Reminder of important clinical lesson

Profound and persistent painful paclitaxel peripheral neuropathy in a premenopausal patient

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The authors herein report the case of a 35-year-old woman undergoing adjuvant therapy for node positive breast cancer, who presented with short and rapidly progressive history of bilateral lower limb symptoms of peripheral neuropathy following therapy with paclitaxel. MRI of her neural axis revealed no leptomeningeal enhancement or focal metastatic lesions. Neurophysiological tests favoured toxic sensory axonal polyneuropathy. She remains symptomatic following discontinuation of therapy 20 months ago, and is under review with pain management.

BACKGROUND

Paclitaxel (Taxol) is an antineoplastic agent that is derived from the bark of the Western Yew, *Taxus brevifolia*. Paclitaxel exerts anticancer activity by binding tubulin and by stabilisation of non-functional microtubule bundles, thereby blocking normal mitotic spindle development and subsequent cell division.¹ Because it promotes microtubule assembly, the development of a predominantly sensory neuropathy is one of its most common and toxic side-effects.²

We herein report the case of a Caucasian woman of Irish extraction who presented with clinical and neurophysiological evidence of paclitaxel-induced neurotoxicity.

CASE PRESENTATION

The Caucasian housewife and mother in her mid-30s presented with a short, history of profound bilateral lower limb sensory disturbance, weakness and marked painful burning sensation in her extremities that was limiting her mobility and compromised her quality of life significantly.

She denied any reports of physical trauma, any other significant neurological disturbances and no gastrointestinal or genitourinary disturbances. Within her medical history, she was not known to suffer with diabetes mellitus, but 5 years prior had suffered with herpetic neuralgia following an episode of herpes zoster, warranting review by the Acute Pain Team, but has been off prescribed medications for over 4½ years. Within her family history, there were no familial neurological conditions. She admitted to social alcohol usage which she ceased since embarking on her oncological treatment.

She had started her treatment 16 weeks prior for her right-sided breast cancer, T2 N1 M0 – grade III ductal carcinoma, oestrogen receptor positive (Er +ve), progesterone receptor positive (PgR +ve) and Her-2 neu receptor negative with 1 out of 24 positive lymph nodes, for which

she has undergone a right-sided mastectomy and axillary node clearance. She had started on adjuvant dose-dense chemotherapy of adriamycin and cyclophosphamide with pegylated granulocyte-colony stimulating factor (G-CSF) support. She tolerated this well in the outpatient setting without delay or need for blood product support. This was followed by the weekly administration of paclitaxel; her first cycle was given with minimal short-lived side-effects of joint discomfort and lower limb sensory disturbance which resolved before she received her second cycle.

On review of her third cycle, haematological indices revealed moderate neutropaenia 0.89. Her therapy was deferred, but she represented 2 days later with reports of low-grade pyrexia, feeling generally unwell and malaise which was associated with marked discomfort in both her legs which restricted her mobility. She was admitted to the hospital and treated according to the febrile neutropaenia protocol in Mid-Western Regional Hospital. She had an uncomplicated recovery following 5 days of broad-spectrum antibiotic therapy. However, her symptoms of bilateral lower limb burning pain returned and worsened significantly, with her not being able to get out of bed to weight bear, as this exacerbated her discomfort. The Palliative Medicine team was consulted regarding her pain management. This involved the introduction of multiple agents including oxycodone, haloperidol, pregabalin and amitriptyline.

The cause of these progressive symptoms was potentially attributed to the cytotoxic therapy, but however investigations were performed to rule out metastatic progression of her underlying malignant disease. MRI of the brain and whole spine revealed no leptomeningeal enhancement, no focal intracranial enhancing lesion was identified and no evidence of metastatic bony disease in the cervical, dorsal or lumbar vertebrae was noted (see preliminary MRI images in figures 1 and 2).

Figure 1 MRI brain – postgadolinium.

INVESTIGATIONS

Lumbar puncture was performed, with normal opening pressure. Cerebrospinal fluid (CSF) samples were taken, CSF white cell counts <5.0, glucose was 3.7 mmol/l, lactate dehydrogenase was 20 IU/l, protein 0.6 g/l, negative for oligoclonal bands, cytosin and cytology revealed no malignant cells.

These results made malignant infiltration less likely and favoured the initial possibility of neurotoxicity from the chemotherapy. She was referred for nerve conduction studies (NCSs) and needle electromyography (EMG), which revealed reduction in sensory amplitudes in the lower limbs and, normal amplitudes in the upper limbs. EMG in her lower limbs did not show any denervation and the findings were consistent with a toxic sensory axonal polyneuropathy.

TREATMENT

Taxane therapy was discontinued, as the neurological symptoms although controlled with medication and had allowed her limited mobility now, had not completely resolved 20 months later. She has tolerated her adjuvant radiotherapy without complication and was commenced on her hormonal therapy with tamoxifen. She remains under regular follow-up with Palliative Medicine team regarding her analgesia, which has been recently rotated to include methadone. MRI of her neural axis was repeated 6 months later, and remains unchanged. She also had her

NCSs and EMG repeated, and no significant improvement was demonstrated.

