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Incidences of Urinary Incontinence with Paclitaxel Use in the Curative Breast Cancer Treatment Setting: A Case Series

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Abstract

Background: Although peripheral neuropathy is a well-known side effect of taxanes used in chemotherapy regimens, this report discusses three cases of transient autonomic neuropathy resulting in urinary incontinence (UI) identified during treatment for breast cancer with paclitaxel. This case study aims to highlight UI as an underreported symptom of paclitaxel treatment, discuss treatment options for UI in this setting, highlight the importance of discussing this potential side effect with patients, and increase awareness amongst healthcare providers.

Methods: The University of Miami EMR was used to find the notes, treatment, and imaging from three patients who had experienced UI following treatment with paclitaxel.

Results: All three patients experienced UI within the first five doses of paclitaxel and returned to baseline urinary status following the completion of treatment. Symptoms were relieved by using bladder-selective muscarinic antagonists (tolterodine or oxybutynin), temporarily withholding treatment, reducing the taxane dose, or reducing the total number of treatments.

Conclusions: After investigating three cases of urinary incontinence in women undergoing breast cancer treatment with paclitaxel, we propose that autonomic neuropathy with urinary incontinence is a potentially underreported side effect in the context of paclitaxel treatment for breast cancer. There are opportunities to improve patients' quality of life, cancer treatment, and clinical status by recognizing this side effect and prompting medical interventions.

Keywords: Breast cancer; Urinary incontinence; Paclitaxel; Taxane; Survivorship

Introduction

Taxanes are a type of mitotic inhibitor and antimicrotubule agent used in chemotherapy regimens for cancer treatment [1]. Paclitaxel is a taxane used as a single agent or combined with other cytotoxic and immunotherapy agents for patients with ovarian, breast, cervical, endometrial, and other cancers [2]. Paclitaxel halts the rapid division of the malignant cells by targeting the beta-tubulin subunits of microtubules and stabilizing the microtubule polymer. Blocking the progression of mitosis and prolonging mitotic checkpoint inhibitors' activation results in apoptosis [3,4]. Although this mechanism of action renders paclitaxel a successful chemotherapeutic agent, it can also drastically impair neuronal development and function, resulting in clinical neuropathy [5]. Peripheral neuropathy is a well-known side effect of taxol therapies; however, it has recently become apparent that paclitaxel can also cause autonomic dysfunction [6].

Although autonomic neuropathy due to paclitaxel is poorly cited in literature and drug reports, it does occur. This side effect is of considerable concern to patients undergoing chemotherapy due to its multi-system effects, including symptoms such as fatigue, difficulty concentrating, orthostatic intolerance, palpitations, constipation, diarrhea, early satiety, erectile dysfunction, and urinary retention or incontinence [7]. Reports of autonomic dysfunction due to paclitaxel have been documented as early as 1993 in a case report of two patients who developed severe

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orthostatic hypotension following completion of a 24-hr infusion of paclitaxel at 170-250 mg/m^2 for ovarian cancer treatment [8]. Another study in 2016 describes patients treated for ovarian cancer with paclitaxel and carboplatin chemotherapy who experienced significant parasympathetic cardiac and adrenergic cardiovascular reactions [6]. Most recently, a 2022 study found that in a group of adults receiving a paclitaxel-based regimen for four or more months, about 40% of patients reported two out of five autonomic symptoms, including dizziness, diarrhea, constipation, bloating, and difficulty with controlling the bladder [9]. These reports highlight the prevalence of autonomic neuropathy among patients treated with paclitaxel and the breadth of symptom presentation.

Despite evidence of this side effect, drug reports fail to note autonomic neuropathy as a side effect of paclitaxel reliably. In the FDA report on paclitaxel, updated in 2020, peripheral/sensory neuropathy side effects predominate, with only one mention of autonomic neuropathy in the context of paralytic ileus. The report mentions, "*Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure*" [10]. Due to the lack of documentation and research on these side effects, it is difficult to recognize and address them in a clinical context.

This case study examines three cases of breast cancer patients who experienced urinary incontinence during paclitaxel treatment. This report aims to highlight UI as an underreported symptom of autonomic neuropathy in breast cancer treatment with paclitaxel and address the importance of discussing this side effect with patients to appropriately identify, assess, and manage this significant side effect.

