root ganglia neurons [102]. *COMT* and *TPMT*, which encode enzymes that metabolize catecholamine-containing chemical and thiopurine drugs via methylation [103], respectively, might be associated with cisplatin-related hearing loss [104, 105].

Glutathione *S*-transferases (GSTs), a family of enzymes that have an important role in detoxification, have been extensively studied for the relation of SNPs with neurotoxicity induced by platinated compounds. GSTs are involved in detoxification through glutathione conjugation of electrophilic compounds (e.g., *GSTM1* and *GSTM3)*. A *GSTP1* SNP (rs16953), for example, has been investigated in relation to peripheral neurotoxicity of platinum compounds in 24 studies (Table 1). Among these, 9 studies reported an association of this SNP with the course and severity of peripheral neurotoxicity [68, 74, 77, 80, 85, 88–90, 93], whereas other researchers reported contradicting results in 15 studies with regard to the association of *GSTP1* gene variants with neurotoxicity [67, 71, 72, 75, 78, 81, 83, 84, 86, 87, 91, 94–97]. Moreover, recent meta-analysis showed no significant associations between *GSTP1* Ile105Val polymorphism and oxaliplatin-induced neuropathy in a dominant model (odds ratio [OR] = 1.08, 95% confidence interval [CI] 0.67–1.74, $p = .754$), a recessive model (OR = 1.67, 95% CI 0.56–4.93, $p = .357$), and allelic analysis (OR = 1.22, 95% CI 0.67–2.24, $p = .513$) [106]. This inconsistency between the findings might be explained by the difference in the cancer type, ethnicity of the population studied, and/or number of the patients enrolled in each study [19].

Other studies evaluated the association of platinum-induced peripheral neurotoxicity with different SNPs in *ERCC1* [67, 68, 77, 71, 74, 78–87], *ERCC2* [71, 88], and *XRCC1* [71, 73], which are parts of the nucleotide excision repair (*ERCC1* and *ERCC2)* and base excision repair (*XRCC1)* pathways and are required for repair of DNA lesions [107]. Although Lee et al. [73] reported the polymorphism Arg399Gln (rs25487) in *XRCC1* associated with less grade 2–4 sensory neuropathy in Korean patients treated with oxaliplatin-based treatment, the recent meta-analysis found it to be generally associated with poor clinical outcomes [108]. *AGXT* prevents accumulation of glyoxylate in the cytosol by converting it into glycolate, which is subsequently metabolized by lactate dehydrogenase into oxalate, the metabolite of oxaliplatin [109]. Pharmacogenetic analyses evaluated also cytochrome P450s [65–68], which are major enzymes of drug metabolism and bioactivation (e.g., *CYP2C8* and *CYP3A5)*, and *ITGB3* [92], which belongs to the large family of integrins, known to participate in cell adhesion and cell surface-mediated signaling.

A recent study has provided evidence that SNPs in voltage-gated sodium channel genes (*SCNAs*; e.g., *SCN4A*-rs2302237 and *SCN10A*-rs1263292) can play a causal role in oxaliplatin-based peripheral neurotoxicity [20, 57] (Table 1). A polymorphism in *SCN1A* (rs3812718) was also reported to be associated with decreased neurotoxicity [85]. However, these

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Table 1. Studies on the genes with or without significant correlations with incidence and/or severity of platinum-induced peripheral neurotoxicity

Target gene		Relevance to platinum agents	SNP/deletion	With association		Without association	
				Studies	Patients	Studies	Patients
ABC	*ABCB1*	Drug transporters (membrane efflux proteins)	rs2032582			4 [65–68]	1,591
	ABCC1		rs2074087	1 [69]	144		
			rs35587			1 [69]	144
	ABCC2		rs1885301	1 [69]	144		
			rs2273697			1 [69]	144
			rs3740066	1 [69]	144		
			rs4148396	1 [69]	144		
			rs717620	1 [69]	144		
	ABCG2		rs2622604			1 [69]	144
			rs3114018	1 [70]	181	1 [70]	206
ACYP2			rs843748	2 [71][a]	343		
AGXT		Detoxification enzyme	rs34116584	1 [72]	135	3 [69, 73, 74]	518
			rs4426527	1 [72]	135	3 [69, 73, 77]	570
			N/A del74bp			1 [69]	144
BTG4			rs4936453	2 [71]	343		
CAMK2N1			rs12023000	2 [71]	343		
CCNH		Cell cycle progression	rs2230641	2 [70]	206	1 [70]	181
COMT		Detoxification enzyme	rs4646316			1 [76]	66
DLEU7			rs797519	2 [71]	343		
ERCC	*ERCC1*	DNA repair mechanisms	rs11615	2 [74, 75]	169	15 [67, 68, 71, 77–88]	3,242
			rs3212986			1 [71]	247
	ERCC2		rs13181			1 [71]	247
			rs179993			1 [71]	247
			rs1052559			1 [88]	63
FARS2			rs17140129	2 [71]	343		
			rs6924717	2 [71]	343		
FOXC1			rs2338	2 [71]	343		
GST	*GSTM1*	Detoxification enzymes	N/A deletion	1 [88]	63	9 [69, 75, 78, 85, 86, 88–91]	1,472
	GSTM3		N/A deletion	1 [84]		1 [92]	107
	GSTP1		rs1695	9 [68, 74, 77, 80, 85, 88–90, 93]	1,408	15 [67, 71, 72, 75, 78, 81, 83, 84, 86, 87, 91, 94–97]	2,747
			rs947894			1 [69]	144
			rs1138272			1 [69]	144
			rs6591256			1 [76]	66
	GSTT1		Deletion			2 [88, 92]	170
ITG	*ITGA1*	Cell adhesion and cell surface-mediated signaling	rs830884	2 [71]	343		
	ITGB3		rs5918	1 [92]	55		
SCNA	*SCN1A*	Voltage-gated sodium channels	rs2298771			1 [71]	247
	SCN2A		rs17183814			1 [98]	62
	SCN4A		rs2302237	1 [20]	200		
	SCN9A		rs6746030			1 [20]	200
	SCN10A		rs1263292	1 [20]	200		
	SCN10A		rs6800541			1 [20]	200
TAC1			rs10486003	2 [71]	343		
TPMT		Detoxification enzyme	rs4380755			1 [76]	66
			rs5008499			1 [76]	66
XRCC1		DNA repair mechanism	rs25487	1 [73]	292	1 [71]	247

[a]Won et al. conducted the study in two settings, with 96 discovery and 247 validation samples.

Abbreviations: *ABCB1* or *C1/C2/G2,* ATP-binding cassette subfamily B, member 1 or C1/C2/G2; *ACYP2*, acylphosphatase 2, muscle type; *BTG4*, B-cell translocation gene 4; *AGXT,* alanine-glyoxylate aminotransferase; *CCNH*, cyclin H; *COMT,* Catechol-O-methyltransferase; *CAMK2N1*, calcium/calmodulin-dependent protein kinase II inhibitor 1; DLEU7, deleted in lymphocytic leukemia, 7; *ERCC1*, excision repair cross-complementation group 1; *ERCC2,* alias *XPD*, Xeroderma-Pigmentosum group-D; *FARS2*, phenylalanyl-tRNA synthetase 2, mitochondrial; *FOXC1*, forkhead box C1; *GSTM*, μ class of glutathione *S*-transferases; *GSTP1/TT1,* glutathione *S*-transferases P1/TT1; *ITGA1*, integrin, α1; *ITGB3*, integrin β3; N/A, not applicable; *SCNA*, voltage-gated sodium channel α-subunit; *SNP,* single nucleotide polymorphism; *TAC1*, tachykinin, precursor 1; *TPMT,* thiopurine *S*-methyltransferase; *XRCC1*, x-ray repair cross-complementing protein 1.

