Proposed medications for taxane-induced myalgia and arthralgia (Review)

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Abstract. Taxanes inhibit the disassembly of microtubules, which are involved in mitosis and axoplasmatic transport, and may cause the degeneration of peripheral, mainly small, sensory nerves. Peripheral neurotoxicity is a dose-limiting side-effect of taxanes. Neuroprotective agents may aid in the reduction of neurotoxicity, thus allowing the intensification of cytostatic therapy in patients. An increasing number of medications for the prevention of taxane-induced arthralgia and myalgia are becoming available to oncology teams. The most widely studied medications include so-called analgesics such as *Shakuyaku-kanzo-to* (a herbal medicine), corticosteroids and antihistamines. Arthralgias and myalgias (muscle spasms, fasciculations and prolonged contractions) may be extremely distressing for patients. New anti-epileptic drugs, particularly gabapentin and pregabalin, have proven to be safe and effective in the treatment of taxane-induced neurotoxicity. The aim of this review was to examine the topical choices available for the protective management of taxane-induced neurotoxicity monitored in preliminary case studies and clinical trials. At present, there is no standard of care for the prevention of taxane-induced arthralgia and myalgia. In combination with taxane-based chemotherapeutic regimens, these medical agents may be crucial in the treatment of a variety of types of cancer.

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1. Introduction

Taxane-related neuropathy remains a challenging clinical problem causing delays in treatment and worsening the quality of life for patients. Taxane-based cytotoxic chemotherapeutic agents are among the most potent agents for the treatment of a variety of types of cancers including breast, lung, and ovarian cancers (1,2). By inhibiting microtubules, taxanes cause neurotoxicity that may decrease the quality of life for patients and necessitate discontinuation of chemotherapy.

These events typically occur one to three days following taxane therapy and may significantly affect the quality of life of patients for several days. Patients are at increased risk if they have previously received neurotoxic drugs. The mechanism of taxane-induced neuropathy is thought to be due to aggregation of intracellular microtubules in neuronal cells (1-3). Taxanes also cause intrinsic toxicity and injury to cells. However, the exact mechanism of neurotoxicity is not known at this time. Types of neuropathy caused by taxanes include peripheral neuropathy, motor weakness, myalgia, and arthralgia (3-6). Between 60 and 90% of patients receiving taxanes develop mild to moderate neuropathy and as many as 30% of treated patients are likely to develop a disabling sensory neuropathy (3-6). The high incidence of toxic neuropathy is a significant limiting factor for patients receiving taxanes (2,5-7). Agents that potentially reduce the incidence or severity of taxane-related neurotoxicities are required. Multiple medications have been evaluated for that purpose (Table I) (3,6,8-12). However, none of these medications have been approved for taxane-induced neuropathy.

2. Melatonin

It has been suggested that melatonin, a pineal hormone, exerts a neuroprotective effect in preclinical and clinical studies (3,13-16). Melatonin decreases peripheral nerve injury and motoneurone loss in melatonin-treated axotomized rats (13,14). Melatonin is thought to exert a neuroprotective effect that would attenuate the neuropathological changes in

Table I. Possible medications for taxane-induced neuropathy.

Agent	Administration route and dose	Complications	Refs.
Melatonin	Oral, 21 mg/day, from day 1 to day 28 of taxane infusion	Nausea, vomiting, fatigue	(3,15)
Amifostine	IV, 175 mg/m^2, prior to chemotherapy	Sores on the lips, mouth, or tongue	(23)
Gabapentin	Oral, 900 mg/day 2 days before and for 5 days after taxane infusion	Mild dizziness	(25)
Pregabalin	Oral, 225-450 mg/day, at the time	Very few; somnolence, dizziness, peripheral edema	(31,32)
Glutathione	Div, 1500 mg/m^2, prior to chemotherapy	No significant complications	(34)
Shakuyaku-kanzo-to	Oral, 75 g/day, from day 1 to day 8 of taxane infusion	Mild myopathy	(37,38)
Corticosteroid	Oral, 20 mg starting 24 h after the chemotherapy and continuing for a total of 5 days	No significant complications	(39)
Glutamine	Oral, 30 g/day throughout taxane chemotherapy	No significant complications	(42)

