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MINIREVIEW

Genetic determinants of taxane-induced peripheral neuropathy

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ABSTRACT

The efficacy of taxane-containing regimens has been demonstrated for various cancers, particularly ovarian, endometrial, breast, lung, and prostate cancers. However, extensive taxane-induced toxicities limit their use. Prediction and management of many toxic complications in cancer patients have evolved significantly over the last decade.

Peripheral neuropathy is the most typical non-hematological taxane-related complication, and it has a multifactorial pathogenesis. It is often dose-dependent and progressive during therapy and sometimes even after treatment. Unfortunately, the prediction of these common adverse events remains unclear.

In the past few years, several polymorphisms of candidate genes with a possible role in the development of this consequence were studied.

This minireview aims to highlight the critical yet underappreciated roles of genetic predictors that may increase susceptibility to taxane-induced peripheral neuropathy in cancer patients *(Ref. 40)*. Text in PDF *www.elis.sk*

KEY WORDS: taxanes, paclitaxel, docetaxel, peripheral neuropathy, risk factors, genetic polymorphisms.

Introduction

Since 1984, taxanes have found extensive use in the treatment of various malignancies, including ovarian, endometrial, breast, and prostate cancers (1). However, the clinical benefit of these widely used cytostatics, specifically paclitaxel and docetaxel, has been limited by their toxicity and the development of resistance in cancer cells. The toxicity profile of paclitaxel and docetaxel includes hypersensitivity reactions, peripheral neurotoxicity, hematotoxicity, and dermatotoxicity, while cases of central neurotoxicity are rare. Although some types of taxane-induced toxicities are relatively well-managed, peripheral neuropathy remains a challenging issue (2, 3).

The incidence of all grades of taxane-induced peripheral neuropathy (TIPN) in patients treated with paclitaxel varies from 57% to 83%, with 2% to 33% of cases classified as severe. Similarly, with docetaxel, the incidence of TIPN ranges from 11% to 64%, with 3% to 14% classified as severe (4). Given the prevalence of this condition, a better understanding of its pathophysiology and early recognition of those at risk are crucial. Despite the significant progress in understanding the mechanisms of action of chemotherapeutic agents on the nervous system, the specific pathogenetic mechanisms of individual taxanes remain poorly understood (5).

The most widely accepted theory is based on the inhibition of tubulin depolymerization, leading to the excessive formation of atypical clusters of microtubules which accumulate in cells and disrupt their functions. These changes in the cytoskeleton disrupt mitosis, which is the principal antitumor effect of taxanes. Intact microtubules are essential for axonal transport, and the increased stability of axonal microtubules induced by taxanes can lead to axon loss or degeneration, impairing mitochondrial function and axonal transport (6–8). The peripheral nervous system is particularly vulnerable. Paclitaxel increases pain sensitivity through increased expression of TRP (transient receptor potential) channels, particularly TRPV4 (transient receptor potential vanilloid 4). Studies in knockout mice have shown improvements in neuropathic pain (9).

Patients treated with taxanes (paclitaxel, docetaxel) often develop sensory neuropathy. Acute pain syndrome occurs in up to 70% of patients, typically 1–3 days after chemotherapy, presenting as diffuse myalgia or arthralgia that tends to regress spontaneously within a week (10, 11). However, TIPN can be progressive and may manifest even after cancer remission (3). The typical taxane-related symptoms include transient or persistent distal symmetric

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paresthesias and burning pain in the limbs, with spontaneous improvement occurring months to years after treatment completion. The plantar area of the feet and the tips of the fingers on the limbs are commonly affected. Sensory symptoms such as numbness and reduced sensitivity to heat and touch are also prevalent (12, 13).

Motor impairment and gait disturbances may occur at higher taxane doses.

Rarely, symptoms associated with changes in autonomic nervous system, such as arrhythmias and orthostatic hypotension, can be induced by taxanes. Treatment-related risk factors include individual taxane dose and cumulative dose (3, 12), with the incidence of TIPN increasing with dose. Additionally, diabetes mellitus and older age are independent predictive factors (14). Notably, a history of autoimmune disease has been associated with a lower incidence of neuropathy (15).

Significant interindividual variability is observed in the incidence of peripheral neuropathy among patients receiving taxane treatment, even with uniform regimens and identical dosages (13). Precise predictive biomarkers for an increased risk of peripheral neuropathy remain unclear.

