Article ID: WMC005788 ISSN 2046-1690

Audit of Paclitaxel induced Peripheral Neuropathy in Early Breast Cancer

Peer review status:
No

Corresponding Author:
Dr. Esther Una Cidon,
Medical Oncologist, Oncology Department, University Hospital Dorset, Castle Lane East, BH7 7DW - United Kingdom

Submitting Author:
Dr. Esther Una Cidon,
Medical Oncologist, Oncology Department, University Hospital Dorset, Castle Lane East, BH7 7DW - United Kingdom

Article ID: WMC005788

Article Type: Original Articles

Submitted on:06-Aug-2022, 05:36:28 PM GMT **Published on:** 08-Aug-2022, 01:56:47 AM GMT

Article URL: http://www.webmedcentral.com/article_view/5788

Subject Categories:CANCER

Keywords: Steroids, peripheral neuropathy, paclitaxel, paresthesia, chemotherapy, numbness

How to cite the article: Una Cidon E. Audit of Paclitaxel induced Peripheral Neuropathy in Early Breast Cancer. WebmedCentral CANCER 2022;13(8):WMC005788

Source(s) of Funding:

N/A

Competing Interests:

N/A

Audit of Paclitaxel induced Peripheral Neuropathy in Early Breast Cancer

Author(s): Una Cidon E

Abstract

Paclitaxel induced peripheral neuropathy (PIPN) is predominantly sensory. It usually appears with higher cumulative doses (>1,400 mg/m^2), being less frequent with weekly regimens or lower doses.Â Â

Numbness, paresthesias and burning pain in a glove-and-stocking distribution, distal and symmetrical are the most frequent symptoms. Although mild symptoms tend to improve or resolve within months after cessation of paclitaxel, more intense symptoms may last for longer or even persist.

PIPN risk factors have been researched for a long while but findings are still inconclusive.

In this scenario, we carried out an audit on a small cohort of patients diagnosed with early breast cancer, receiving weekly paclitaxel as part of their adjuvant or neoadjuvant regimen of chemotherapy with the aim of knowing the incidence of peripheral neuropathy, the intensity of symptoms, and the role of several potential risk factores on the appearance of PIPN.Â

Introduction

Paclitaxel induced peripheral neuropathy (PIPN) remainsÂ the main dose-limiting toxicity of paclitaxel, mainly because of the absence of any preventative or therapeutic approach.Â Unfortunately, it does not help the fact that its mechanism is still unclear (1).

A small study has pointed that wearing frozen gloves and socks for 90 minutes while receiving paclitaxel infusion, may control PIPN, but further studies are warranted before making a recommendation (2).Â

Other studies, carried out in mice, have shown that treatments such as lithium and ibudilast may protect them when administered before the paclitaxel infusion, showing that the alteration of the paclitaxel / NCS-1 / InsP3R pathway might prevent PIPN (3).Â

Duloxetine is recommended as the only potential treatment of patients with established painful chemotherapy-induced peripheral neuropathy by the American Society of Clinical Oncology. Nonetheless, the amount of benefit from duloxetine is limited (4).

PIPNÂ is predominantly sensory, and it tends to appear with higher cumulative dosage. However, it has also been described with lower dose or following weekly regimens (5,6).Â

A meta-analysis has shown that PIPN affects 44% to 98% of patients and these typically complain of numbness, tingling, or spontaneous and evoked pain to mechanical and cold stimuli in their hands and feet. These symptoms are usually symmetrical (1).Â

There are several ways of assessment of PIPN. NCI-CTCAE is a subjective way to evaluate PIPN. The neuropathy is assessed by the professional who visits the patient and grades the toxicity on a scale of 1 to 5, depending on the severity (7).

This method's limitation is mainly the subjectivity of interpretation. However, it is a rapid and easy way of evaluation (8).

Mild symptoms tend to improve or even dissapear after stopping paclitaxel; more intense symptoms may last for longer periods, or even persist, leaving a neurological deficit (6).Â

Therefore, paclitaxel is a significant cause of sensory abnormalities and chronic pain, able to affect significantly patients' quality of life. This leads initially to dose reductions or delays and finally to premature cessation of the treatment, with the potential negative impact on patients oncology outcomes (1,9).Â

Although many efforts have been put into research to understand the risks factors that could predict the appearance of PIPN, findings are multiple and inconclusive (10).Â

Claimed risk factors, apart from the chemotherapy itself, are thyroid dysfunctions, lack of multiple vitamins such as B12, folic acid or vitamin D among others. Diabetes mellitus is another risk factor, older age and some medications used concomitantly (10).Â

Some studies have found an association with high body mass index (BMI), which has been linked to PIPN severity (10).Â

We have not found any studies reporting on the preventing role of adjuvant steroids after each infusion of paclitaxel, and as such, the prescription for these is dependent on the consultant oncologist.

Therefore, we decided to perform an audit in a small cohort of our patients diagnosed with early breast

cancer (EBC) receiving adjuvant or neoadjuvant regimens of chemotherapy containing weekly paclitaxel, aiming at knowing the incidence of PIPN, the severity, the risk factors found and the role of adjuvant steroids on PIPN if any.Â

Methods

Audit of patients diagnosed with EBC receiving neoadjuvant or adjuvant treatment with 12 weekly paclitaxel either monotherapy or in combination with carboplatin every three weeks.

We collected data about sex, age, weight, body mass index (BMI), body surface area (BSA), type of chemotherapy received, presence of anaemia or lymphopenia, the recommendation of adjuvant steroids, thyroid levels, the presence of diabetes, any lack in vitamins or electrolytes, etc.

We determined the risk factors for PIPN by using univariate and multivariate statistical techniques. The chi-square test was used in the univariate analysis.

