Taxane-Induced Neuropathic Pain: Current Evidence and Treating Strategies

Vincenzo Pota[1], Maria Beatrice Passavanti[1], Pasquale Sansone[1], Manlio Barbarisi[2], Maria Caterina Pace[1] and Caterina Aurilio[1*]

[1]Department of Women, Child, General and Specialistic Surgery, University of Campania "L. Vanvitelli", Napoli, Italy

[2]Institute of Neurosurgery, University of Cattolica, Rome, Italy

[*]**Corresponding author:** Caterina Aurilio, Department of Women, Child, General and Specialistic Surgery, University of Campania "L. Vanvitelli", Napoli, Italy, Tel: 00393664485084; E-mail: caterina.pace@libero.it

Received date: February 26, 2018; **Accepted date:** March 6, 2018; **Published date:** March 22, 2018

Abstract

Chemotherapy-induced peripheral neuropathy (CIPN) is a disabling adverse event of most of commonly used antineoplastic agents. Previous studies have focused on several chemotherapeutic agents and reported that CIPN incidence varies from 19% to >85%. The mechanisms underlying CIPN are currently unknown. However, different theories have been proposed including microtubules dysfunction, mitochondrial dysfunction and mitochondrial toxicity, Glial pathway, substance P pathway, adenosine receptor pathway. CIPN is not simply to treat, and most randomized controlled trials failed to identify an effective therapy. Recent evidence supports the efficacy of serotonin (5-HT) and norepinephrine (NE) dual reuptake inhibitors (SNRI) in the treatment of neuropathy-related pain. Based on current evidence, we can speculate that duloxetine and topical menthol would improve CIPN pain as symptomatic treatment while, based on preclinical data, pifithrin-μ could be considered in future for the prevention of CIPN.

Keywords: Neuropathic cancer pain; Chemotherapy induced peripheral neuropathy; Microtubules

Background

Chemotherapy-induced peripheral neuropathy (CIPN) is a disabling adverse event of most of commonly used antineoplastic agents. T e development of CIPN could lead to dose reduction or chemotherapy withdrawn, increasing cancer-related morbidity and mortality [1,2]. CIPN is a predominantly sensory neuropathy that sometimes can be characterized also by motor and autonomic changes. Taxanes include paclitaxel (Taxol) and docetaxel (Taxotere) that act by inhibiting the disassembly of microtubules by way of binding to the beta-tubulin subunit. As a consequence of taxane inhibition, microtubules become more stable and so dysfunctional, leading to cell death by way of altering the physiological tubule dynamics required for cell division and vital interphase processes. Paclitaxel is used mainly as chemotherapeutic agents for ovarian, breast and non-small cell lung cancer, while docletaxel for breast, non-small cell lung, prostate, gastric, head and neck cancer. Paclitaxel induces a bilateral, distal, symmetrical axonal neuropathy with sensory symptoms (numbness, tingling and burning pain) with in a stocking-and-glove distribution. Moreover a symmetrical loss of sensation carried by both large fbers (proprioception, vibration) and small ones (temperature, pinprick)

Pathogenesis

Microtubules

Early morphological studies reported neural degeneration when paclitaxel was injected into the sciatic nerve [4-6]. The clinical relevance of these studies is controversial because of the excessive endoneural concentrations of paclitaxel. Recently Flatters et al. have

level of SO/PN in mitochondria with alteration of bioenergetics [21]. Kali Janes in a study published on PAIN in 2013 examined if PN was a mediator of bioenergetic defcits and mitochondrial dysfunction in PNSAs during CIPN [22] and, if a PN scavenger, like MnTE-2-PyP (Mn(III) 5,10,15,20-tetrakis(N-n-hexylpyridinium-2-yl)porphyrin, could be mitoprotective and could prevent CIPN. Tey conducted

4.45) for duloxetine-treated patients compared to 0.87 (95% CI: 1.09, 2.82) in the placebo group (p=0.03). Antidepressants are among the oldest drugs used for the treatment of neuropathic pain. They originally came to be used in the treatment of chronic pain, and in particular neuropathic pain, because some of the patients suffering from chronic pain are also depressed, and these drugs relieve pain as well as depression. However, an independent analgesic action has been reported for TCAs since the 1960s. The relief can be more rapid in some patients and appears to occur at a lower dose than the antidepressant effect. An early concept of the mechanism of antidepressant analgesia was that these drugs are capable of potentiating the activity of the descending inhibitory pathways extending from the brain stem to the dorsal horn of the spinal cord, mainly by inhibiting the reuptake of serotonin and noradrenaline that descending fibers release into the spinal synapses between nociceptors (or first-order neurons) and the spinothalamic neurons (or second-order neurons) [34].

Another sintomapthic therapy could be the menthol. There is mounting evidence that that endogenous neural circuitry underlying cooling-induced analgesia may represent a novel therapeutic target [35,36]. Fallon et al. have demonstrated that a topical agent, by the activation of the transient receptor potential melastatin (TRPM) ion channel, have produced significant analgesia [37]. Subsequently he conducted a proof-of-concept study with the objective to demonstrate if 4-6 weeks of treatment with topical 1% menthol in aqueous cream alleviate neuropathic pain. He enrolled Fifty-one patients and used the short-form BPI to assess pain and the Hospital Anxiety and Depression scale (HADS). He also examined functional performance like walking ability (using a GAITRite®), hand dexterity and Quantitative Sensory Testing (QST). 40 of 51 patients completed the treatment. 10 patients dropped out for different reasons. 82% of patients improved in their pain scores. HADS improved too as well as HADS anxiety score and catastrophising. Finally the authors observed an improvement in walking velocity and cadence, while there was no significant improvement in hand dexterity. The authors noted also that the percentage of distal limb skin with abnormal sensation in response to brush, cool and warm stimuli became more distal [38].