IV, intravenous; Div, intravenous injection by drop.

the vagal ganglia following a severe hypoxic insult (13,14). Clinical studies have evaluated the role of melatonin for counteracting chemotherapy-toxicity, particularly myelosuppression and immunosuppression (14-16). Melatonin has been found to inhibit the production of free radicals, which are involved in mediating the toxicity of chemotherapy (15,16). In a preliminary study by Lissoni *et al* (16), 80 patients with a variety of metastatic solid tumors received chemotherapy with or without melatonin. The tumors included 35 lung cancer, 31 breast cancer and 14 gastrointestinal tract tumors. Lung cancer patients were treated with cisplatin and etoposide, breast cancer patients with mitoxantrone, and gastrointestinal tract tumor patients with 5-fluorouracil plus folates. Patients were randomised to receive chemotherapy alone or chemotherapy plus melatonin (20 mg/day, orally, in the evening). Thrombocytopenia was significantly less frequent in patients concomitantly treated with melatonin. Malaise and asthenia were also significantly less frequent in patients receiving melatonin. Additionally, stomatitis and neuropathy were less frequent in the melatonin group, albeit without statistically significant differences. This pilot study suggests that the concomitant administration of the pineal hormone melatonin during chemotherapy may prevent certain chemotherapy-induced side-effects, particularly myelosuppression and neuropathy. The effectiveness of chemotherapy was not altered by the addition of melatonin.

A randomized clinical trial by Nahleh *et al* (3), examined 22 consecutive patients beginning chemotherapy for breast cancer with paclitaxel or docetaxel. Patients received 21 mg of melatonin daily. Mild neuralgia was reported in 45% (n=10) of patients, while the majority (55%) of the patients reported no neuropathy. Compliance with melatonin (>60% of dose) was observed in most patients (86%). No patient reported daytime sedation. Patients receiving melatonin during taxane chemotherapy had a reduced incidence of neuropathy. Melatonin may therefore be useful in the prevention or reduction of taxane-induced neuropathy and in maintaining quality of life. Larger trials are necessary to explore the role of melatonin in neuropathy treatment and prevention.

3. Amifostine

Amifostine, a phosphorylated amino-thiol prodrug and analogue of cysteamine, was originally developed by the Walter-Reed Army Institute of Research to protect individuals from the effects of radiation in the event of nuclear warfare (8). Currently, amifostine is being used as a chemo- and radioprotective agent to minimize anti-tumor therapy-induced toxicities (17). Furthermore, amifostine is described as an agent that selectively protects normal tissues without reducing anti-tumor activity (17,18). A number of clinical studies have demonstrated that amifostine protects against cisplatin-induced neuropathy, cisplatin and cyclophosphamide-induced neurotoxicity and paclitaxel-induced neurotoxicity (19). However, randomized clinical studies were unable to confirm these results in paclitaxel-treated patients (20,21).

In another multicenter randomized trial (22), patients were randomly assigned to receive carboplatin and paclitaxel with or without amifostine (910 mg/m^2) every 21 days for six cycles. In total, 187 patients were accrued: 93 patients with amifostine and 94 patients without amifostine. Amifostine

showed no significant effects on the incidence of leucopenia or mucositis. However, amifostine was protective against neurotoxicity (grade 3-4 neurotoxicity). Amifostine is therefore capable of exerting a degree of protection from the cumulative toxicity associated with this regimen. Findings of a placebo-controlled trial (23) showed that amifostine improved sensory neuropathy with regards to objective neurological assessment, but there were almost no differences in self-estimated specific sensory or motor symptoms. Furthermore, amifostine was able to ameliorate pre-existing neurotoxicity induced by cisplatin.

Results of an *in vitro* study using the rat pheochromocytoma cell line showed that amifostine was capable of protecting NGF-differentiated PC-12 cells from paclitaxel-induced neurotoxicity, but not from vincristine-induced neurotoxicity (8). These results need to be confirmed in other randomized trials with this combination. Disadvantages with regards to non-neurological toxicities and inconsistent results for quality of life necessitate further evaluation of neuroprotection with amifostine as well as alternative approaches to prevent platinum-taxane-induced neurotoxicity.

