



## PALLIATIVE CARE CASE OF THE MONTH

### “Paclitaxel- Associated Acute Pain Syndrome” A Novel Neuropathy?”

by

Ritu Soni, MD

&

Jennifer Pruskowski, PharmD

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**Case:** Mr. K is a 73-year-old Caucasian male who was diagnosed with transitional cell carcinoma of the bladder with metastases to the liver and intra-abdominal lymph nodes. He received neoadjuvant treatment with dose-dense methotrexate, vinblastine, doxorubicin and cisplatin (DD-MVAC). His treatment course was complicated by severe fatigue requiring frequent hospitalizations and cancer progression resulting in discontinuation of DD-MVAC and initiation of systemic chemotherapy with carboplatin and paclitaxel. His regimen consisted of carboplatin dosed to a target area under the curve of 5 mg/mL/min and paclitaxel 175 mg/m<sup>2</sup> every 21 days.

Since his cancer diagnosis, Mr. K had right upper quadrant pain related to hepatic metastases. His pain was well controlled, averaging at a level of 2-3/10, on a regimen of fentanyl 25 mcg/hr transdermal patch every 72 hours and oxycodone 5 mg every 4-6 hours as needed for breakthrough pain. He took about two oxycodone tablets a day. Additionally, he developed bilateral lower-extremity pain that he initially noticed after his first cycle of carboplatin-paclitaxel. The pain felt like a constant dull ache in his calves and thighs, 8-10 in intensity, with occasional sharp pain in his knees and hips. It limited his activity level and ability to sleep. He couldn't identify any clear precipitating factors and did not report any associated weakness or incontinence of stool or urine. The pain was worse 3-4 days after chemotherapy, requiring him to take six to seven tablets of oxycodone over 24 hours for breakthrough pain. Subsequently during the week after chemotherapy, his breakthrough analgesic requirement decreased to about two to three tablets of oxycodone a day. His examination was notable for chronic stable pitting ankle edema and a normal neurological exam.

**Discussion:** Paclitaxel is a commonly used antineoplastic agent with proven activity in several malignancies including advanced ovarian, breast, lung, head and neck, genitourinary cancers as well as refractory lymphoma. Neurotoxicity is frequently a dose-limiting factor in administration of the drug.

The effectiveness of paclitaxel against a wide range of tumors makes it vital to mitigate the adverse effects and improve its tolerability.

Paclitaxel is known to be associated with peripheral neuropathy. Similar to most chemotherapy-induced peripheral neuropathies (CIPN), paclitaxel-associated neuropathy is predominantly sensory and develops after a cumulative dose. However, taxanes can also induce acute toxicities. A unique pain syndrome manifesting as myalgias and arthralgias has been described with taxanes. This syndrome, reported in about 60-88% of patients receiving taxanes, is more common with paclitaxel than with docetaxel.

#### Paclitaxel-Associated Acute Pain Syndrome: Clinical Characteristics

Paclitaxel-associated acute pain syndrome (P-APS) is a distinct clinical entity from the classic paclitaxel related chronic peripheral neuropathy. Arthralgias and myalgias develop about one to three days after paclitaxel administration, peak on day four and largely resolve in seven to ten days (Figure 1). The most common manifestation is a diffuse aching pain, predominantly in the lower extremities, hips and lower back, although it can be generalized as well. Some patients experience localized aches in large axial muscles, such as shoulder and paraspinal muscles. Less than 25% of patients develop subjective muscle weakness and identify walking or weight bearing as precipitating factors. Although over 55% patients describe the pain intensity to be moderate to severe, nonprescription pain medications are used approximately twice as often as opioids in the week after the chemotherapy dose.

With paclitaxel monotherapy, the pain intensity with the first cycle does not correlate with the pain severity with subsequent paclitaxel doses. However, in those patients who receive concurrent carboplatin, the severity of pain with the first chemotherapy cycle appears to predict pain levels with successive chemotherapy (Figure 2). The mechanism is unclear, as carboplatin is not commonly known to be associated with acute arthromyalgia.

*Personal details in the case published have been altered to protect patient privacy.*

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(Discussion Continued)

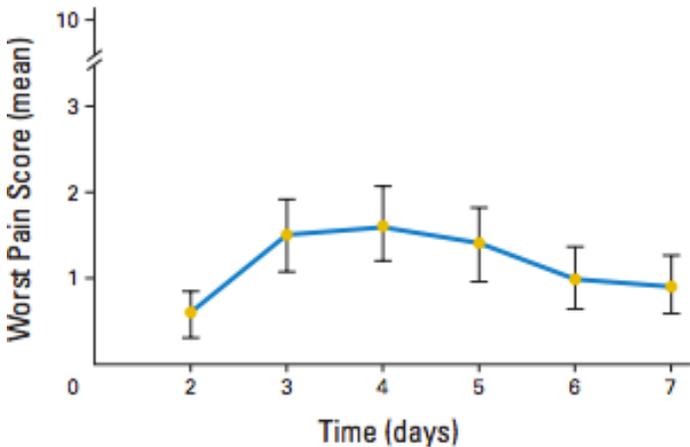


Figure 1. Mean maximal daily patient-reported pain scores during the first paclitaxel week.