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results still need to be validated by appropriate larger and prospective studies. Won et al. [71], in a genome-wide pharmacogenomic approach, identified nine novel polymorphisms associated with and predictors of severe oxaliplatin-induced peripheral neurotoxicity, including rs10486003 (tachykinin, precursor 1 [*TAC1*]), rs2338 (forkhead box C1 [*FOXC1*]), rs830884 (integrin α1 [*ITGA1*]), rs843748 (acylphosphatase 2, muscle type [*ACYP2*]), rs4936453 (B-cell translocation gene 4 [*BTG4*]), rs17140129 and rs6924717 (phenylalanyl-tRNA synthetase 2 [*FARS2*]), rs12023000 (calcium/calmodulin-dependent protein kinase II inhibitor 1 [*CAMK2N1*]), and rs797519 (deleted in lymphocytic leukemia, 7 [*DLEU7*]) [71]. These genes may account for the mechanism of neurotoxicity prevention by calcium-magnesium infusions or may be associated with the important oxalate and glyoxylate outcome pathway [72]. However, none of the SNPs in the discovery samples (96 patients with colon cancer) surpassed genome-wide significance, and these SNPs were not significant in their validation set (247 patients with colorectal cancer; $p = .05$–.19) [71]. However, the authors noted that this limitation might be overcome by increasing the sample size in a prospective analysis.

Some evidence demonstrated that mitogen-activated protein kinase pathways, including extracellular signal-regulated kinase 1/2 (ERK1/2), c-Jun N-terminal kinase (JNK)/stress-activated protein kinase (Sapk), and p38, might also have a causal effect on chemotherapy-induced peripheral neuropathies [110]. Normally, there is a balance between ERK1/2 and p38 activation, which regulates neuronal apoptosis, and JNK/Sapk, which preserves neuronal degeneration. This balance is also altered by platinum derivatives [109].

Neuroprotection

Neuroprotective Agents, Mechanisms, and Controversies

Several model systems have been used to study the nature of overall neurotoxicity and the effect of potential neuroprotective drugs. These include overall neurotoxicity signs in the animal, specific models including the DRG of rats [111–113], the structure of the cerebral ganglia of snails [114–116], in vitro models such as neurite extension [117–121], and evaluation of biomarkers of neurotoxicity such as cyclin B [122]. These models have been very useful to select proper potential neuroprotective drugs to be evaluated in the clinic. Unfortunately, preventive and therapeutic treatment options are not sufficient so far to bypass neurotoxicity [9, 19, 123]. However, a few drugs can, to some extent, protect against platinum-induced peripheral neurotoxicity (Table 3). Neuroprotective drugs include the following.

Detoxicants

Sodium thiosulfate (STS) is a reactive thiol agent used clinically as an antidote to cyanide or nitroprusside poisoning, and at high molar excess, it binds to and inactivates the electrophilic platinum compound. Its use includes otoprotection [169–173] (discussed separately under "Neuro- Versus Chemoprotection").

Amifostine is an organic thiophosphate also regarded as a cytoprotective and detoxicant agent [117]. There are successful in vitro results supporting amifostine neuroprotection against cisplatin [120], as well as against oxaliplatin [122]. Some clinical data, with different levels of reliability (Table 3), indicated that amifostine exerts some protection against peripheral neurotoxicity of carboplatin plus paclitaxel combination therapy [127–129, 131], oxaliplatin [126], and cisplatin [133, 134], whereas two other studies have failed to show significant neuroprotection against carboplatin plus paclitaxel combination therapy [130] and cisplatin [132] (Table 3). BNP7787 (Dimesna, Tavocept, 2,2′-dithio-bis-ethanesulfonate) has also shown some cytoprotective activities in vitro [174]. This effect was not confirmed in the clinical setting, although the study was unblinded with no placebo-controlled group and high risk of bias [135].

NGF Stimulants

Circulating nerve growth factor (NGF) levels are reduced in cancer patients with neuropathy caused by neurotoxic agents [175]. In addition, Schmidt et al. [176] showed in a mouse model that NGF exerted a major effect on the metabolism of transmitters associated with nociception, pain, and sensation in cervical dorsal root ganglia in various models of neurotoxicity, including the cisplatin-induced neuropathy. Thus, NGF in high doses may protect DRG neurons exposed to cisplatin [176], as well as against oxaliplatin-induced peripheral neurotoxicity [177]. They hypothesized that this effect could be due to NGF's ability to preserve the correct neuronal differentiation status by blocking the cell cycle in the G0 phase.

The synthesis of NGF can be stimulated by Org 2766 [34, 156, 159], leukemia inhibitory factor (rhuLIF) [162], retinoic acid [161, 178], glutamine [144], and acetyl-L-carnitine [179–181]. The two latter may also increase glutathione production [182, 183]. Two clinical trials [158, 159] with relatively small sample sizes showed some degree of Org 2766 neuroprotection in patients with peripheral neurotoxicity induced by cisplatin, whereas two other studies could not find a significant decrease in the incidence and severity of neuropathy [156, 157] (Table 3). Furthermore, derivatives of erythropoietin, a protein signaling cytokine, (e.g., carbamylated erythropoietin and asialoerythropoietin) have been successful in vitro and in animal models [184, 185].

Retinoic acid (all-trans-retinoic acid) is a stimulator of NGF and the expression of its receptor, activator of retinoid acid receptors with neuroprotective profile [177]. It is also a prodifferentiating agent that counteracts platinum-induced neuronal apoptosis through activating both JNK/Sapk and ERK1/2 [177]. Additionally, Arrieta et al. [186] reported a decrease in incidence and severity of neuropathy induced by cisplatinpaclitaxel combination when retinoic acid was administered.

Antioxidants or Antioxidant-Related Agents

α-Lipoic acid, a physiologic antioxidant with some neuroprotective activity [187], has recently been tested in a well-designed clinical trial [125] in which no significant decrease in incidence and severity of peripheral neurotoxicity induced by cisplatin and oxaliplatin has been reported (Table 3). α-Tocopherol (vitamin E), as another antioxidant, acts against free radicals. Four trials have evaluated the effect of vitamin E in preventing platinum, mainly cisplatin-induced peripheral neurotoxicity, and showed significantly lower incidence and severity of neuropathy in the vitamin E group compared with