Genetic determinants of taxane-induced peripheral neuropathy

Single nucleotide polymorphisms (SNPs) identified through genome-wide association studies (GWAS) have been correlated with an elevated risk of taxane-induced peripheral neuropathy. These SNPs are associated with proteins related to the Schwann cell function, cell surface collagen receptors, receptors involved in neuronal apoptosis, neuronal crest cell development, and even to an enzyme participating in voltage-gated sodium channels (5).

Ephrin receptor gene polymorphisms

Several studies have also shown that the presence of polymorphisms in DNA repair genes are associated with taxane toxicity (16).

Ephrin receptor A (EPHA) genes belong to the family of membrane-bound receptor tyrosine kinases. Under physiological conditions, ephrin receptors and ephrins are involved in cell-cell contact-dependent intercellular interactions, in controlling cell morphology, adhesion, mobility, proliferation and differentiation, and have a key role in neuronal development (17). Experimental evidence has shown that mutations in these genes contribute to tumor progression, cell proliferation and metastatic growth (18). Exceeding the threshold plasma concentration of taxanes is a proven trigger of peripheral neuropathy in breast cancer patients. Ephrin receptor polymorphisms are an important predictor for personalized dosing of taxanes (19). Individual adjustment of the dose of the active substance significantly reduces the risk of peripheral neuropathy. A proportion of patients can develop symptomatic neuropathy despite the dose reduction. It could be explained by an inherent predisposition and other clinical factors (20). Genome-wide association studies have also detected candidate polymorphisms in EPHA genes (EPHA4 rs17348202, EPHA5 rs7349683, EPHA6 rs301927), in which a significantly increased risk of paclitaxel-induced PN was observed. Recently, in their study, Marcath et al. demonstrated a significant association of a specific EPHA5 polymorphism (rs7349683) with a direct effect on increasing the susceptibility in the development of PN (21). Replication of the published results remains a challenge, as multiple confounding factors must be considered when predicting toxicity (22).

Polymorphisms of cytochrome P450 genes

Cytochrome P450 2C8 (CYP2C8) belongs to the family of cytochrome P450 epoxygenases, which are the main metabolisers of more than 60 molecules of various drugs (23). Single nucleotide polymorphisms in CYP genes are important markers of interindividual differences in drug metabolism and potetial predictors of taxane-induced neuropathy (24). CYP2C8 is the primary enzyme that mediates the metabolism of paclitaxel, which is the most commonly used taxane in breast cancer. Its function lies in interference with microtubules (25). Alteration of the rate of elimination of taxane drugs has been investigated in the two most common polymorphisms CYP2C8*2 and CYP2C8*3 compared with the wild-type variant CYP2C8*1 (26). The results from *in vitro* studies focused on taxane metabolism depending on the presence of polymorphisms vary slightly, but most confirm their association with changes in metabolism and the subsequent development of neuropathy. In their 2015 study, Frederiks et al. describe significantly reduced CYP2C8 gene activity with the presence of a polymorphic variant compared to its wild-type form (27). In the case of both the polymorphic variants CYP2C8*2 and CYP2C8*3, the amino acid residues are not located at the active site of the gene, but on the surface of the protein. This suggests that the SNPs in question affect those mechanisms of metabolism that are not related to direct substrate binding. The CYP2C8*3 haplotype typically carries two variants, p.R139K (c.416G>A) and p.K399R (c.1196A>G), located in exons 3 and 8. The allele itself is mainly typical of the Caucasian population (up to 14%), and is rare in the Asian and African American populations (28). A significant pharmacogenomic study supporting the association of the candidate CYP3C8*3 allele and the development of neuropathy by Hertz et al. from 2013, focuses on the direct genotype-phenotype correlation. This study tested the specific hypothesis that the CYP2C8*3 variant increases the risk of paclitaxel-induced neuropathy. The established hypothesis was confirmed in two patient cohorts, providing significant evidence of this association (29).

Polymorphisms of genes involved in reorganization of the actin cytoskeleton

Knowing of dysfunctional genes or proteins associated with inherited forms of peripheral neuropathies provides an explanation for understanding the importance of nerve demyelination (30). An important gene that has been studied in preclinical models of neuropathy and clinical case reports of demyelinating neuropathies FGD4 gene (frabin). FGD4 gene encodes a protein involved in

the regulation of the actin cytoskeleton and cell shape. In animal models, frabin deficiency induces demyelination during early nerve development. Several studies demonstrate the key role of FGD4 gene for nerve myelination (31). Pathogenic variants of this gene are linked to Charcot-Marie-Tooth disease type 4H of peripheral neuropathy (32).