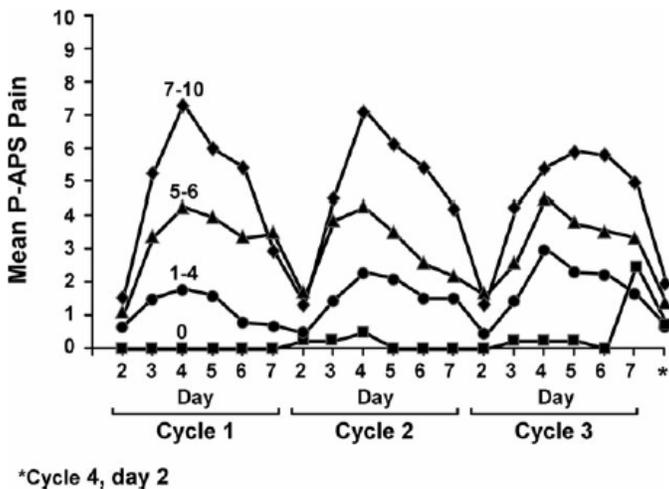


Figure 2. Worst mean maximum P-APS scores over several weeks of paclitaxel, segregated by the worst mean maximum pain scores for the first week.

Risk factors

Data suggest a higher incidence and severity of paclitaxel related acute pain with higher individual doses, particularly doses greater than or equal to 135 mg/m<sup>2</sup>. The associations with cumulative dose and infusion duration, however, are not clear. To date, no relationship has been observed between arthralgias/myalgias and patient characteristics (i.e. age, sex, height, hepatic or renal function, sites of metastases or prior chemotherapy), paclitaxel pharmacokinetics or concurrent administration of platinum-based drugs.

Limited studies have demonstrated that patients who develop severe forms of P-APS after their first exposure to paclitaxel are at a higher risk of developing chronic peripheral neuropathy. Further studies investigating this association are underway.

Mechanism

The exact pathophysiology of P-APS is unknown. There is no convincing evidence suggesting that the pain is related to pathologic alteration of joints, bones or muscles. Since paclitaxel primarily acts by stabilizing microtubules and inhibiting cell division, it has been hypothesized that the pain results from disruption of microtubule-dependent axonal transport resulting in a progressive axonopathy. Furthermore, based on clinical symptoms (generalized nature, absence of focal neurological deficits, increase in pain on weight bearing suggesting mechanical hyperalgesia) and animal studies, it has been postulated that paclitaxel sensitizes nociceptors, particularly small sensory neurons, which ultimately results in P-APS. The potential association between the severity of P-APS and more classic CIPN further supports the possibility of P-APS being an early manifestation of neuropathy.

Prevention and Treatment

Currently there are no well-established treatments to prevent or treat P-APS. Interventions with non-steroidal anti-inflammatory drugs, corticosteroids, antihistamines, opioids and glutamine have yielded inconclusive results. A small retrospective trial showed that gabapentin, when given as secondary prophylaxis, significantly reduced the severity of pain in 90% of patients who developed P-APS following either one or two cycles of paclitaxel. Further studies are warranted to identify definitive treatment options.

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**Case Resolution:** Mr. K continued to have similar episodes of severe diffuse lower extremity myalgias and arthralgias during the week following each of his chemotherapy cycles, with milder residual pain thereafter. Investigations to rule out potential musculoskeletal etiologies were unrevealing. His opioid regimen was increased to fentanyl 50 mcg/hr transdermal patch every 72 hours and oxycodone 5-10 mg every 3 hours as needed for breakthrough pain. He was started on gabapentin 300 mg orally at bedtime, which was eventually increased to 300 mg orally twice a day. He was also started on dexamethasone 2 mg orally daily. His pain improved only minimally with the aforementioned interventions. He developed depressive symptoms and was referred for behavioral therapy. In view of his progressive clinical and psychological decline, paclitaxel was held altogether for his sixth cycle of chemotherapy. Subsequently, although he was noted to have progression of the cancer, his myalgias and arthralgias gradually subsided, and the pain remained well controlled without further changes in his opioid regimen.

**References:**

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