Table 2. Polymorphisms associated with platinum-induced peripheral neuropathy

Gene	SNP	Cancer (patients)	Neurotoxic agent	Assessment	Association	Reference
ABCC1	rs2074087	Colorectal (144)	Oxaliplatin (FOLFOX4)	Oxaliplatin specific scale	More severe PIPN for C/C or G/C vs. G/G genotypes ($p = .0170$)	Cecchin et al. (2013) [69]
ABCC2	rs717620	Colorectal (144)	Oxaliplatin (FOLFOX4)	Oxaliplatin specific scale	More severe PIPN for TT or C/T vs. C/C genotypes ($p = .0164$)	Cecchin et al. (2013) [69]
	rs1885301				More severe PIPN for A/A or G/A vs. G/G genotypes ($p = .0072$)	
	rs3740066				More severe PIPN for T/T or C/T vs. C/C genotypes ($p = .0231$)	
	rs4148396				More severe PIPN for T/T or C/T vs. C/C genotypes ($p = .0048$)	
ABCG2	rs3114018	Colon (181)	Oxaliplatin (FOLFOX/CAPOX)	NCI-CTC v2 or v3	Increased rate of severe PIPN for A/A vs. A/C vs. C/C genotypes ($p = .016$)	Custodio et al. (2014) [70]
ACYP2	rs843748	Colorectal (343)[a]	Oxaliplatin (FOLFOX or XELOX)	NCI-CTC v3	More severe neuropathy associated with G allele ($p = 1.01 \times 10^{-5}$)	Wo et al. (2012) [71]
AGXT	rs34116584	Colorectal (135)	Oxaliplatin (FOLFOX4)	NCI-CTC v1 | and Oxaliplatin specific scale	More severe PIPN for C/T and T/T vs. C/C genotypes ($p < .001$)	Gamelin et al. (2007) [72]
	rs4426527				More severe PIPN for A/G and G/G vs. A/A genotypes ($p < .001$)	
BTG4	rs4936453	Colorectal (343)[a]	Oxaliplatin (FOLFOX or XELOX)	NCI-CTC v3	More severe neuropathy associated with T allele ($p = 9.86 \times 10^{-5}$)	Wo et al. (2012) [71]
CAMK2N1	rs12023000	Colorectal (343)[a]	Oxaliplatin (FOLFOX or XELOX)	NCI-CTC v3	More severe neuropathy associated with A allele ($p = 8.81 \times 10^{-5}$)	Wo et al. (2012) [71]
CCNH	rs2230641	Colon (206)	Oxaliplatin (FOLFOX or CAPOX)	NCI-CTC v3	Increased rate of severe PIPN for C/C vs. C/T vs. T/T ($p = .042$)	Custodio et al. (2014) [70]
DLEU7	rs797519	Colorectal (343)[a]	Oxaliplatin (FOLFOX or XELOX)	NCI-CTC v3	More severe neuropathy associated with G allele ($p = 8.21 \times 10^{-5}$)	Wo et al. (2012) [71]
ERCC1	rs11615	Colorectal (51)	Oxaliplatin (FOLFOX6)	NCI-CTC v3	Higher incidence of PIPN (grade 1) for C/T and T/T vs. C/C genotypes ($p = .016$)	Inada et al. (2010) [74]
	rs3212986	Ovarian (118)	Cisplatin/carboplatin (+ paclitaxel/docetaxel)	NCI-CTC v2	Higher incidence of PIPN (grades 3–4) for C/C vs. C/A or A/A genotypes ($p = .019$)	Kim et al. (2009) [75]
FARS2	rs17140129	Colorectal (343)[a]	Oxaliplatin (FOLFOX or XELOX)	NCI-CTC v3	More severe neuropathy associated with A allele ($p = 3.23 \times 10^{-5}$)	Wo et al. (2012) [71]
	rs6924717		Oxaliplatin (FOLFOX or XELOX)		More severe neuropathy associated with C allele ($p = 3.23 \times 10^{-5}$)	Wo et al. (2012) [71]
FOXC1	rs2338	Colorectal (343)[a]	Oxaliplatin (FOLFOX or XELOX)	NCI-CTC v3	More severe neuropathy associated with G allele ($p = 4.63 \times 10^{-6}$)	Wo et al. (2012) [71]
GSTM1	Deletion	Colorectal (63)	Oxaliplatin (mFOLFOX-6)	NCI-CTC v3	More severe PIPN (grades 2–3) for A/G or G/G vs. A/A genotypes ($p = .03$)	Kumamoto et al. (2013) [88]
GSTM3	rs1799735	Ovarian (104)	Cisplatin	NCI-CTC[b]	Lower incidence of PIPN for AGG/AGG genotype ($p = .055$)[c]	Khrunin et al. (2010) [84]

(continued)

Table 2. (continued)

Gene	SNP	Cancer (patients)	Neurotoxic agent	Assessment	Association	Reference
GSTP1	rs16953	Colorectal (52)	Oxaliplatin	NCI-CTC v3	Higher incidence of PIPN (grades 2–3) for A/G or G/G vs. A/A genotypes ($p = .03$)	Hong et al. (2011) [77]
		Colorectal (166)	Oxaliplatin (FOLFOX4)	NCI-CTC[b]	Higher incidence of PIPN: for G/G and A/G vs. A/A genotypes ($p < .01$)	Chen et al. (2010) [80]
		Colorectal (51)	Oxaliplatin (FOLFOX6)	NCI-CTC v3	Higher incidence of PIPN (grade 1) for A/A vs. A/G and G/G genotypes ($p = .032$)	Inada et al. (2010) [74]
		Colorectal (520)	Oxaliplatin (FOLFOX4 or IROX)	NCI-CTC v2	More severe PIPN (grades 3–4) for T/T genotype ($p = .003$)	McLeod et al. (2010) [68]
		Colorectal (166)	Oxaliplatin (FOLFOX4)	Oxaliplatin specific scale	More severe PIPN for G/G > A/G > A/A genotypes ($p < .001$)	Ruzzo et al. (2007) [85]
		Colorectal (59)	Oxaliplatin	Oxaliplatin specific scale	Higher PIPN incidence (grade 3) for A/A vs. A/G and G/G genotypes ($p = .02$)	Lecomte et al. (2006) [89]
		Colorectal (66)	Oxaliplatin (mFOLFOX-6)	NCI-CTC v3	More severe PIPN (grades 2–3) for A/G or G/G vs. A/A genotypes ($p = .05$)[c]	Kumamoto et al. (2013) [88]
		Gastric (85)	Oxaliplatin (FOLFOX6)	NCI-CTC v2	More severe PIPN for A/A vs. A/G and G/G genotypes ($p = .005$)	Li et al. (2010) [93]
		Testicular (238)	Cisplatin (+ bleomycin, etoposide or vinblastine)	SCIN	More severe PIPN for A/A genotype ($p = .012$) or A/G vs. G/G genotypes ($p = .003$)	Oldenburg et al. (2007) [90]
ITGA1	rs830884	Colorectal (343)[a]	Oxaliplatin (FOLFOX or XELOX)	NCI-CTC v3	More severe neuropathy associated with T allele ($p = 1.74 \times 10^{-6}$)	Wo et al. (2012) [71]
ITGB3	rs5918	Colorectal (55)	Oxaliplatin	TNS	More severe PIPN for T/T genotype vs. C/T and C/C genotypes ($p = .044$)	Antonacopoulou et al. (2010) [92]
SCNA	rs2302237	Colorectal (200)	Oxaliplatin (FOLFOX4)	NCI-CTC v3 and TNS	More severe ($p = .0029$) and higher incidence of acute ($p = .019$) and chronic ($p = .037$) PIPN for C/T vs. C/C and T/T genotypes	Argyriou et al. (2013) [20]
	rs1263292				Higher incidence of PIPN for C/T vs. C/C and T/T genotypes ($p = .023$)	
TAC1	rs10486003	Colorectal (343)[a]	Oxaliplatin (FOLFOX or XELOX)	NCI-CTC v3	More severe neuropathy associated with C allele ($p = 4.84 \times 10^{-7}$)	Wo et al. (2012) [71]
XRCC1	rs23885	Colon (292)	Oxaliplatin	NCI-CTC v3	Less severe ($p = .050$)[c] and latter-onset ($p = .041$) PIPN for A/G and A/A vs. G/G genotype	Lee et al. (2013) [73]