4. Gabapentin

Gabapentin is a second-line antiepileptic that has been widely used in the treatment of neuropathic and myofascial pain syndromes. A single case report (24) and a preliminary retrospective study (25) described their findings of using gabapentin in the prevention of taxane-induced arthralgias and myalgias. In a study by Nguyen and Lawrence (25), gabapentin (300 mg three times daily) was taken 2 days prior to and for 5 days following taxane infusion. In 9 of 10 patients, gabapentin reduced or prevented myalgias and arthralgias with subsequent exposure to paclitaxel or docetaxel. Of these responders, 3 patietns were asymptomatic, and 6 patients had only mild myalgias that did not interfere with daily activities. According to the National Cancer Institute toxicity scale, 6 patients had at least two grade reductions in symptoms. The remaining 3 responders had one grade reduction. A single patient developed severe myalgia and arthralgia despite prophylactic gabapentin; this patient had concurrent human immunodeficiency virus (HIV) infection, severe psychiatric disease and neuropathy.

5. Pregabalin

Pregabalin is a new antiepileptic drug approved in the USA and Europe as adjunctive therapy for partial seizures in adults. It has also been approved for treatment of pain from diabetic neuropathy and post-herpetic neuralgia, and is being considered for approval for treatment of anxiety disorders due to its anxiolytic effects (26-29). Pregabalin is similar to gabapentin regarding structure and mechanism of action. Compared to gabapentin, pregabalin is characterized by a more rapid response time. Consequently, pregabalin has been preferred to gabapentin to obtain the most rapid response possible for a extremely distressing symptoms. Pregabalin does not bind to plasma proteins and it is not subject to the hepatic metabolism; these characteristics make it particularly attractive for patients with advanced cancer, who often present with low levels of plasma proteins and/or hepatic failure (26,30). A case report of a patient undergoing chemotherapy with gemcitabine and oxaliplatin for pancreatic adenocarcinoma is available (26-29). The patient in this case report was treated with pregabalin for oxaliplatin-induced hyperexcitability syndrome. Pregabalin was prescribed at a dose of 50 mg three times daily and the patient exhibited marked improvement in her symptoms within 12 h, becoming almost asymptomatic within 72 h (31). This patient did not exhibit any known adverse effects secondary to pregabalin. In a case report by Porzio *et al* (32) pregabalin was effective in the treatment of cetuximab-related severe itch. A 62-year-old man, affected by a primary intestinal-type adenocarcinoma of the nasal cavity, locally advanced, was treated by cetuxinab-based chemotherapy. Due to a sever itch, pregabalin was started at 75-100 mg twice daily. The itch was ameliorated significantly, as were other symptoms such as depression, anxiety and asthenia.

These results led us to assess the efficacy of pregabalin for treatment of neuropathic pain associated with taxane in a group of patients with ovarian malignancies (32). However, studies should be conducted to confirm this effect of pregabalin on taxane-induced neuropathy, as well as to study long-term adverse reactions of this drug.

6. Glutathione

Glutathione-S-transferases regulate the cell response to oxidative stress. Mir *et al* (33) previously emphasized the importance of oxidative stress in taxane toxicity and observed the relationship between the glutathione-S-transferase isoforms and docetaxel-induced peripheral neuropathy. A single randomized, double-blind, placebo-controlled trial was performed to assess the efficacy of glutathione prevention of oxaliplatin-induced neurotoxicity. Patients (n=52) were randomized to receive a 1500 mg/m^2 glutathione infusion over 15 min or normal saline prior to oxaliplatin infusion. The glutathione group showed significantly less grade 2 or higher neurotoxicity (34).