Case Presentation

Case #1

A 53-year-old White postmenopausal female was diagnosed with ER/PR positive and HER2 negative invasive ductal carcinoma of the right breast. Following a lumpectomy with sentinel lymph node biopsy, this was staged as a pathological T1bN1aM0. The molecular profiling with OncotypeDx showed a recurrence score of 18, and Mammaprint showed a high-risk profile.

Two months after her surgery, she initiated adjuvant chemotherapy with dose-dense doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 every two weeks. She tolerated treatment well except for a rash, unrelieved by antihistamine, but improved with topical steroid treatment. She completed 4 cycles of this regimen in April 2018.

This chemo regimen was followed by taxane therapy with weekly paclitaxel 80 mg/m^2. However, after the second dose, the patient could not sense the need for urination and experienced urinary incontinence over three days. Due to this atypical and acute neurologic symptom, a thorough neurological workup was conducted. Neuroimaging studies of the complete neural axis showed no evidence of CNS tumor involvement, leptomeningeal enhancement, or cord compression or involvement to explain the UI. Neurology was consulted, and it was concluded that due to the timing and nature of the presentation, the UI appeared to be directly related to the taxane infusion and represented autonomic dysfunction due to autonomic neuropathy. Her case was discussed at the oncology tumor board, and a paper was discussed that cited the loss of bladder function associated with taxane use, considered to be secondary to autonomic neuropathy [11].

In order to continue with curative intent treatment, the patient started taking oxybutynin 10 mg daily for her urinary symptoms. As her symptoms improved, she was switched from paclitaxel to docetaxel 30mg/m^2 weekly in May 2018. Two hours after her subsequent treatment with docetaxel, she had another episode of urinary incontinence. She reported mild peripheral neuropathy but also symptoms of diarrhea, nausea, and arthralgias after starting docetaxel; therefore, she switched back to treatment with paclitaxel at a 10% dose reduction (72mg/m^2). Oxybutynin was changed to tolterodine 4 mg daily.

After two treatments of 10% dose-reduced paclitaxel and the continued use of tolterodine, she reported a significant improvement in urinary incontinence, only noting persistent urgency. Therefore, she continued treatment with weekly paclitaxel. She tolerated this treatment well, but after nine treatments, she reported worsening peripheral neuropathy and recurrence of UI. She discontinued paclitaxel after nine out of the twelve planned treatments.

Upon completion of chemotherapy, urinary incontinence almost wholly resolved, brain fog resolved, and peripheral neuropathy improved gradually. By January 2019, she reported that all symptoms of UI had resolved.

Case #2

A 38-year-old White premenopausal female with locally advanced ER positive, PR, and HER2 negative left breast invasive ductal carcinoma, initiated neoadjuvant chemotherapy with doxorubicin and cyclophosphamide in December 2020. She completed 4 cycles by February 2021, then initiated neoadjuvant weekly paclitaxel 80 mg/m^2 IV shortly after that.

Within a few hours of her initial dose of paclitaxel, she reported uncontrollable urinary incontinence. After two additional treatments, her symptoms persisted without improvement. Urinary workup included a urinalysis, which showed cloudy urine, trace amounts of ketones, protein, slightly elevated WBCs, and squamous epithelial cells. The urine culture showed a non-uropathogenic gram-positive organism, likely representing colonizers from external and internal genitalia. Kidney function on the comprehensive metabolic panel was normal. No further testing was recommended. She started taking tolterodine 4 mg daily, which she continued until the completion of her neoadjuvant treatment and ultimately resolved her symptoms of UI.

After five doses of paclitaxel, the patient developed peripheral neuropathy. Her symptoms improved minimally on gabapentin 300 mg TID, so this treatment was replaced by duloxetine 30 mg BID with acupuncture therapy. Her peripheral neuropathy improved but persisted. Consequently, she underwent a 10% dose reduction of paclitaxel, 72 mg/m^2 IV weekly, for her final five doses of paclitaxel and completed eleven of the twelve planned doses in May 2021.