[a]This study has been conducted in two settings, with 96 discovery and 247 validation samples. The *p* values mentioned are for the combined groups, which were also significant for each SNP in each group.
[b]Version of the scoring scale was not reported.
[c]Trends toward significance.
Abbreviations: *ABCC1/C2/G2*, ATP-binding cassette subfamily C, member 1 or C2/G2; *ACYP2*, acylphosphatase 2, muscle type; *AGXT*, alanine-glyoxylate aminotransferase; *BTG4*, B-cell translocation gene 4; *CAMK2N1*, calcium/calmodulin-dependent protein kinase II inhibitor 1; CAPOX, capecitabine and oxaliplatin; *CCNH*, cyclin H; *DLEU7*, deleted in lymphocytic leukemia, 7; *ERCC1*, excision repair cross-complementing group 1; *FARS2*, phenylalanyl-tRNA synthetase 2, mitochondrial; FOLFOX, folinic acid (leucovorin), fluorouracil and oxaliplatin; *FOXC1*, forkhead box C1; *GSTM*, μ class of glutathione *S*-transferases; *GSTP1*, glutathione *S*-transferases P1; IROX, irinotecan plus oxaliplatin; *ITGA1*, integrin α1; *ITGB3*, integrin β3; mFOLFOX, modified FOLFOX; NCI-CTC, National Cancer Institute–Common Toxicity Criteria; PIPN, platinum-induced peripheral neurotoxicity; SCIN, scale for chemotherapy-induced long-term neurotoxicity; *SCNA*, voltage-gated sodium channel α-subunit; SNP, single-nucleotide polymorphism; *TAC1*, tachykinin, precursor 1; TNS, total neuropathy score; v, version; XELOX, oxaliplatin, capecitabine; *XRCC1*, x-ray repair cross-complementing protein 1.

CME

Table 3. Randomized controlled trials on neuroprotective agents for the prevention of platinum-induced peripheral neurotoxicity

Agent	Mechanism of action	Total patients (treated vs. control)/tumor type	Neurotoxic agent(s)	Neuroprotection	Study design/overall risk of bias[a]	Reference
NAC	A nutritional supplement thought to increase whole blood concentrations of glutathione; it also activates ERKs and p38 MAPK, to mediate the neuroprotective effect of NAC	14 (5:9)/colorectal cancer	Oxaliplatin	Decrease in incidence and severity of grades 2–4 neurotoxicity assessed by NCI-CTC ($p < .05$); no significant changes in incidence and mean SNAP amplitude	Prospective, randomized, placebo-controlled/ intermediate (dissimilarity of groups, small-sized trial, randomization, blinding, concealment allocation, outcome data not described, etc.)	Lin et al. 2006 [124]
α-Lipoic acid	A physiologic antioxidant with neuroprotective activity	243 (122:121); 29% completed the trial (34: 36)/gastrointestinal cancers (176), lung cancer (27), genitourinary cancers (14), other (15)	Cisplatin or oxaliplatin	No significant decrease in incidence and severity of neurotoxicity assessed by NCI-CTC, FACT/GOG-Ntx, and BPI score	Prospective, randomized, double-blind, placebo-controlled trial[b]	Guo et al. 2014 [125]
Amifostine	Detoxicant: an organic thiophosphate cystamine analog with cytoprotective activity	92 (46:46)/advanced or relapsed colorectal or gastric cancer with variable metastatic disease to liver, lung, and other sites	Oxaliplatin (FOLFOX4)	Decrease in incidence of grades 1–4 neurotoxicity assessed by NCI-CTC ($p < .007$); changes in severity and neurophysiologic assessment NR	Prospective, randomized, placebo controlled trial/ low (blinding and concealment allocation not described)	Lu et al. 2008 [126]
		90 (45:45)/advanced ovarian carcinoma	Carboplatin, paclitaxel	Decrease in incidence of neurotoxicity grades 2–3 assessed by NCI-CTC ($p < .05$); changes in severity and neurophysiologic assessment NR	Randomized phase II study/high (nonplacebo trial, observers unblinded unclear participant blinding, and incomplete data reporting, randomization and concealment allocation not described)	De Vos et al. 2005 [127]
		72 (37:34)/ovarian cancer	Carboplatin, paclitaxel	A significant protective effect observed for 2-PD, TRA, VPT, VDT, and NCI-CTC neuropathy scores	Randomized double-blind placebo-controlled trial/ low (unable to separate the effects of carboplatin from those of paclitaxel, similarity of groups unclear, etc.)	Hilpert et al. 2005 [128]
		38 (19:19)/NSCLC	Carboplatin, paclitaxel	Decrease in incidence of grades 1–2 neurotoxicity assessed by NCI-CTC ($p = .018$); no significant decline in mean SNAP amplitudes	Prospective, randomized/ intermediate (small sample size, unblinded participants, no placebo, incomplete outcome data, etc.)	Kanat et al. 2003 [129]
		60 (30:30)/unresectable stage III NSCLC	Carboplatin, paclitaxel	No significant changes in incidence or neurophysiologic	Randomized double-blind trial/low (only two doses of carboplatin, small sample size, etc.)	Leong et al. 2003 [130]

(continued)

Table 3. (continued)

Agent	Mechanism of action	Total patients (treated vs. control)/tumor type	Neurotoxic agent(s)	Neuroprotection	Study design/overall risk of bias[a]	Reference
				assessment; changes in severity NR		
		187 (93:94)/advanced ovarian cancer	Carboplatin, paclitaxel	Decrease in severity of grades 3–4 neurotoxicity; assessed by NCI-CTC (p = .021); changes in incidence and severity NR	Phase III prospective multicenter randomized trial/low (not placebo controlled, unclear blinding, incomplete outcome data etc.)	Lorusso et al. 2003 [131]
		20 (10:10)/cervical cancer	Cisplatin	No significant changes in incidence and severity of neuropathy	An open, single-blinded pilot study/high (open, single-blinded, no allocation concealment, small trial, etc.)	Gallardo et al. 1999 [132]
		73 (36:37)/advanced head and neck cancer	Cisplatin	Decrease in incidence of subclinical neurotoxicity assessed by VPT (p = .03); changes reported in severity NR	Prospective, randomized, placebo-controlled/ intermediate (unclear blinding, randomization and allocation concealment, etc.)	Planting et al. 1999 [133]
		242 (122:120)/ovarian cancer	Cisplatin	Decrease in severity of grades 1–3 neurotoxicity (p = .029); assessed by NCI-CTC; incidence and neurophysiologic assessment NR	Prospective, randomized/ low (not placebo-controlled, etc.)	Kemp et al. 1996 [134]
BNP7787	Detoxicant: neuroprotective	151 (76:75)/advanced NSCLC	Cisplatin, docetaxel	Unable to separate the effects of cisplatin from those of docetaxel	Phase II randomized study[b] (unblinded and not placebo-controlled)	Miller et al. 2008 [135]
Calcium-magnesium	Chelate with oxaliplatin metabolite and protect the voltage-gated sodium channels from alteration	20 (10:10)/colorectal cancer	Oxaliplatin (XELOX or mFOLFOX6)	No significant decrease in severity of neurotoxicity based on motor nerve excitability assessed by EMG	Randomized, double-blinded, placebo-controlled, crossover study[b]	Han et al. 2013 [136]
		353 (118:116:119) divided into three groups of CaMg/CaMg; CaMg/ placebo; placebo/placebo before and after chemotherapy/colon cancer	Oxaliplatin (FOLFOX4 or 6)	No significant changes in severity of grades 2–4 assessed by NCI-CTC; no significant changes in EORTC CIPN-20 sensory, motor, or autonomic scales; changes in incidence and neurophysiologic assessment NR	Phase III randomized, placebo-controlled, double-blind study/low	Loprinzi et al. 2014 [137]
		102 (50:52)/colorectal cancer	Oxaliplatin	Lower incidence of grades 2–4 neurotoxicity; assessed by NCI-CTC (p = .018); changes in severity	Prospective, randomized, placebo-controlled, double-blind/low (insufficient sample size	Grothey et al. 2011 [138]