Through mutations of frabin in Schwann cells of fully myelinated nerve fibers, it has been shown that this protein is essential for proper nerve development and myelin maintenance. Also, the activation of Cdc42 molecules per se is highly dependent on the function of frabin in healthy peripheral nerves (Murakai et al, 2019). Mutations in the genes for Cdc42 lead to myelin changes that are similar to the deficits caused by changes in the FGD4 gene. This fact points to a critical role of FGD4-Cdc42 for the maintenance of myelin homeostasis. The regulation in question involves the influence of Schwann cell endocytosis which is a fundamental mechanism of pathophysiological responses in peripheral nerves (33). The recent findings that polymorphisms of the FGD4 gene have a significant association with the development of taxane-induced sensory neuropathy are consistent with its physiological functions being essential for proper functioning of the nervous system. Just as Charcot-Marie-Tooth disease is characterized by slow progressive demyelination of sensory and motor neurons, weakness, muscle atrophy or loss of sensory function, the paclitaxel-induced polyneuropathy shares selected features of this disease, including the development of secondary demyelination (34). FGD4 gene polymorphisms associated with higher risk of paclitaxel-induced neuropathy are a common potential predictive marker of this adverse effect (35).

Polymorphisms in genes encoding pseudolipid phosphatases

Myotubularin (MTM1) is a lipid phosphatase that is involved in excitation–contraction coupling, endosomal trafficking, cytoskeletal organization, and apoptosis. Mutation of the gene encoding MTM1 is an essential part in myotubular myopathy. Myotubularin itself is primarily a lipid phosphatase acting on phosphatidyl inositol 3-phosphate (PI3P). PI3Ps act as mediator molecules to mediate temporally and spatially controlled signals. The information about the timing and location of their production is received by phosphoinositide-binding proteins and mediates signals for rearrangement of the cytoskeleton and cell membranes (36). Its homolog, myotubularin-related 2 (*MTMR2)* gene, is associated with the development of Charcot-Marie-Tooth disease (37). Charcot-Marie-Tooth type 4 (CMT4) is an autosomal recessive severe form of neuropathy with genetic heterogenity. CMT4B1 is caused by mutations in the MTMR2 and as a member of the myotubularin family, the MTMR2 protein is crucial for the modulation of membrane trafficking. Some members of the myotubularins lack phosphatase activity due to an inherited active site mutation. In this case, these are the so-called pseudophosphatases including genes encoding SET-binding factor (SBF), which are able to inhibit the cell growth signal depending on its subcellular localization (38). Significant differences in the prevalence of SBF2 polymorphisms within European and African American populations were found. It has been shown that patients of the African American population have a significantly increased risk of moderate-to-severe neuropathy induced by taxane treatment (39). SBF2 gene mutations are associated with the development of the Charcot-Marie-Tooth subtype of disease that manifests as an inherited form of polyneuropathy. The almost exclusive involvement of the peripheral nervous system observed in the Charcot-Marie-Tooth 4B subtype, in which the MTMR13/SBF2 genes are essential, suggests that the Schwann cells are sensitive to the disruption of endolysosomal trafficking, which may be affected specifically by SBF2 polymorphisms (40).

Conclusion

Taxane-induced peripheral neuropathy is a serious problem in cancer patients, potentially resulting in diminished quality of life associated with the risk of injuries and falls. In recent years, a significant progress has been achieved in the knowledge of the pathogenetic mechanisms of neurotoxicity of taxanes. Genetic polymorphisms, which may contribute to the development of peripheral neuropathy following taxane treatment, are studied in greater detail.

However, it is important to note that the application of this knowledge in routine clinical practice remains currently still limited.

In cases where patients have a predisposition to taxane-induced peripheral neuropathy, it becomes imperative to carefully reconsider the necessity for prescribing potentially neurotoxic chemotherapy. Furthermore, as the number of patients achieving long-term complete remission continues to rise, the question of how to optimally manage persistent polyneuropathy has come to the forefront. We believe that this minireview provides valuable insights into the complexity of pathophysiology and promising genetic predictors of taxane-induced peripheral neuropathy in cancer patients.

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