Effect of cryotherapy on dose of adjuvant paclitaxel in early-stage breast cancer

Rosenbaek, F; Holm, H S; Hjelmborg, J V B; Ewertz, M; Jensen, Jeanette Dupont

Published in:
Supportive Care in Cancer

DOI:
10.1007/s00520-019-05196-z

Publication date:
2020

Document version:
Accepted manuscript

Citation for pulished version (APA):
Rosenbaek, F., Holm, H. S., Hjelmborg, J. V. B., Ewertz, M., & Jensen, J. D. (2020). Effect of cryotherapy on dose of adjuvant paclitaxel in early-stage breast cancer. *Supportive Care in Cancer*, *28*(8), 3763-3769. https://doi.org/10.1007/s00520-019-05196-z

Original article

Effect of cryotherapy on dose of adjuvant paclitaxel in early-stage breast cancer

F. Rosenbaek[1,2], H. S. Holm[1], J. v. B. Hjelmborg[3], M. Ewertz[1,2], J. D. Jensen[1,4*]

[1]Department of Oncology, Odense University Hospital, Odense, Denmark, [2]Institute of Clinical Research, University of Southern Denmark, Denmark, [3] Department of Epidemiology and Biostatistics, University of Southern Denmark, Denmark, [4] OPEN, Odense Patient data Explorative Network, Odense University Hospital, Odense, Denmark

**Correspondance to*: Dr. Jeanette Dupont Jensen, Department of Oncology, Odense University Hospital, Sdr. Boulevard 29, Odense, DK-5000 Denmark, Tel +45 61660094, E-mail: Jeanette.Dupont.Jensen@rsyd.dk

Disclosures
The authors have no disclosures

Abstract

***Background*:** Chemotherapy-induced peripheral neuropathy (CIPN) is a dose-limiting toxicity of paclitaxel. Though no pharmacological agents have been identified to prevent CIPN, cryotherapy with frozen gloves and socks may reduce the risk of developing CIPN and thereby increase the likelihood of patients completing the planned dose of paclitaxel.

***Patients and methods*:** Among women with early-stage breast cancer who received at least one cycle of paclitaxel, 119 were included in the 2016-cohort who received cryotherapy when they developed symptoms of CIPN, and 96 patients in the 2017-cohort who received prophylactic cryotherapy. From electronic patient records, data were abstracted on dates and doses of adjuvant paclitaxel, dose reductions, cycle delays, symptoms of CIPN, and whether and when frozen gloves and socks were used. The outcome was the proportion of patients completing the planned 720 mg/m^2 of paclitaxel cumulated over nine cycles. The hazard ratio (HR) of a dose-limiting event due to CIPN was estimated in a Cox proportional hazards model.

***Results*:** In the 2016-cohort cryotherapy was needed due to symptoms of CIPN in 54 (45%) patients. Significantly more patients, 77% in the 2017-cohort, completed the planned dose of 720 mg/m2 compared with 64% in the 2016-cohort, *p*=0.017. The HR of a dose reduction or cessation due to CIPN, adjusted for age and HER-2 status, was 0.50 (95% Confidence Interval 0.30-0.84), *p*=0.009, for the 2017-cohort compared with the 2016-cohort.

***Conclusions*:** The results of this study suggest that prophylactic cryotherapy may reduce the risk of a dose-limiting event due to CIPN and increase the proportion of patients completing the planned dose of paclitaxel in adjuvant treatment of early-stage breast cancer. Despite this, CIPN remains to be an important dose-limiting toxicity of paclitaxel.

***Key words*:** breast cancer, cryotherapy, paclitaxel, neuropathy

Key Message

While there are no pharmacological agents known to prevent chemotherapy-induced peripheral neuropathy (CIPN), this study demonstrates that cryotherapy with frozen gloves and socks has the potential to reduce the risk of a dose-limiting event due to CIPN among breast cancer patients receiving weekly paclitaxel in the adjuvant or neo-adjuvant setting. By using cryotherapy from the first cycle of paclitaxel, more patients can complete the planned dose intensity. However, CIPN still remains to be an important dose-limiting toxicity of paclitaxel.

Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a dose-limiting toxicity of taxanes such as paclitaxel and docetaxel. Prevention of CIPN has been tested in more than 40 randomized clinical trials but no consistent or conclusive clinically meaningful benefits have been demonstrated when pharmacologic agents, such as anticonvulsants, antidepressants, vitamins, minerals, and other chemoprotectants have been compared with placebo controls(1). Among 1,725 Danish breast cancer patients receiving adjuvant treatment with docetaxel, 34% developed CIPN, with those developing CIPN receiving significantly lower cumulative doses of docetaxel than those who did not(2). Cryotherapy with frozen gloves and socks were used to prevent nail toxicity but turned out also to reduce the risk of CIPN with an Odds Ratio of 0.56 (95 % confidence intervals (CI) 0.38–0.81). These results were confirmed for paclitaxel in a prospective self-controlled trial(3).