DISCUSSION

Paclitaxel was one of the first taxanes used in clinical trials, and exerts activity in several solid tumours types including breast, ovary, lung and head and neck malignancies.³ Paclitaxel when administered in sequence to an anthracycline-containing regimen has been shown to improve overall survival and disease-free survival in patients with lymph node positive breast cancer.^{4 5}

The use of paclitaxel can be associated with the development of a peripheral neuropathy (PN).⁴ PN occurs when there is an alteration in the integrity or function of peripheral motor, sensory or autonomic nerves⁶ and can be divided into axonopathy (axonal abnormality) or myelinopathy (myelin sheath abnormality).⁷ PN induced by paclitaxel may present with symptoms and signs of an axonopathy with or without myelinopathy. The mechanism for this is not fully understood, but the viability and proper function of peripheral nerves require proteins and other nutrients to be actively transported along long axons from a neuron's cell body to its distal synapses, and paclitaxel-based therapy potentially interrupts this active transport mechanism.^{7 8}

PN seen with paclitaxel infusions may have sensory features in patients with paraesthesia, numbness and pain;^{4 9} these normally start in the feet and then proceed to the

Figure 2 T2 MRI brain – postgadolinium.

hands.⁷ As in this case, her symptoms presented were restricted to her lower limbs. Paraesthesia occurs in distal lower extremities with ‘glove and stocking’ distribution, and is more severe on plantar surfaces.¹⁰ In most patients, the severity of symptoms seen is mild to moderate, and should potentially disappear with the discontinuation of the paclitaxel.⁶ Unfortunately, her symptoms have persisted and indeed worsened despite cessation of the taxane therapy, with her still requiring large dose of opioids and adjunct agents to allow her to maintain a reasonable quality of life, control her pain and reduce paraesthesiae. Paroxysmal pain experienced normally occurs 2–4 days following paclitaxel infusions, and usually involves the muscles and bones of the lower limbs.¹¹ Her painful symptoms developed more than 4 days following her last cycle of paclitaxel, and did not ameliorate with the discontinuation of her therapy, and have led to significant loss in her quality of life.

Identification of potential risk factors or ‘penny-dropping’ signs to help stratify patients in risk groupings and ultimately to limit potential toxicities from paclitaxel-induced PN, theoretically would seem a viable consideration, but there is conflicting data and overall in conclusion on this practise.^{8–9} However, possible predictors for the development of more severe PN include, age, male gender, medical comorbidities or pre-existing PN.^{9–12} In this case, the patient was young woman without significant comorbidities, but she had been treated for herpetic neuralgia

over 4 years previously, and had not been on any medication for the same in the intervening period. But the caveat in all is that these features cannot reliably predict final neurological outcome, and consequently, should only be used as a guide.¹³

Electrophysiological testing remains the sole objective means of evaluating PN induced by paclitaxel; NCSs and EMG can identify the axonal degeneration and demyelination patterns, whereby low compound muscle action potential and fibrillation and slow conduction velocity, prolonged distal latencies without fibrillation can be detected.^{7–14} In this case, these tests showed reduced sensory amplitudes consistent with axonal neuropathy. Histological sampling could confirm the neuronal damage from paclitaxel as results are unlikely to alter the clinical management of this condition, but the biopsy itself may cause further damage to the nerve.⁷

Neuroimaging has a limited role in the evaluation of paclitaxel-induced PN; MRI can be helpful in some cases to help delineate pathological changes in the dorsal column of the spinal cord and involvement of central pathways.^{2–9} For this case under review, we elected to proceed with an MRI to rule out leptomeningeal enhancement from her underlying malignancy, given her limited exposure to paclitaxel and marked symptomatology.

At present, there is no available antidote for paclitaxel-induced PN, either to help prevent the occurrence of chemotherapy-induced PN or reduce its long-term

effects.⁹ Reduction or removal of the offending agent from a therapeutic regimen serves as the most effective means of reduction of the PN.⁷ Issues with respect to potential compromise of chemotherapy regimes and delivery of the most effective anticancer treatment must be entertained, as balancing the reality of toxicity presents as a therapeutic dilemma.⁹ For a majority of patients with paclitaxel-induced PN, the PN improves gradually within 9 months of completion of therapy, but can persist for up to 2.5 years.²¹⁵ In this case, she has not noted any improvement since stopping her therapy almost 24 months ago. Paroxysmal pain experienced with use of paclitaxel has been reported to respond favourably to amitriptyline.¹⁶ Other side effects experienced as part of the paclitaxel-induced PN including myalgia and arthralgia might be dampened with use of gabapentin in most cases.⁷ As in the case, amitriptyline and pregabalin (a sister drug to gabapentin) are being used in the amelioration of her symptoms.

Learning points

- ▶ She had clinical and neurophysiological features of paclitaxel-induced PN.
- ▶ She still has ongoing symptoms of PN, but pharmacological management of these symptoms has allowed her to maintain her quality of life, and has allowed to continue with the remainder of the adjuvant therapies for her breast cancer.
- ▶ This case can serve as a means of reminding colleagues that early detection of paclitaxel-induced PN, especially in a patient with a background of previous neuropathic condition, may lead to prevention of impairment of quality of life, and as in this case, there has been limited resolution of PN in the expected time-frame despite early withdrawal of taxane therapy.
- ▶ Understanding paclitaxel-induced PN has high clinical and public health significance, especially with survival rates from breast cancer steadily improving.
- ▶ There is limited evidence to guide pharmacological management of taxane-induced PN, hence prevention of this condition or limiting its progression is essential.

Competing interests None.

Patient consent Not obtained.

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