(continued)

Table 3. (continued)

Agent	Mechanism of action	Total patients (treated vs. control)/tumor type	Neurotoxic agent(s)	Neuroprotection	Study design/overall risk of bias[a]	Reference
				and neurophysiologic assessment NR	and follow-up, unclear allocation concealment, etc.)	
		732 (551:181)/colorectal cancer	Oxaliplatin (plus capecitabine, bevacizumab with or without cetuximab	Only reduced grade 1 neurotoxicity assessed by NCI-CTC; changes in severity and neurophysiologic assessment NR	Retrospective analyses without randomization/ high (neither randomized or blinded, and no allocation concealment)	Knijn et al. 2011 [139]
		33 (17:16)/metastatic colorectal cancer	Oxaliplatin (FOLFOX6)	No significant changes in incidence and severity of neurotoxicity assessed by DEB-NTS and NCI-CTC	Prospective, randomized, placebo-controlled/low (small sample size)	Ishibashi et al. 2010 [140]
		19 (9:10)/colorectal cancer	Oxaliplatin (FOLFOX4 or XELOX)	No significant changes in incidence and severity of neurotoxicity grades 1–3 assessed by NCI-CTC, oxaliplatin-specific scale and NCS	Prospective, randomized, placebo-controlled/low (small trial)	Chay et al. 2010 [141]
Carbamazepin	A sodium channel blocker that exerts its effect by inhibiting hyperexcitability of the channel on oxaliplatin	36 (19:17)/advanced colorectal cancer	Oxaliplatin (FOLFOX)	No significant changes in incidence and severity of neurotoxicity assessed by Levi's scale	Randomized, controlled multicenter phase II study/low (small sample size)	von Delius et al. 2007 [142]
Diethyldithio-carbamate	Chelating agent and antioxidant: prevents the degradation of extracellular matrix, as an initial step in cancer metastasis and angiogenesis	195 (96:99)/ovarian, SCLC, and NSCLC	Cisplatin	Adverse effects were reported in all study participants and lower levels of cisplatin administration; changes in severity and neurophysiologic assessment NR	Prospective, randomized, placebo controlled multicenter trial/low (insufficient sample size considering the variety of center types, etc.)	Gandara et al. 1995 [143]
Glutamine	Neurotrophic: induces NGF synthesis	86 (42:44)/metastatic colorectal cancer	Oxaliplatin	Lower incidence of grades 1–2 neurotoxicity; assessed by NCI-CTC ($p = .04$); severity assessment NR; no significant changes in neurophysiologic assessment	Randomized pilot study/ high (neither blinded nor placebo-controlled)	Wang et al. 2007 [144]
Glutathione	Antioxidant: a physiologic free radical scavenger, chelator for heavy metals that decreases the initial accumulation of platinum adducts in the neurons,	185 (94:91)/ovarian, fallopian tube, and primary peritoneal cancers (86), lung cancer (53), other types (22)	Carboplatin, paclitaxel	No significant changes in incidence and severity of neuropathy grades 1–4 assessed by EORTC QLQ-CIPN20, and NCI-CTC reported; changes in	Phase III randomized, double-blind placebo-controlled study/low	Leal et al. 2014 [145]

(continued)

Table 3. (continued)

Agent	Mechanism of action	Total patients (treated vs. control)/tumor type	Neurotoxic agent(s)	Neuroprotection	Study design/overall risk of bias[a]	Reference
	and modulator of MAPKs, including JNK/Sapk ERKs and p38 pathways with which apoptosis is inhibited			neurophysiologic assessment NR		
		27 (14:13)/colorectal cancer	Oxaliplatin (FOLFOX4)	Lower incidence of grades 1 and 3 neurotoxicity; assessed by NCI-CTC ($p = .0037$); changes in severity and neurophysiologic assessment NR	Prospective, randomized, placebo-controlled/ intermediate (small sample size, unclear randomization and blinding, etc.)	Milla et al. 2009 [146]
		52 (26:26)/colorectal cancer	Oxaliplatin	Decrease in incidence and severity of grades 1–4 neurotoxicity; assessed by NCI-CTC, and sensory nerve conduction studies (sural, median, or ulnar); severity assessment NR; no significant changes in neurophysiologic assessment	Prospective, randomized placebo-controlled/low (incomplete outcome data, etc.)	Cascinu et al. 2002 [147]
		20 (11:9)/NSCLC and head and neck cancer	Cisplatin	No significant decrease in incidence of neurotoxicity assessed by WHO neurotoxicity measure and motor nerve conduction studies	Prospectively randomized placebo- controlled pilot trial/intermediate (insufficient sample size, unclear randomization, and blinding)	Schmidinger et al. 2000 [148]
		151 (74:77)/ovarian cancer	Cisplatin	Significantly less tingling assessed by NCI/WHO; HAD and Rotterdam scales (functional scales); changes in severity and neurophysiologic assessment NR	Prospective, randomized, placebo-controlled/low (blinding and outcome data not clearly described, etc.)	Smyth et al. 1997 [149]
		50 (25:25)/ovarian cancer	Cisplatin	Decrease in incidence of neurotoxicity assessed by NCI/WHO criteria and sensory nerve conduction studies (sural, median, or ulnar; $p < .01$); changes in severity NR	Prospective, randomized, placebo-controlled/low (relatively small trial, long-term follow-up unclear, incomplete outcome data, etc.)	Cascinu et al. 1995 [150]
		33 (16:17)/relapsing ovarian cancer	Cisplatin	No significant changes in incidence and severity of neuropathy assessed by SNAP and NCI/WHO	Prospective, randomized, placebo-controlled study/ low (lack of information about randomization and blinding and small sample	Colombo et al. 1995 [151]

(continued)

Table 3. (continued)