Very interesting are the literature data about the prevention of CIPN. Krukowski et al. proposed that prevention of chemotherapy-induced mitochondrial dysfunction may be a promising avenue for inhibition of CIPN [39]. The small-molecule inhibitor pifthrin-μ (PFT-μ), 2-phenyl-ethynesulfonamide, is a specific inhibitor of stress-inducible Hsp70, which induced tumor cell death but markedly showed less toxic to non- transformed cells.41 Heat shock protein (Hsp) family is a group of conserved molecular chaperons that facilitate proper protein folding, modification, and transportation, and are known as inhibitors of apoptosis [40]. Hsp70 is a member of Hsps, and Hsp70 over- expression has been reported to be associated with a wide range of malignances [40]. The small-molecule inhibitor pifthrin-μ (PFT-μ) has been identified for its capacity to inhibit mitochondrial p53 accumulation without impacting p53 transcriptional activity. His group have previously demonstrated that the disruption of the p53 mitochondrial pathway and the intraperitoneally administration of PFT-μ protects against cerebral neuronal loss in a rodent model of neonatal ischemic brain damage. In this model, PFT-μ prevented mitochondrial accumulation of p53 in the brain, thereby reducing oxidative stress and maintaining ATP production [41].

They hypothesized that the protection of neuronal mitochondria by PFT-μ might also be a mean to prevent CIPN. Therefore, they also

reduction in tumor cell survival of more than 50%. Addition of PFT-μ to the cultures of tumor cells and paclitaxel further reduced ovarian tumor cell survival in comparison with paclitaxel alone (striped bars).

Additionally, PFT-μ (20 mM) alone also decreased tumor cell survival (solid bars). These data provide evidence that PFT-μ does not inhibit but conversely enhances the antitumor effect of paclitaxel. Next, they investigated if PFT-μ also prevented cisplatin-induced neuropathy. Mice were treated with cisplatin (2.3 mg/kg) alone or in combination with PFT-μ, and mechanical allodynia was measured. In mice treated with cisplatin alone, decreased paw withdrawal thresholds were measured after cisplatin administration at weeks 3, 5, and 7. Systemic PFT-μ administration completely prevented cisplatin-induced changes in paw withdrawal threshold and thereby cisplatin-induced mechanical allodynia.

After examination of literature on gabapentin and CIPN prevention we found only anecdotal reports [42]. A pilot study was conducted to obtain data to support or refute the utility of pregabalin for the prevention of P-APS (acute pain syndrome) and CIPN [42,43]. Shinde et al. published a multicentric, randomized, double-blinded, pilot trial. They recruited 46 patients with 1:1 randomization in order to be treated or with Pregabalin 75 mg or placebo twice daily, starting from the first dose to chemotherapy till to the last one. CIPN was measured using the European Organization for Research and Treatment of Cancer Quality of Life (EORTC-QLQ) CIPN20 questionnaire. Growth curve models and AUC analysis, showed no significant differences in the EORTC CIPN20 sensory sub-scale (p=0.88 and p=0.46, respectively) between arms as well as there were no differences in the motor neuropathy or autonomic neuropathy subscales. They found only a small difference in numbness symptom. So these data are unable to determine if gabapentinoids was effective in established CIPN and to provide support in order to conduct a formal phase III clinical trial.

Conclusions

All mechanisms exposed have a crucial role in the development of CIPN: Microtubules dysfunction; Mitochondrial dysfunction and

induced neuropathic pain by modulating spinal glial-restricted redox-dependent signaling pathways. Pain 155: 2560-2567.

28. Chiba T, Oka Y, Kambe T, Koizumi N, Abe K, et al. (2016) Paclitaxel-induced peripheral neuropathy increases substance P release in rat spinal cord. Eur J Pharmacol 770: 46-51.
29. Saarto T, Wiffen PJ (2007) Antidepressants for neuropathic pain. Cochrane Database Syst Rev 17: CD005454.
30. Attal N, Bouhassira D, Baron R, Dostrovsky J, Dworkin RH, et al. (2011) Assessing symptom profles in neuropathic pain clinical trials: Can it improve outcome? Eur J Pain 15:441-443.
31. Dworkin RH, Turk DC, Katz NP, Rowbotham MC, Peirce-Sandner S, et al. (2011) Evidence-based clinical trial design for chronic pain pharmacotherapy: A blueprint for Action. Pain 152: S107-S115.
32. Aurilio C, Pace MC, Pota V, Sansone P, Barbarisi M, et al. (2009) Opioids switching with transdermal systems in chronic cancer pain. J Exp Clin Cancer Res 7: 28-61.
33. Smith EM, Pang H, Cirrincione C, Fleishman S, Paskett ED, et al. (2013) Efect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: A randomized clinical trial. JAMA 309: 1359-1367.
34. Fornasari D (2017) Pharmactherapy for neuropathic pain: A review. Pain Ther 6: S25-S33.
35. Liu Y, Qin N (2011) TRPM8 in health and disease: Cold sensing and