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Natural History of Paclitaxel-associated Acute Pain Syndrome: A Case Report of Rare Side Effect of Paclitaxel

Siti Salima, Ali Budi Harsono, Aisyah Aisyah, Kemala Mantilidewi*

Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Padjadjaran, Dr. Hasan Sadikin Hospital, Bandung, West Java, Indonesia

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***Correspondence:** Kemala Isnainiasih Mantilidewi, Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Padjadjaran - Dr. Hasan Sadikin Hospital, Bandung, West Java, Indonesia. E-mail: kemala.i.mantilidewi@unpad.ac.id
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Abstract

BACKGROUND: One of the harshest side effects following anticancer agent treatments is chemotherapy-induced neuropathic pain. After surgical staging, chemotherapy combination of paclitaxel carboplatin could be a choice of therapy for Stage II or more advanced stage of ovarian cancer. Different side effects may appear after the application of paclitaxel.

CASE REPORT: Here, we show an uncommon case of paclitaxel-acute pain syndrome (P-APS), and how we deal with such cases according to our experiences. One uncommon side effect is P-APS, which can be treated effectively with the administration of non-steroidal anti-inflammatory drugs, corticosteroid, and supportive therapy.

CONCLUSION: One uncommon side effect of Paclitaxel induced neuropathic can be treated effectively with the administration of non-steroidal anti inflammatory drugs, corticosteroid, and supportive therapy.

Introduction

Ovarian cancer is one of the lethal gynecological cancers after cervical cancer. The American Cancer Society estimates in 2021 there will be 21,410 new ovarian cancer cases causing 13,770 deaths in the United States [1]. The National Cancer Institute states that the rate of new ovarian cancer cases is 11.2/100,000 with a death rate of 6.7/100,000 women per year [2]. Ovarian cancer is often referred to as the silent killer because of the nature of the cancer is asymptomatic thus causing delayed onset of symptoms, and until now there is lack of proper screening method [3], [4]. These cause patients would come in the advanced stage.

The management of advanced ovarian cancer includes surgery combines with chemotherapy with platinum compounds and taxanes, although carrying various side effects [5], [6], [7], [8]. Paclitaxel is a chemotherapy drug frequently used in the breast, ovarian, lung, and head and neck cancers that have side effects of acute and sub-acute pain called paclitaxel associated acute pain syndrome (P-APS) [9], [10], [11], [12]. The presence of acute pain in patients is often associated with chemotherapy-induced peripheral neuropathy (CIPN).

CIPN is a widely known harmful effect of anti-cancer drugs [13]. Neuropathic pain symptoms are reported to exist in nearly 19–85% of the cancer patients after they received the administration of anticancer drugs such as platinum compounds, proteasomes inhibitors, and antitubulins (e.g. vinca alkaloids and taxanes) [14], [15]. The frontline chemotherapeutic agent, paclitaxel, is used to treat a number of solid tumors, but the presence of a high incidence of CIPN severely devastates the patient's quality of life, which leads to dose reduction or even treatment discontinuation [16].

Painful symptoms, the characteristic of a neuropathic pain syndrome, are usually the manifestation of peripheral neuropathy, which can develop to dysfunction of sensory perception in the most severe cases. Furthermore, motor and/or autonomic peripheral neuropathy may also take place [8], [13].

However, there have not been working agents or clinical protocols to effectively stop and reverse CIPN. Although the mechanisms of CIPN are not known

entirely, growing evidence confirms that paclitaxel administration improves sensitivity to mechanical and cold stimuli (mechanical and cold allodynia) targeting peripheral sensory neurons in the dorsal root ganglia (DRGs), which leads to oxidative stress and neuroinflammation, resulting in degeneration of intraepidermal nerve fiber density [17], [18]. Here, we share natural history of the application of paclitaxel chemotherapy to a patient along with successful management for removing the P-APS.

Case Presentation

The case is about a 35-year old female in Bandung City, West Java, Indonesia, diagnosed with stage IIIA1 ovarian cancer. She received complete surgical staging with histopathology result of muscinous cystadenocarcinoma of left ovary and the presence of pelvic lymph node metastasis.

The following post-operative management was chemotherapy paclitaxel with a dosage of 175 mg/m^2 IV for 6 h in every 3 weeks for 6 courses, administered together with carboplatin with dosage of area under the curve (AUC) 5. Upon starting her first course of chemotherapy, the patient complained about shooting pain at her left gluteus spreading to the left sole in particular at her toe after 12 h of the treatment, with the numerical rating scale (NRS) showing at scale 9-10. In the beginning, she was treated with nonsteroidal anti-inflammatory drug orally as outpatient. The pain did not go away for 3 days with reduction of pain at the scale only to 6-7, and then it disappeared within 1 week.

After the observation on the temporal characteristic of the pain, the paclitaxel carboplatin chemotherapy was administered for her second course. During this course, the pain relapsed earlier which was 10 h after the application of chemotherapy. Pain scale was 9 by NRS, but this time the patient was hospitalized for pain treatment and supplemented with nonsteroidal anti-inflammatory drug orally, methylcobalamin 1500 mcg/day orally along with prednisone 5 mg twice a day orally. The pain became less intensive to 5, and after 7 days of her being hospitalized, the pain disappeared.

