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Complications of Treatment

Chemotherapy-induced neuropathy: A comprehensive survey

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ABSTRACT

Chemotherapy induced peripheral neuropathy (CIPN) is a potentially dose limiting side effect of commonly used chemotherapeutic agents like taxanes, vinca-alkaloids, platinum compounds, bortezomib and thalidomide.

Supposed pathogenetic mechanisms of CIPN are axonopathy through dying back axon damage and neuronopathy in which the cell bodies of the dorsal root ganglia are involved. The exact pathophysiology however is not clear and different underlying mechanisms have been proposed for different classes of anti-cancer drugs.

Sensory symptoms, like pain, numbness and tingling are most common, but motor weakness, autonomic dysfunction and even cranial nerve involvement may occur. CIPN can be painful and/or disabling, causing significant loss of functional abilities and decreasing quality of life. This can lead to dose reductions, discontinuation of treatment and may thus, ultimately, affect survival.

Risk factors for CIPN include dose per cycle, cumulative dose, treatment schedule, duration of infusion, administration of other chemotherapeutics, comorbidity and pre-existing peripheral neuropathy.

The exploration of polymorphisms in genes associated with incidence or severity of neuropathy might result in identifying individuals being at higher risk of neurotoxicity. An update on genes possibly associated with CIPN is given.

CIPN may be reversible or be more or less permanent. Many preventive and treatment strategies have been explored, without significant efficacy up till now.

In this review we describe the different drug-related characteristics of CIPN, pharmacogenomic studies, neurophysiological findings, treatment and outcome, and neuroprotective strategies.

Introduction

Chemotherapy induced peripheral neuropathy (CIPN) is a common and potentially debilitating side-effect of cancer treatment. Because of better treatment options like new anti-emetics and hematopoietic colony stimulating factors for other serious side-effects CIPN becomes more often a dose limiting factor. Despite its clinical relevance and common occurrence, the pathophysiology of CIPN in the different groups of chemotherapy is still largely unknown. Mechanisms of CIPN are axonopathy through axon damage and neuronopathy in which the cell bodies of the dorsal root ganglia are involved. The primary axon damage starts at the most vulnerable part of the nerve, i.e. the end of the longest nerves, after which it spreads centrally (dying back neuropathy). The exact pathophysiology however is not elucidated and different underlying mechanisms have been proposed for the different classes of anti-cancer drugs.

Symptoms are predominantly sensory, like pain, numbness and tingling. Sometimes there are motor symptoms like weakness, autonomic neuropathy and incidentally cranial nerve involvement. CIPN can be painful and/or disabling, causing significant loss of functional abilities and decreasing quality of life. This can lead to dose reductions, discontinuation of treatment, and may thus, ultimately, affect overall survival. In routine practice CIPN is evaluated using clinical parameters. Usually objective assessment of neuropathic signs is performed with bedside clinical examinations, sometimes with additional electrophysiological studies. There are several scales to evaluate CIPN; commonly used are the common toxicity criteria of the national cancer institute (NCI-CTC) and the total neuropathy score (TNS). TNSc, mISS, NCI-CTC and the EORTC QLQ-C30 questionnaire with its CIPN20 module are the most reliable tools for accurately grading CIPN [1].

Electromyography and nerve conduction studies have only limited usefulness in the clinical setting. Compared to clinical

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examination nerve conduction studies in patients treated with cisplatin showed no diagnostic advantage [2]. Semi-quantitative assessment of sensory threshold or of muscle strength has been advocated, but standardization of the instruments and of the methods have never been achieved.

In this review we summarize the characteristics and management of CIPN caused by different chemotherapeutic agents.

Taxanes

Taxanes include paclitaxel (Taxol) and docetaxel (Taxotere). These chemotherapeutic agents inhibit the disassembly of microtubules by binding to the beta-tubulin subunit in the microtubules. The principal function of microtubules is the formation of the mitotic spindle during cell division. Consequently, microtubules become extraordinarily stable and dysfunctional, leading to death of the cell by disrupting the normal tubule dynamics required for cell division and vital interphase processes [3]. Paclitaxel is used in the treatment of ovarian-, breast- and non small cell lung cancer. Docetaxel is used in the treatment of breast-, non small cell lung-, prostate-, gastric and head- and neck cancer. Main toxicities of these microtubule-stabilizing agents are haematologic toxicity, especially in docetaxel and peripheral neuropathy.

Pathogenesis of the neuropathy

The exact mechanism of taxane induced neuropathy is not elucidated. Axonal microtubules are important for the development and maintenance of neurons. Microtubule elongation contributes toward the growth and structure of neurites. They form the major participating elements mediating axonal anterograde and retrograde transport of for example neurofilaments, degradative organelles and endosomes containing signaling platforms [4].