Agent	Mechanism of action	Total patients (treated vs. control)/tumor type	Neurotoxic agent(s)	Neuroprotection	Study design/overall risk of bias[a]	Reference
					size, incomplete outcome data, etc.)	
		54 (27:27)/ovarian cancer	Cisplatin	Decrease in SNAP amplitude (sural, median, or ulnar; $p = .043$) and VPT; changes in severity of neurotoxicity not significant; changes in incidence NR	Prospective, randomized, placebo-controlled/ intermediate (unblinded, relatively small trial, unclear randomization and allocation concealment, reporting bias, etc.)	Bogliun et al. 1992 [152]
Goshajinkigan(Kampo medicine; composed of 10 natural ingredients)	Acts via release of dynorphin, nitric-oxide production, and reducing transmitter proteins and sensory receptors associated with C-fiber activation	89 (44:45)/colorectal cancer	Oxaliplatin (FOLFOX4 or mFOLFOX6)	Suggestive of a decrease in incidence of grade 2–3 neurotoxicity assessed by NCI-CTC and FACT/GOG-Ntx, but insignificant; changes in severity and neurophysiologic assessment NR	Phase II, multicenter, randomized, double-blind, placebo-controlled trial[b]	Kono et al. 2013 [153]
		45 (22:23)/nonresectable or recurrent colorectal cancer	Oxaliplatin (FOLFOX6)	Lower incidence of grades 3 neurotoxicity; assessed by DEB-NTC ($p < .01$; unblinded control); Severity and neurophysiologic assessment NR	Prospective randomized controlled study/low (relatively small sample size with unblinded control group, etc.)	Nishioka et al. 2011 [154]
Nimodipine	Calcium channel antagonist that might attenuate chelating effect by increasing calcium serum levels	50 (24:26)/ovarian cancer	Cisplatin	The trial was terminated because of side effects; the available data suggested that nimodipine exacerbated (not prevented) neurotoxicity; incidence, severity and neurophysiologic assessment NR	Randomized placebo-controlled study/high (small trial with unreliable measures and inadequate follow-up period)	Cassidy et al. 1998 [155]
Org 2766	Neurotrophic: an adrenocorticotropic hormone analog with neurotrophic effects	196 (129:67)/epithelial ovarian cancer	Cisplatin	No significant changes in incidence and severity of neurotoxicity; VPT increased in both groups during the study (worse outcome)	Prospective, randomized, placebo-controlled/low (unclear randomization and allocation concealment, etc.)	Roberts et al. 1997 [156]
		42 (19:23)/testicular and adenocarcinoma of unknown primary	Cisplatin (and different combinations of etoposide, bleomicin, and ifosphamide)	Neurophysiologic assessment not suggestive of neuroprotection; changes	Prospective, randomized, placebo-controlled/low (insufficient sample size, unclear randomization and	van Gerven et al. 1994 [157]

(continued)

Table 3. (continued)

Agent	Mechanism of action	Total patients (treated vs. control)/tumor type	Neurotoxic agent(s)	Neuroprotection	Study design/overall risk of bias[a]	Reference
				in incidence and severity NR	blinding, incomplete outcome data, etc.)	
		20 (7:11)/epithelial ovarian cancer	Cisplatin	VPT increased significantly less in active arm than placebo; changes in incidence and severity NR	Prospective, randomized, placebo-controlled/ intermediate (insufficient sample size, unclear randomization, substantial dropout, incomplete outcome data, etc.)	Hovestadt et al. 1992 [158]
		55 (33:22)/epithelial ovarian cancer	Cisplatin	VPT increased approximately twofold, significantly less than the nearly eightfold increase in the placebo group; changes in incidence and severity NR	Prospective, randomized, placebo-controlled/low (relatively small trial, etc.)	van der Hoop et al. 1990 [159]
Oxcarbazepine	Sodium channel inhibitor: protects the alteration of voltage-gated sodium channels by oxalate	40 (20:20)/colon cancer	Cisplatin	Significant decrease in incidence and severity of neurotoxicity assessed by NSS, TNS, SNAP, and peroneal motor responses	Prospective, randomized, open label with blind assessment/intermediate (relatively small trial with an unblinded control arm, etc.)	Argyriou et al. 2006 [160]
Retinoic acid (all-trans-retinoic acid)	Stimulator of NGF and the expression of its receptor, activator of retinoid acid receptors with neuroprotective profile; it is also a prodifferentiative agent able to activate both JNK/Sapk and ERK1/2	92 (45:47)/advanced NSCLC	Cisplatin, paclitaxel	Decrease in incidence and severity of grade 2–4 neuropathy assessed by motor and sensory response amplitudes and NCI-CTC	Prospective, randomized, placebo-controlled/low (short period of evaluation, etc.)	Arrieta et al. 2005 [161]
rhuLIF	Neurotrophic: a IL-6 class cytokine that upregulates NGF synthesis, which affects nerve regeneration by inhibiting differentiation	117 (75:42)/different solid tumors	Carboplatin, paclitaxel	Worse neuropathy endpoints in the active therapy arm for changes in velocity in the median nerve; no significant changes in CPNE score and VPT; changes in incidence of neuropathy NR	Randomized, double-blinded, placebo-controlled phase II trial/ low	Davis et al. 2005 [162]
Venlafaxine	Serotonin-norepinephrine reuptake inhibitor: modulates the oxidative stress in the nervous system and may block sodium channels	48 (24:24)/different solid tumors	Carboplatin/paclitaxel	Decrease in NPSI (pins and needles; $p < .001$); no significant decrease in NPSI pain triggered by cold; changes in incidence and neurophysiologic assessment NR	Randomized, double-blind, placebo- controlled phase III trial/ intermediate (small sample size, unclear allocation concealment, etc.)	Durand et al. 2012 [163]

(continued)

Table 3. (continued)

Agent	Mechanism of action	Total patients (treated vs. control)/tumor type	Neurotoxic agent(s)	Neuroprotection	Study design/overall risk of bias[a]	Reference
Vitamin E	Antioxidant: protects biologic membranes by inhibiting peroxidation of polysaturated fatty acids, and a protector against platinum accumulation in the DRG	189 (96:93)/colorectal, breast, lung, and other cancers	Cisplatin (8), carboplatin (2), oxaliplatin (50), taxanes (109), or combinations of each	Inclusion of a large number of participants receiving taxanes was confounding; changes in neurophysiologic assessment NR	Randomized, double-blind, placebo- controlled phase III trial/low (different types of cancers with no comparable distribution and insufficient sample size for platinum groups, etc.)	Kottschade et al. 2011 [164]
		108 (54:54) after dropout (17:24)/different solid tumors	Cisplatin	Significant decrease in incidence and severity of neurotoxicity grades 3–4 assessed by TNS and SNAP (sural and median)	Randomized, placebo-controlled trial/high (substantial dropout rate, excluding intention-to-treat analyses, etc.)	Pace et al. 2010 [165]
		30 (14:16)/solid tumors	Cisplatin, paclitaxel	Significant decrease in incidence and severity of neurotoxicity assessed by NSS/NDS; reduced median SNAP amplitudes in control group	Prospective, randomized, open label with blind assessment/high (relatively small trial and lack of a placebo group and reliable measures; excluding intention-to-treat analyses, etc.)	Argyriou et al. 2006 [166]
		27 (13:14)/lung, ovarian, rhino-pharyngeal, gastric, testicular, esophagus, ethmoid, and tongue cancers	Cisplatin	Significant decrease in incidence and severity of neurotoxicity; reduced median SNAP amplitudes in control group	Prospective, randomized, placebo-controlled/high (small size and excluding intention-to-treat analyses; control participants were untreated)	Pace et al. 2003 [167]
Xaliproden	A synthetic neuromodulant that activates MAPK pathways, which minimizes neuritic damage	649 (325:324)/metastatic colorectal cancer	Oxaliplatin (FOLFOX4)	Efficient in reducing grade 3–4 neurotoxicity evaluated by sensory action potential (17% vs. 11% with placebo); but no significant difference in overall incidence (73% of both arms)	Randomized, double-blind, placebo- controlled phase III trial[b] (unpublished data)	Cassidy et al. 2006 [168]

