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Taxane induced neuropathy in patients affected by breast cancer: Literature review

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Summary

Taxane induced neuropathy (TIN) is the most limiting side effect of taxane based chemotherapy, relative to the majority of breast cancer patients undergoing therapy with both docetaxel and paclitaxel. The symptoms begin symmetrically from the toes, because the tips of the longest nerves are affected for first. The patients report sensory symptoms such as paresthesia, dysesthesia, numbness, electric shock-like sensation, motor impairment and neuropathic pain. There is a great inter-individual variability among breast cancer women treated with taxanes, in fact 20–30% of them don't develop neurotoxicity. Actually, there is no standard therapy for TIN, although many medications, antioxidants and natural substances have been tested in vitro and in vivo. We will summarize all most recent literature data on TIN prevention and treatment, in order to reach an improvement in TIN management. Further studies are needed to evaluate new therapies that restore neuronal function and improve life quality of patients.

Keywords: Neurotoxicity; Taxane; Breast cancer; Pharmacogenomics; Antioxidants; Antidepressants; Anticonvulsants; Vitamins

1. Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a disabling side effect of many chemotherapeutic agents, especially of those that target microtubules. It has been mainly described in patients treated with platinum salts, vinca alkaloids (vinorelbine and vincristine) and taxanes (paclitaxel and docetaxel). Taxanes are some of the most important drugs in the treatment of breast cancer, for the great benefit in disease free survival and overall survival in adjuvant setting [1]; therefore, women undergoing this treatment frequently suffer for taxane-induced neuropathy (TIN). Taxanes can cause neuronal damage on axons, myelin and dorsal root ganglion, stabilizing microtubules and consequently interfering with mitosis and with intracellular transport of protein and substances between axons and cells [2]; once microtubule transport is damaged, the neuronal cell can't survive and undergoes apoptosis [3]. Unfortunately, TIN is very common: more than 80% of breast cancer patients treated with taxanes develop neuropathy, sometimes leading to early discontinuation of treatment [4,5]. Actually, there are no guidelines to characterize TIN and its diagnostic system is still suboptimal (neurological assessment with evaluation of signs and symptoms and physical examination); consequently, this problem is often underestimated.

2. Clinical features

TIN is a therapy dose limiting, distal sensory neuropathy that involves hands and feet (glove and stock distribution). The symptoms begin symmetrically from the toes, as a "dying back", because the tips of the longest nerves are affected for first. After more doses, the disease extends up from the feet to the ankle and lower legs, and then also to hands, wrist and arms [6]. The patients report sensory symptoms such as paresthesia, dysesthesia, numbness, electric shock-like sensation, motor impairment, impaired balance for the diminished plantar sensation and resultant altered proprioception, sensation of pinprick, altered vibration and temperature perceptions, reduced functional capacity and, in 25–30% of the cases, a real neuropathic pain [4–7]. The pain can be described as severe in 25% of the patients, many trials report a score of 7/10 in visual analog scale [5,8]. The ability to manipulate objects can be compromised, and patients can cause by themselves mechanical or temperature-induced injuries. All the peripheral nerves (sensory, motor and autonomic) can be damaged by taxanes, but large myelinated sensory nerve fibers are the most susceptible [2,3].

The symptoms can appear during chemotherapy, increasing after the end of the courses, lasting up to 48 months after the first infusion of taxane, or they can never improve in some cases [9]. Upper and lower extremity motor weakness can less frequently occur, such as autonomic neuropathy symptoms (constipation, hypotension, urinary retention). The patients can experience allodynia (pain caused by non painful stimuli) and decreased or disappeared reflexes. The clinical examination is very important, because the patient usually can't recognize that the problem exists, till the symptoms become severe. Also an acute pain syndrome linked to paclitaxel therapy has been described, characterized by severe pain in the back, hips, shoulders, thighs and legs, occurring during the first week following paclitaxel administration [10]. There is no difference in the incidence of TIN between the two taxanes, paclitaxel and docetaxel.

TIN significantly compromise the quality of life of the patients, and this becomes a serious problem for long-term breast cancer survivors. In case of TIN, the oncologists usually decrease the dose of taxane or discontinue the therapy; but, when a patient describes a severe TIN, these measures appear ineffective. Furthermore, TIN is usually not responsive to pharmacological approach: antidepressants, anticonvulsants, and analgesics are only symptomatic treatments, sometimes ineffective [11].

3. Pathophysiological mechanisms

Actually, there are no specific trials focused on the study of TIN, and literature data regarding its pathogenesis, therapy and management are inconclusive. The pathophysiological mechanism of TIN is complex and remains still unknown,