After completing neoadjuvant chemotherapy, she underwent bilateral mastectomies with left axillary sentinel lymph node biopsy and immediate reconstruction showing a nearly complete pathological response, staged as ypT1mi N0(sn) M0. The 77-gene panel from Ambry Genetics identified a pathogenic mutation p. E318K of the MITF gene.

Case #3

A 49-year-old Hispanic premenopausal female was diagnosed with locally advanced right breast invasive ductal carcinoma in March 2021, ER moderately positive (11-50%) and PR weakly positive (1-10%), HER2 negative by FISH. The 47-gene panel from March 2021 was negative for any pathogenic variants.

She initiated neoadjuvant chemotherapy with doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 every two weeks in April 2021 and completed four cycles with a partial response demonstrated on the mammogram. She then initiated neoadjuvant weekly paclitaxel 80 mg/m^2 in June 2021. After the second dose, she reported bladder heaviness, increased pressure, increased urination frequency at night, and one incident of urinary incontinence. She started tolterodine 4 mg daily for the UI and continued paclitaxel at the same dose. After three weeks, she reported no symptoms of UI. Of note, she also reported mild bilateral peripheral neuropathy in her hands and feet during her treatment, which was managed with gabapentin 300 mg TID and acupuncture therapy. Her peripheral neuropathy improved, and she completed curative intent treatment.

Discussion

These three cases of urinary incontinence in women undergoing

breast cancer treatment with paclitaxel highlight an underreported side effect of this commonly used chemotherapy regimen. All three patients experienced UI within the first five doses of paclitaxel. All patients reported symptom improvement with the use of tolterodine, a selective muscarinic antagonist; however, two patients required a dose reduction followed by treatment discontinuation due to worsening peripheral neuropathy or UI. In the case of the patient who discontinued treatment, UI entirely resolved months after completing chemotherapy. The similarities of each patient's presentation and negative differential diagnostic workups lead us to the determination that this symptom correlates with initiating paclitaxel treatment and is typically transient. Due to the documentation of autonomic neuropathy symptoms as a potential side effect of paclitaxel and the acuity of UI coinciding with paclitaxel treatment, paclitaxel was considered the most likely cause of UI in these cases.

A literature search was conducted to determine the prevalence and management of UI side effects in the setting of breast cancer treatment. Most reports involving urinary incontinence with taxanes appear on cancer websites and blogs, with patients discussing their shared experiences. In contrast, few scientific papers highlight this side effect. A PubMed search using the keywords "paclitaxel," "autonomic neuropathy," and "incontinence" resulted in the following publications citing this side effect associated with chemotherapy in the setting of non-breast cancer treatments [12,13].

A 2018 study by Cho *et al.* is a cross-sectional study including 158 patients, both men and women, with stage III/IV gastric or lung cancer treated with at least one cycle of platinum-based drug and/or paclitaxel, of which 20.2% of patients reported severe lower urinary tract symptoms. Of note, more than 70% of patients who received chemotherapy continued to experience lower urinary tract symptoms for several months or even years afterward, and the incidence of lower urinary tract symptoms increased in severity with age. This study demonstrated an association between chemotherapy and irritative effects on the bladder in a mixed population [12]. A prospective cohort study by Strauchon et al. in 2020 included 62 women with ovarian, fallopian, peritoneal, or endometrial cancer undergoing carboplatin/paclitaxel chemotherapy who experienced an increased incidence of stress and urge urinary incontinence. Although they could not distinguish between the effect of pelvic surgery and UI, they did determine a positive association of symptoms during chemotherapy [13]. Most recently, a prospective study by Wudtisan et al. in 2023 included 110 women treated for gynecologic cancers (ovarian, uterine, and cervical being the most common), with either carboplatin plus paclitaxel or cisplatin plus paclitaxel, demonstrated that the urinary symptoms worsened when comparing severity pre-treatment and mid-treatment, with a tendency for improvement in severity between mid-treatment and post-treatment [14].

Because each of these studies used a combination of platinum drugs plus paclitaxel, it is difficult to ascertain whether the chemotherapy-related symptoms are due to either one of the drugs used or both. To our knowledge, there is no current peer-reviewed documentation of urinary incontinence in breast cancer patients treated with solely paclitaxel. This work may open an avenue for future research to determine whether these symptoms of UI are directly related to paclitaxel use rather than platinum plus paclitaxel treatments.