[a]Strength of evidence is according to the 2014 American Society of Clinical Oncology Clinical Practice Guideline [123] and 2014 Cochrane systematic review [9].
[b]Not assessed by American Society of Clinical Oncology or Cochrane studies.
Abbreviations: 2-PD, two-point discrimination; CPNE, composite peripheral nerve electrophysiology; DEB-NTS, Debiopharm Neurotoxicity Scale; DRG, dorsal root ganglion; EMG, electromyography; EORTC QLQ-CIPN20, European Organization for Research and Treatment of Cancer quality of life questionnaire to assess chemotherapy-induced peripheral neuropathy; ERK, extracellular signal-regulated kinase; FACT/GOG-Ntx, Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity Scale; FOLFOX, folinic acid (leucovorin), fluorouracil, and oxaliplatin; HAD, hospital anxiety and depression; IL, interleukin; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; mFOLFOX, modified FOLFOX; NAC, *N*-acetylcysteine; NCI-CTC, National Cancer Institute–Common Toxicity Criteria; NCS, nerve conduction studies; NDS, neurological disability score; NGF, nerve growth factor; NIS, neuropathy impairment scale; NPSI, Neuropathic Pain Symptom Inventory; NR, not reported; NSS, neurological symptom score; NSCLC, non-small cell lung cancer; OSS, oxaliplatin-specific scale; rhuLIF, recombinant human leukemia inhibitory factor; Sapk, stress-activated protein kinase; SCLC, small cell lung cancer; SNAP, sural, superficial peroneal, and ulnar sensory nerve action potential; TNS, total neuropathy score; TRA, tendon reflex activity; VDT, vibration disappearance threshold; VPT, vibration perception threshold; WHO, World Health Organization; XELOX, oxaliplatin and capecitabine.

the control group [164–167], although all were with high risk of bias and low strength of evidence (Table 3).

Reduced glutathione is a natural neuroprotectant antioxidant derived from the γ-glutamyl transpeptidase with a high affinity for heavy metals, which may prevent the accumulation of platinum in the DRG [146, 147, 149, 150]. Additionally, it is a natural free-radical scavenger and can also stimulate NGF receptors [188]. Five different clinical trials demonstrated the potential of glutathione in reducing the incidence and severity of neuropathy induced by oxaliplatin [146, 147] or cisplatin [149, 150, 152], whereas three others could not find significant neuroprotective effect against carboplatin (carboplatin-paclitaxel combination) [145] or cisplatin-induced peripheral neurotoxicity [148, 151] (Table 3). Similarly, oral glutamine, another derivative of the γ-glutamyl transpeptidase, may reduce the incidence and severity of oxaliplatin-induced peripheral neuropathy [144], although based on a randomized, but neither blinded nor placebo-controlled trial.

N-Acetylcysteine is a glutathione precursor that is believed to increase the blood concentration of glutathione [124]. The only available clinical trial on *N*-acetylcysteine in a small population revealed some potential neuroprotective effects against oxaliplatin-induced peripheral neurotoxicity [124] (Table 3). D-Methionine, a sulfur-containing nucleophilic antioxidant, has also shown successful neuroprotection against cisplatin-induced neurotoxicity in cortical network in vitro [189].

Electrolytes, Chelators, and Ion Channel Modulators

The electrolytes calcium and magnesium may act as chelators against oxalate accumulation and will probably protect the voltage-gated sodium channels from alteration [140]. Among six available randomized clinical trials conducted to evaluate the efficacy of calcium/magnesium infusion against oxaliplatin-induced peripheral neurotoxicity (Table 3), two preliminary studies were unsuccessful in showing any protection by intravenous calcium/magnesium [140, 141]. Knijn et al. [139], in a retrospective analysis study on patients with oxaliplatin-induced peripheral neurotoxicity, could only find reduced rate of grade 1 peripheral neurotoxicity, considering the high risk of bias. Later, two clinical studies have shown some levels of neuroprotection against the development of oxaliplatin-induced neuropathy [138]. However, the two most recent trials did not confirm the neuroprotective role of calcium/magnesium against oxaliplatin-induced neuropathy [137, 136]. Moreover, Han et al. [136] have shown that calcium and magnesium infusions do not alter the pharmacokinetics of either intact oxaliplatin or free platinum, whereas there was no evidence of a pharmacokinetic interaction between calcium/magnesium and oxaliplatin, meaning that these infusions may provide no benefit in reducing acute oxaliplatin-induced peripheral neurotoxicity.

Carbamazepine and oxcarbazepine are known as antiseizure drugs. They block voltage-sensitive sodium channels and some calcium channels, which might protect the voltage-gated sodium channels from alteration by oxalate [55, 190]. These two agents have also been tested in clinical trials with relatively small sample sizes, with one showing neutral effect [142] and the other suggesting benefit, although with an unblinded control arm [160] (Table 3).

Nimodipine is a calcium channel blocker that did not show significant neuroprotection against cisplatin in the only clinical trial ever done [155]. Although the trial had to be terminated because of severe gastrointestinal toxicity, the results by that time did not support neuroprotection. A multicenter trial on diethyldithiocarbamate, a chelating agent and antioxidant that prevents the degradation of extracellular matrix as an initial step in cancer metastasis and angiogenesis, did not demonstrate a significant chemoprotective effect against cisplatin-induced neurotoxicity [143] (Table 3).

Other Compounds

There are also some data supporting the preventive effect of other agents against platinum-induced peripheral neurotoxicity. Acetyl-L-carnitine is a natural compound that plays a role in intermediary metabolism and has an antioxidant activity [191]. In vitro data support its effectiveness for platinum-induced neurotoxicity [179], but a recent randomized double-blinded placebo-controlled trial discouraged its administration for a non-platinum agent [192]. Xaliproden is a 5-hydroxytryptamine $(HT)_{1A}$ agonist that also acts as a neuromodulator with neurotrophic and neuroprotective effects in vitro [193] and had positive results in a clinical setting as well [168], although the results have yet to be published. Venlafaxine is a serotonin-norepinephrine reuptake inhibitor that also modulates the oxidative stress in the nervous system and may block sodium channels, which showed some neuroprotective effect in a small clinical trial [163].

Goshajinkigan (Kampo medicine), composed of 10 natural ingredients, is frequently used for alleviating symptoms of diabetic peripheral neuropathy in Japan; it is shown to have some neuroprotective potentials [194, 195]. Moreover, its safety and efficacy for preventing oxaliplatin-induced peripheral neurotoxicity have been tested in two clinical trials [153, 154] (Table 3). Nishioka et al. [154] reported a significantly lower incidence of grade 3 peripheral neurotoxicity, although based on a small sample size with unblinded control group. The findings of a phase II, multicenter, randomized, double-blind, placebo-controlled trial by Kono et al. [153] were also suggestive of reduced but insignificant rate of peripheral neurotoxicity grade 2 and 3 in patients treated with oxaliplatin compared with placebo (incidence of grade 2 neuropathy until the eighth cycle: 39% and 51% in the Kampo and placebo groups, respectively [relative risk, 0.76; 95% CI 0.47–1.21]; and grade 3: 7% vs. 13% [0.51, 0.14–1.92]).

Nondrug Approach

There are other modalities that might enhance the effectiveness of the treatment while diminishing side effects or prevent peripheral neurotoxicity. It might be helpful to identify risk factors for neurotoxicity, such as pre-existing neuropathy, inherited neuropathies, age-related axonal loss, diabetes mellitus, alcohol abuse, and poor nutritional status, that may predispose to more severe symptoms from platinum-induced peripheral neurotoxicity [196].

Timing in drug administration to account for biological rhythms (chronotherapy) seems also very important [197], because there are drugs and disease conditions, including cancers suggestive of an optimal circadian time of drug administration [198]. However, in a meta-analysis on five

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randomized controlled trials with 958 patients, there was no significant difference in the incidence of peripheral sensory neuropathy after chronomodulation [199].