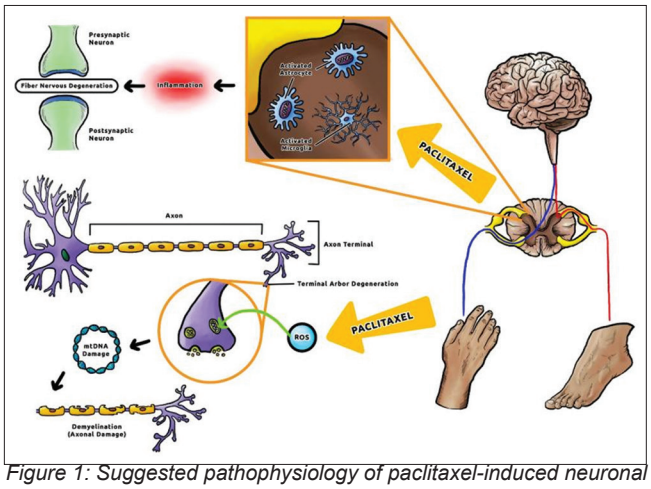

Figure 1: Suggested pathophysiology of paclitaxel-induced neuronal injury

As we identified the pain relapsing in the second course of paclitaxel carboplatin chemotherapy, the conclusion was that the patient had suffered from P-APS. Consequently in the third course of chemotherapy paclitaxel was replaced with Gemcitabine 750 mg/m^2 IV on day 1 and day 8 parallel with carboplatin AUC 5 on day 1, repeated in 21-day cycles. There was a significant pain reduction to scale 2 by NRS. The patient agreed to continue taking the nonsteroidal anti-inflammatory drug orally when needed.

Discussion

In this case, the patient felt severe pain 12 h after the administration of paclitaxel. In contrast to Reeves's *et al*. study, the pain associated with paclitaxel administration would increase on day 4 after paclitaxel administration [11]. Reeves's study showed the most common type of pain was itching while shooting pain has a low percentage of pain types, around 18%. In current case, pain was felt in the hips and lower extremities; this is in line with another cohort study by Reeves [12].

CIPN is experienced by as many as 19–85% of patients administered with chemotherapeutic drugs, like paclitaxel [14], [15]. Nevertheless, CIPN is still inevitable as there is no clinical treatment that might prevent or reverse CIPN yet [14], [15]. At the current study, we are studying a case of paclitaxel-induced neuropathy and our findings in treating such a case.

Some physiopathological mechanisms have already been identified for CINP comprising alterations in axonal transport, mitochondrial damage, increasing ion channel activity and inflammation in the central nervous system (CNS) [11], [12]. We suggested the mechanisms involved in P-APS/CIPN may require several pathways, as manifested in Figure 1.

Paclitaxel is one the foremost efficacious chemotherapeutic drugs, yet it is attributed to the development of CIPN symptoms comprising among others persistent shooting, stabbing, or burning pain, and most often loss of sensation of "numbness" [11], [12]. Although mice given with the chemotherapeutic agent cisplatin demonstrated noteworthy sensory motor deficit using the well characterized adhesive removal test as an indication of numbness, the same deficits were not seen in

those administered with paclitaxel not seen in mice administered with paclitaxel [12]. However, it is well documented that paclitaxel-treated animals have improved sensitivity to mechanical stimuli (mechanical allodynia), and this particular increased sensitivity is widely applied as a readout for the development of CIPN [19].

There is no single theory that can explain the difference between P-APS and CIPN since then. However, several studies conducted by Reeves can support that P-APS and CIPN are different clinical groups but manifest neurological disorders [11]. In clinical trials using mice, there was damage to DRG 24 h after administration of paclitaxel, and this supports the theory that P-APS is a manifestation of neurological toxicity [20].

Degeneration of peripheral nerves can occur due to malfunctioning of the mitochondria and microtubules which will affect axonal transport caused by chemotherapy drugs [21]. Platinum agents caused damage to DRG with apoptotic activation by changing the Schwan and satellite cells [22], [23].

Furthermore, chemotherapy drugs cause damage to mitochondrial DNA and electron transport chain proteins and trigger reactive oxygen species (ROS) as known as oxidative stress [24]. The stress factor strongly influences the production of ROC in cells. ROS caused phospholipids' damage, resulting in demyelination, oxidized proteins, and an increase in carbonyl by-products, which can activate transient receptor potential vanilloid (TRPV) channels [24].

TRPV receptors are found mainly in the peripheral nervous system's nociceptive neurons, including the CNS. The activated TRP channels allowing ions such as sodium to flow into the cell. TRPV is involved in the transmission and modulation of pain and causing diverse painful stimulation [25].

The overexcitation of peripheral nociceptors of which the intracellular ROS stimulates, caused the increase of pro-inflammatory mediators such as (interleukin [IL]-1β, tumor necrosis factor-α, bradykinin, and nerve growth factors) [26]. These functional disorders lead to peripheral neuropathic injuries in the neurons and cause complaints ranging from mild-to-severe rate pain in patients with cancer-induced chemotherapy. Therefore it is necessary to prevent and manage CIPN in patients. However, there are no specific interventions recommended in the management and prevention of CIPN.

Administration of prednisone in humans has been reported to reduce P-APS [27]. Furthermore, randomized control trials using mice reported that minocycline (a selective microglia/macrophage inhibitor and anti-inflammatory cytokine IL-10) could reduce mechanical allodynia [28]. Damage to the DMG was associated with pain in the P-APS responsible for CIPN. Dexamethasone administration has also been reported to be safe and beneficial in reducing the severity of P-APS [29].

Conclusion

One uncommon side effect of Paclitaxel induced neuropathic can be treated effectively with the administration of non-steroidal anti inflammatory drugs, corticosteroid, and supportive therapy.

Authors' Contributions

All authors contributed equally.

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