The lack of literature about urinary incontinence in the setting of breast cancer treatment may be due to stigmatization around UI and poor patient-medical provider communication about this side effect leading to underreporting by patients. Additionally, contrary to gynecologic cancers where UI may be expected and discussed as a consequence of treatment, UI symptoms may seem unrelated to breast cancer treatments and uncomfortable for patients to discuss with their physician.

A 2021 paper documenting the under-detection and under-treatment of UI in 7,000 adults, both male and female 50 years and older, highlighted the stigmatization and poor communication surrounding urinary continence between the patient and their physician [15]. It was found that only 40% of older individuals with UI reported this symptom to their physician despite the poorer quality of life and high frequency of symptoms. This study highlighted the need to educate older people on UI and seek help for this symptom. It also noted the importance of addressing UI as a regular part of patient-centered care to decrease the underreporting of this problematic side effect [15]. A Lancet paper also discusses the under-reporting of UI in women and the significant impacts on quality of life, "Although the prevalence of urinary incontinence may be surprising to many clinicians, women with the disorder often under-report or delay seeking treatment for several years after the problem has become bothersome. The effect of incontinence on quality of life is important and is often not appreciated by healthcare providers," This paper also mentions the use of the MESA questionnaire to increase the detection of UI, as well as determining the specific subgroup [16].

These reports highlight the cycle that under-reporting UI perpetuates decreased documentation of this side effect in the medical literature, resulting in incomplete communication between the patient and physician. Due to the decreased quality of life associated with UI, physicians need to initiate the conversation about UI as a side effect of treatment, baseline urinary status, and realistic expectations to normalize this symptom and increase patient comfort. As physician-patient communication on UI improves, and reports of UI go up, we expect more communication on this topic, decreased stigmatization, and decreased stress on patients undergoing this side effect due to paclitaxel, reversing the cycle (**Figure 1**)

It is crucial for healthcare professionals to ask about this symptom in a patient-centered approach in order to stop this cycle. More discussion of UI with patients may result in improved patient education and awareness, decreased stigmatization, and increased reporting of UI, thereby reversing the cycle of underreporting.

Although there are currently too few cases to determine any definite risk factors amongst these patients, the cross-sectional study by Cho cited increased age and decreased physical activity as risk factors for lower urinary tract symptoms in cases of patients with advanced cancer who experienced chemotherapy-induced peripheral neuropathy [12]. Additionally, it is still unclear if these symptoms of autonomic neuropathy are transient, as seen in these breast cancer cases, or if there are more long-term deficits, as seen in the study by Cho et al. Future studies might include further investigating risk factors for autonomic neuropathy and UI in this setting, as well as interventions to prevent or decrease the incidence of these side effects.

There is a need for more peer-reviewed studies on this side effect of paclitaxel to increase awareness within the medical community and with breast cancer patients treated with paclitaxel. There is much more to be studied in this field, and we hope that this initial case study can open avenues for future studies on the prevention and

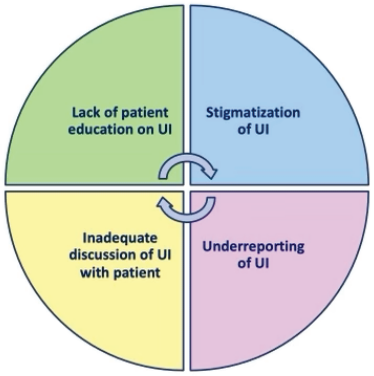

Figure 1: A cycle exists between underreporting and poor patient-provider communication on urinary incontinence.

improvement of UI as a side effect in patients undergoing treatment as well as through cancer survivorship.

Conclusion

In conclusion, after investigating three cases of urinary incont`inence in women undergoing breast cancer treatment with paclitaxel, we propose that autonomic neuropathy with urinary incontinence is a potentially underreported side effect in this setting. These symptoms may be relieved by selective muscarinic antagonists to complete curative intent treatment. An open discussion of this side effect and the patient's baseline urinary status is encouraged to improve physician-patient communication, patient quality of life, and treatment efficacy in paclitaxel-induced urinary incontinence.

Statements and Declarations

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