Finally, regarding the paucity of evidence about preventive and therapeutic strategies, treatment modification and drug withdrawal remain the most effective modalities for majority of patients [31], which indeed necessitates more adequately powered preclinical and clinical researches to find better alternative modalities [200, 201].

Neuro- Versus Chemoprotection

It is essential to demonstrate whether the application of a neuroprotective agent might diminish the efficacy of the therapeutic agent. However, this potential adverse effect has been tested with different agents. As an example, cisplatin and carboplatin are used in induction and myeloablative chemotherapy for high-risk neuroblastoma, but because of significant ototoxicity in children, their administration may be compromised. Harned et al. [169] showed that the exposure of six neuroblastoma cell lines to STS, at 6 hours after cisplatin, did not bind to and eliminate the circulating cytotoxic compound and thus did not affect the antitumor effect of the platinum agent, even under hypoxic conditions. However, a significant undesired protection against cisplatin cytotoxicity was seen when the neuroblastoma cells were simultaneously exposed to both cisplatin and STS combinations. Moreover, Harned et al. [169] demonstrated that in a subcutaneous neuroblastoma xenograft model in nu/nu mice, mice receiving cisplatin alone or cisplatin plus STS after 6 hours had significantly better progression-free survival rates ($p < .03$) compared with controls or mice treated with concurrent cisplatin and STS administration. Likewise, Muldoon et al. [170] reported that delaying the administration of STS for 6–8 hours after carboplatin did not reduce its antitumor activity in a human small cell lung cancer xenograft model in the rat, but still protected against ototoxicity in guinea pigs. Moreover, Dickey et al. [171] found that adding STS simultaneously or up to 2 hours postcisplatin protected against the antitumor effect of cisplatin in glioblastoma, SKOV3 ovarian carcinoma, medulloblastoma, and small cell lung cancer cell lines, but that delayed STS administration for 6 hours did not show a significant chemoprotection in any of the cell types.

The use of STS to prevent hearing loss in children with a variety of malignancies has been tested in two phase III randomized trials SIOPEL6 (NCT00652132) [172] and COG ACCL0431 (NCT00716976) [173]. In the preliminary report of COG, presented at the 2014 annual American Society of Clinical Oncology (ASCO) meeting [173], a protective effect of STS was found in reducing the proportion of hearing loss compared with observation (29% versus 55%; $p = .006$). In this trial, 126 cancer patients were randomized to either cisplatin infusions alone or, to prevent cisplatin-induced hearing loss, combined with STS at 16 g/m^2 IV over 15 minutes beginning 6 hours after the completion of each cisplatin dose. The median postdiagnosis follow-up was 2.1 years. However, the potentially lower survival seen in the patients with disseminated disease receiving STS (event-free survival 60% versus 70%, $p = .53$; overall survival 75% versus 89%, $p = .50$) raises some concern of a tumor-protective effect of STS.

Treatment

The efficacy of some antidepressants, anticonvulsants, and a topical gel has been tested in six trials for treatment of platinum-induced peripheral neurotoxicity. Smith et al. [202] studied the effect of duloxetine in a randomized, placebo-controlled, crossover trial of 231 patients with either platinum or taxane neurotoxicity. Patients received 30 mg of duloxetine for the first week and 60 mg of daily duloxetine for 4 more weeks. Duloxetine significantly reduced pain and paresthesia, especially in oxaliplatin group. In contrast, 50 mg of daily amitriptyline or 100 mg of nortriptyline, in two separate trials, failed to demonstrate any significant improvements in patient-reported sensory symptoms, as well as objective scorings [203]. Similarly, trials testing gabapentin at a target dose of 2,700 mg/day [204] or lamotrigine at a target dose of 300 mg/day [205] failed to demonstrate any benefit for treatment of peripheral neurotoxicity. Finally, one trial evaluated a compounded topical gel containing baclofen (10 mg), amitriptyline HCl (40 mg), and ketamine (20 mg) on 208 randomly allocated patients [206], and a significant improvement in motor subscale scores was observed.

Future

There are some promising results favoring the ability of some neuroprotective agents to reduce the rate of subsequent neurotoxicity induced by platinum analogs. However, the most recent update of the Cochrane review on chemo-neuroprotective agents found insufficient data to conclude that any of the available chemoprotective agents is sufficiently effective in preventing or limiting the neurotoxicity of platinum drugs. Albers et al. [9] reviewed 29 randomized controlled trials (RCTs) or quasi-RCTs, in which 2,906 participants received chemotherapy with cisplatin or related compounds. Patients were also evaluated for quantitative sensory testing (primary outcome) or other measures including nerve conduction or neurological impairment rating using validated scales (secondary outcomes) before and 6 months after completing chemotherapy (Table 3). Likewise, the most recent ASCO Clinical Practice Guideline [123] based on a systematic review on 48 RCTs, including 35 RCTs on platinum-induced peripheral sensory neurotoxicity, did not recommend any established agent for the prevention of platinum-induced peripheral neurotoxicity. Only for the treatment of existing oxaliplatin neuropathy, they advised duloxetine, for which intermediate strength of evidence is present, considering the balance between benefit and harm [123].

Altogether, no neuroprotective strategy can yet be recommended for prevention and treatment of platinum-induced neurotoxicity, with a possible exception for duloxetine for oxaliplatin. There is a genetic diversity between patients, leading to differences in drug response including the side effects; hence a neuropathy preventive strategy should be individualized for each patient.

A pharmacogenetic approach might be useful in understanding the cause of peripheral neurotoxicity and tailoring the most suitable chemotherapy for each patient. A genome-wide pharmacogenomic approach may also be useful in identifying novel polymorphism predictors of severe platinum-induced peripheral neurotoxicity that may be used in personalized chemotherapy [71]. However, it is highly

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recommended that the positive and negative effects of the antineoplastic agents be studied in detail in preclinical settings before implementation in clinical practice. In particular, the central nervous system of animals can be used to quantify the effects of platinated compounds on neurons that corroborate clinical data and suggest them as suitable models for studying possible neurotoxicity of platinum agents [111–121]. Some in vitro models can also be used to investigate morphological parameters affected by platinum compounds [122]. These models enable measuring the effect of the drugs on neurons along with testing the neurogenic potential of neuroprotective compounds.

Conclusion

Our knowledge about the pathophysiology of platinum-induced peripheral neurotoxicity and suggested neuroprotective strategies is diverse and not adequately powered. Therefore, a thorough investigation of available evidence is important to design new, solid studies to tailor appropriate treatment to individual patients. This will minimize the burden of peripheral neurotoxicity, optimizing the potentially positive impact of the chemotherapeutic medication.

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Author Contributions

Conception/Design: Abolfazl Avan, Tjeerd J. Postma, Godefridus J. Peters
Provision of study material or patients: Abolfazl Avan, Godefridus J. Peters
Collection and/or assembly of data: Abolfazl Avan
Data analysis and interpretation: Abolfazl Avan, Tjeerd J. Postma, Guido Cavaletti, Elisa Giovannetti
Manuscript writing: Abolfazl Avan, Tjeerd J. Postma, Cecilia Ceresa, Amir Avan, Guido Cavaletti, Elisa Giovannetti, Godefridus J. Peters
Final approval of manuscript: Abolfazl Avan, Tjeerd J. Postma, Guido Cavaletti, Elisa Giovannetti, Godefridus J. Peters

Disclosures

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