Results

This audit included 36 patients. All women diagnosed with EBC.Â

Median age for the whole group 51 with no differences between the two groups (those who developed PIPN and those who did not).

22/36 (61%) developed PIPN. Only 10/36 (27.7%) received steroids as adjuvant treatment and neither of them developed PIPN.

The dose of steroids was Dexamethasone 2mg twice daily for one day, followed by 2mg daily for one day.Â

12/36 (33.3%) received paclitaxel combined with carboplatin. Among patients on this combination, 75% developed PIPN (9 patients)and 25% (3 patients) did not (p 0.06).

Lymphopenia was found in 59% of cases with PIPN and 40.9% of no PIPN (p 0.39).

27 patients had a BSA > 1.7 and 20 (74%) of them developed PIPN; 22% of those with 1.70 or less of BSA developed PIPN (p 0.02).

Patients overweight/obese receiving carboplatin/paclitaxel developed more PIPN when compared to those receiving only paclitaxel (p 0.06).

Patients with "no ideal weight" (either higher or lower) developed more PIPN (p 0.07). Overweight was more frequent in those who developed PIPN regardless of the chemotherapy regimen.Â

Among all cases, PIPN was grade 1 in 64.2% of cases, grade 2 in 21.4% and grade 3 in 14.2% and all these patients showing grade 3 were diabetic.Â

Discussion

PIPN is the main dose-limiting and long lasting adverse event of paclitaxel. The underlying pathways are not well known, although it has been claimed that microtubule aggregation in axons and Schwan cells may be responsible for sensory neuropathy. Motor and autonomic nervous system seem to be less frequent (1,5-6).

Several risks factors have been claimed such as older age, higher BMI or BMA, diabetes or thyroid alterations, some concomitant medications or other chemotherapeutic agents combined, etc (10).

Steroids are administered before paclitaxel infusion to reduce the chances of hypersensitivity reactions, but not always as adjuvant therapy.

We decided to carry out an audit of our patients with EBC treated with weekly paclitaxel, either adjuvant or neoadjuvant, for 12 weeks. This treatment could be as monotherapy or in combination with carboplatin. The aim was to knowÂ the incidence of PIPN, the severity, the risk factors found and the role of adjuvant steroids on PIPN if any.Â

Although this is a very small study and retrospective in nature, we found that those patients who received steroids after the paclitaxel, as an adjuvant medication, did not developed PIPN.Â

We also found that PIPN was more frequent in patients receiving carboplatin in combination with paclitaxel, which is something expected. But our data, also support that those whose BSA is > 1.70 seem to be at higher risk, same as those patients with a "non-ideal weight", either too high or too low, regardless of the type of treatment (combination or monotherapy).Â Â

Multivariate analysis showed that patients overweight/obese receiving carboplatin/paclitaxel developed more PIPN when compared to those receiving only paclitaxel.Â

Although these data come from a very small, retrospective and unicentricÂ study and as such will not change any clinical practice, they may support at least the consideration of adjuvant steroids in those patients considered at higher risk of developing PIPN (mindful of those patients who might be diabetic, in whom a proper diabetic control should be ensured).Â

Conclusions

Although, very small and retrospective in nature, this study suggests that BSA > 1.7, combination with carboplatin, "no ideal weight" and no adjuvant steroids should be considered as risk factors for PIPN.

Prospective studies are needed to confirm these findings, but perhaps addition of steroids as adjuvant treatment should be considered for the apropriate patients considered at high risk.

References

1. Seretny M, Currie GL, Sena ES, *et al*.Â Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: a systematic review and meta-analysis.Â *PAIN*Â 2014;155:2461â€“2470.Â

2. Shigematsu H, Hirata T, Nishina M, Yasui D, Ozaki S. Cryotherapy for the prevention of weekly paclitaxel-induced peripheral adverse events in breast cancer patients. Support Care Cancer 2020;28(10):5005-5011.

3. Hopkins HL, Duggett NA, Flatters SJ.Â Chemotherapy-induced painful neuropathy: pain-like behaviours in rodent models and their response to commonly used analgesics.Â Curr Opin Support Palliat CareÂ 2016;10:119â€“128.Â

4. Lu Y, Zhang P, Zhang Q, *et al*. Duloxetine Attenuates Paclitaxel-Induced Peripheral Nerve Injury by Inhibiting p53-Related Pathways. J Pharmacol Exp Ther. 2020 Jun;373(3):453-462.Â

5. Tofthagen C, McAllister RD, Visovsky C.Â Peripheral neuropathy caused by Paclitaxel and docetaxel: an evaluation and comparison of symptoms.Â *J Adv Pract Oncol*Â 2013;4:204â€“215

6. van den Bent MJ, van Raaij-van den Aarssen VJ, Verweij J, Doorn PA, Sillevis Smitt PA.Â Progression of paclitaxel-induced neuropathy following discontinuation of treatment.Â *Muscle Nerve* Â 1997;20:750â€“752.

7. US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE). Version 4.0. Published May 28, 2009.Â Â

8. Cavaletti G, Frigeni B, Lanzani F, *et al*. Chemotherapy-induced peripheral neurotoxicity assessment: a critical revision of the currently available tools. Eur J Cancer. 2010;46(3):479-494.

9. Pachman DR, Qin R, Seisler D, *et al*.Â Comparison of oxaliplatin and paclitaxel-induced neuropathy (Alliance A151505).Â *Support Care Cancer* Â 2016;24:5059â€“5068.Â

10. Ghoreishi Z, Keshavarz S, Asghari Jafarabadi M, Fathifar Z, Goodman KA, Esfahani A. Risk factors for paclitaxel-induced peripheral neuropathy in patients with breast cancer. BMC Cancer. 2018;18(1):958.Â