7. *Shakuyaku-kanzo-to*

Shakuyaku-kanzo-to, a herbal medicine, is known to relieve menstrual pain, muscle spasm and muscle pain, and it is anticipated to be effective against neuropathy (35). Non-steroidal-anti-inflammatory drugs, vitamin B12 and *Shakuyaku-kanzo-to* are the major medications used in Japan for arthralgia and muscular pain occurring as a consequence of taxane-based chemotherapy (36,37). Fujii *et al* (38) examined 21 cases in which arthralgia and muscular pain occurred in chemotherapy with carboplatin and paclitaxel (including 16 cases as first-line chemotherapy). In all 21 cases, patients ingested 7.5 g of *Shakuyaku-kanzo-to* orally per day for eight days. In 9 cases (43%), *Shakuyaku-kanzo-to* was effective in reducing pain. *Shakuyaku-kanzo-to* was even more effective in reducing pain when combined with carboplatin and paclitaxel as first-line chemotherapy. Paclitaxel combination chemotherapy with *Shakuyaku-kanzo-to* ingested orally may be a safer and more tolerable approach to reducing pain in epithelial ovarian carcinoma.

8. Corticosteroids

Markman and colleagues (12,39) attempted to manage patients treated with paclitaxel in a gynecological oncology program. These patients developed arthralgia/myalgia which was uncontrolled through the use of non-steroidal anti-inflammatory medications. The patients received low-dose oral prednisone (10 mg twice a day starting 24 h following the completion of chemotherapy and continuing for a total of 5 days) with their following paclitaxel course. Of 46 patients treated with the oral prednisone regimen (i.e., those experiencing a subjective feeling of unacceptable discomfort despite the use of non-steroidal anti-inflammatory agents), 39 patients (85%) experienced substantial relief of symptoms. All but one of the responding patients requested continuation of the oral prednisone regimen with subsequent paclitaxel treatment cycles. No significant toxicities were noted in any patient receiving prednisone. This low-dose oral prednisone regimen may result in a substantial improvement in the majority of patients experiencing significant paclitaxel-associated arthralgia/myalgia.

9. Glutamine

Glutamine is vital for several physiological functions, such as nitrogen transfer between tissues and synthesis of RNA, DNA, and certain neurotransmitters. Preclinical data show amelioration of vincristine, cisplatin, and paclitaxel-associated sensory and motor neuropathy by glutamine in rats. The available evidence on the protective action of glutamine on the adverse effects of chemotherapy suggests that glutamine supplementation may decrease the incidence and/or severity of chemotherapy-associated mucositis, irinotecan-associated diarrhea, paclitaxel-induced neuropathy, hepatic veno-occlusive disease in the setting of high-dose chemotherapy and stem cell transplantation and the cardiotoxicity that accompanies anthracycline use. Oral glutamine supplementation may enhance the therapeutic index by protecting normal tissues from, and sensitizing tumor cells to, chemotherapy and radiation-related injury (40,41). In a clinical study (42), when compared with placebo, oral glutamine did not prevent or decrease subjective taste disturbances or alter taste perception associated with taxane chemotherapy. The role of glutamine in supportive care of taxane-associated dysgeusia seems limited. However, the question remains whether taste alterations are a form of neuropathy leading to allodynia (43) or are caused partially by other mechanisms. Further studies are required to confirm or refute this negative observation.

10. Conclusion

Recent clinical trials have expanded the use of taxanes to numerous cancers. A larger number of patients are, therefore, at risk of taxane-induced neuropathy. Possible strategies to decrease the incidence of neuropathy include avoiding taxane use, avoiding cumulative doses, and administering taxanes as continuous infusions over 24 h (7,9). Addition of the medications described above (Table I) have been evaluated to reduce the incidence of neuropathy. However, no therapy has been consistently successful; conventional analgesics [e.g., opioid analgesics (44) and antihistamine (45)] are also inconclusive and/or conflicting. The small number of patients in these clinical trials do not permit definitive conclusions to be drawn regarding patient characteristics that may predict response to these drugs. More studies should be performed to identify these characteristics as well as patients at risk for the development of taxane-induced myalgia and arthralgia, thereby allowing a risk-adapted strategy of medical prevention. Given their comparable cost to most drugs used for taxane-induced neuropathy and encouraging findings reported by the literature, possible medications discussed in the present review are viable treatment options in the prevention of taxane-induced arthralgia and myalgia.

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