Neurotoxicity by taxanes may be caused by disruption of microtubule structure leading to impairment of axoplasmic transport and dying back neuropathy. In vitro studies demonstrated large abnormal microtubule arrays in spinal cord-sensory ganglia following exposure to paclitaxel [5], and addition of paclitaxel to dorsal root ganglia cell cultures inhibited anterograde axonal transport [6].

Another hypothesized mechanism is a toxic effect on mitochondria in primary afferent neurons leading to a deficit in axonal energy supply and chronic sensory neuropathy [7]. In the rat, paclitaxel neuropathy is associated with significant increase of swollen and vacuolated mitochondria in the axons [8]. Paclitaxel opens the mitochondrial permeability transition pore (mPTP), which is a multimolecular complex containing the voltage dependent anion channel. Paclitaxel evoked opening of the mPTP causes the calcium release from the mitochondria. This calcium mediated neuronal excitability is suggested to play a role in neurotoxicity [8]. Bennet et al. [9] described a deficient oxygen consumption in the dorsal root sensory axons from animals treated with paclitaxel, with increased amounts of ATP produced by both respiratory complex I and II. The above explained mechanisms involved in neuropathy may be interrelated.

Symptoms and risk factors

Paclitaxel induces a bilateral, distal, symmetrical axonal neuropathy that is predominantly characterized by sensory symptoms like numbness, tingling and burning pain in a stocking-and-glove distribution. There is often symmetrical loss of sensation carried by both large fibers (proprioception, vibration) and small ones (temperature, pinprick). Achilles tendon reflexes are low or absent. Motor and autonomic dysfunction are rare [10]. The incidence of taxane-induced neuropathy has been variously reported and depends on risk factors including dose per cycle, cumulative dose, treatment schedule, duration of infusion, concurrent administration of other neurotoxic drugs and comorbidity such as diabetes [5,11].

Neuropathic symptoms may begin 24–72 h after paclitaxel treatment with higher dose (250 mg/m^2) but usually occur only after multiple courses at conventional dose (<200 mg/m^2). Severe neurotoxicity precludes the administration of paclitaxel doses above 250 mg/m^2 [3,11,12]. Grade 3 or 4 sensory neurotoxicity occurs in 20–35% of patients receiving 250 mg/m^2 every three weeks compared to 5–12% in large series using doses $\leqslant$200 mg/m^2 every 3 weeks [11]. The weekly schedule is associated with increased neurotoxicity [12]. CTC grade 2/3 neurotoxicity occurs from a cumulative dose of about 1400–1500 mg/m^2 [3,5,10,13].

A higher rate of CIPN occurs when paclitaxel is infused over 3 h instead of 24 h, suggesting that neurotoxicity is related to peak plasma concentration [14]. Weekly administration (80 mg/m^2) was associated with a higher incidence of grade 3/4 sensory neuropathy compared to 3 weekly administration (175 mg/m^2) [15]. On the contrary, a more recent meta-analysis stated that in weekly paclitaxel regimens the incidence of grade 3/4 peripheral neuropathy was lower than in 3-week regimens [16].

At high dose (>250 mg/m^2) proximal weakness can develop with severe muscle aches, for which dose reduction is necessary [17]. Transient mild myalgias can occur at doses of >170 mg/m^2, which start 2 or 3 days following treatment and resolve within 6 days [3].

Symptoms of docetaxel induced neuropathy are similar but usually milder and disappear spontaneously after discontinuation probably because of lower dosing of docetaxel due to more profound hematological toxicity. In patients treated with docetaxel, grade 3/4 neuropathy occurs in 10% or less [11], proportional to the cumulative dose. Hilkens reported severe docetaxel neuropathy following cumulative dosages over 600 mg/m^2 in 4 out of 15 patients [18]. Docetaxel treatment has been associated with Lhermitte's sign, a non-painful electric shock-like sensation that shoots down the spine during neck flexion, indicating involvement of the central dendrites of the dorsal root ganglia in the dorsal columns [19].

Neurophysiological examination

In paclitaxel induced neuropathy, sensory nerve potentials (SNAPs) amplitudes are reduced or absent, in particular of the sural nerve. Compound muscle action potential amplitude can also be reduced. Nerve conduction velocities can be decreased [20]. Likewise, in docetaxel induced neuropathy, low amplitude sensory and motor potentials are measured but conduction velocities are generally normal [11].

Genetic studies

The role of genetic markers to predict CIPN is investigated. Multiple single nucleotide polymorphisms (SNP's) were evaluated in relation to neurotoxicity, and genome wide association studies as well as studies with selected target genes have been performed.

Polymorphisms in genes encoding paclitaxel metabolizing enzymes and transporters may contribute to interindividual toxicity and response.

Polymorphisms in the CYP 2C8 and CYP 3A5 genes encoding paclitaxel metabolizing enzymes were described to be associated with CIPN. A twofold risk of neuropathy in patients with the CYPC2C8*3 variant was reported [21,22]. In addition, an association between polymorphisms in the ABCB1 gene, that encodes ATP binding cassette proteins, which transport various molecules