After the publication of the E1199-trial(4), adjuvant chemotherapy with weekly paclitaxel became an option in January 2016 for Danish breast cancer patients with estrogen receptor positive tumors and recommended for patients with estrogen receptor negative tumors. Most patients preferred weekly paclitaxel from the assumption that a small weekly dose is associated with fewer side effects than docetaxel, given at larger doses every 3 weeks. Since our finding that cryotherapy reduced the risk of CIPN(2), patients treated with paclitaxel were offered cryotherapy when they developed symptoms of CIPN up to the end of 2016. However, it became clear that CIPN was still a problem and that many patients discontinued paclitaxel due to CIPN. From the beginning of 2017, it was therefore decided to offer all patients prophylactic cryotherapy from the first cycle of paclitaxel. This “natural experiment” enables us to compare the cumulative doses of paclitaxel between two cohorts: the 2016-cohort who had cryotherapy when needed and the 2017-cohort who had prophylactic cryotherapy. Our hypothesis was that prophylactic use of cryotherapy for all patients will reduce the risk of developing dose-limiting CIPN and thereby increase the number of patients who were able to complete the 9 planned cycles of paclitaxel, hopefully leading to a better prevention of recurrence of breast cancer.

Patients and Methods

From pharmacy lists of chemotherapy prepared, we identified women with early-stage breast cancer who received neo-adjuvant (NACT) or adjuvant chemotherapy at a single institution (Department of Oncology, Odense University Hospital, Denmark) from 1st January 2016 to 31st December 2017. Patients were eligible if they received at least one weekly cycle of paclitaxel. For patients with HER-2 positive tumors, concomitant trastuzumab was allowed.

In the adjuvant setting in Denmark, the recommended total dose of paclitaxel was 720 mg/m^2 given weekly over 9 cycles, i.e. 80 mg/m^2 per cycle. Some NACT patients received 12 cycles of paclitaxel but only the first 9 cycles were included into this analysis. All infusions were given over 60 minutes after premedication with Prednisolone, Cetirizine, and Ranitidine for the first five cycles. If no hypersensitivity reaction occurred, prednisolone was stopped. The patients were offered Elasto-gel frozen gloves and socks (stored at about minus 20 degrees Celsius for 3 hours prior to use) for a total of 90 minutes, i.e., 15 minutes before and 15 minutes after the infusion of paclitaxel with a change to a second set after the first 45 minutes to maintain the cold temperature. The administration of frozen gloves and socks was documented in the electronic patient record by the nurse who gave the infusion of paclitaxel.

Patient-reported outcomes were assessed by nurses from paper questionnaires filled in by the patients before the start of chemotherapy (baseline), and on the day prior to the next cycle. The questionnaire was built on a Danish translation of the National Cancer Institute Common Toxicity Criteria version 2.0 and allowed patients to rank 10 predefined adverse effects (mucositis, diarrhea, pains in joints and muscles, neuropathy, skin rash, nail changes, nausea, vomiting, fatigue, and edema) graded from 0 (none) to 4 (functional impact). The questionnaire was not validated prior to this study, but has been used by Eckhoff et al(2) in a study of docetaxel-induced peripheral neuropathy and in the Danish READ trial including 2,012 women with early-stage breast cancer(5). For this study, information on neuropathy was abstracted from the electronic patient record if it caused an alteration in dose or timing of paclitaxel, but information on grade of neuropathy was not available in the electronic patient record. If a patient reported symptoms of neuropathy, the next planned cycle of paclitaxel was delayed for one week. If the symptoms ceased within one week, paclitaxel was resumed at a reduced dose and frozen gloves and socks was used in the 2016-cohort. If the symptoms persisted or worsened, treatment with paclitaxel

was discontinued in both the 2016- and the 2017-cohorts. This was not a project-specific approach, but in accordance with normal practice at our institution.

From the electronic patient records, data were abstracted on the following variables: patient demographics, characteristics of the primary tumor, dates and doses of adjuvant paclitaxel, dose reductions, cycle delays, reasons for the latter, and whether and when frozen gloves and socks were used. Data were entered in a REDCap (Research Electronic Data Capture) electronic database made for the purpose(6).

Ethical considerations

All patients received oral as well as written information about the project and signed a permission to abstract their electronic patient record. The project was approved by the Danish Data Protection Agency, but approval from the Scientific Ethical Committee for the Region of South Denmark was not needed.

Statistical analysis

Standard methods were used to compare descriptive measures of patient and tumor characteristics in addition to details of paclitaxel and cryotherapy in the 2016- and the 2017-cohorts. The primary end-point of the analysis was a dose 720 mg/m2 of paclitaxel cumulated over nine cycles. To assess the cumulative dose of paclitaxel given when prophylactic cryotherapy was applied (2017-cohort), compared with cryotherapy administered when the patients developed symptoms of CIPN (2016-cohort), a multiple regression analysis was conducted controlling for age, prior neuropathy, diabetes, type of primary surgery, tumor size, lymph node metastases, estrogen receptor status, and HER-2 status.

The dichotomous outcome of patients completing treatment, i.e. 720 mg/m^2 of paclitaxel cumulated over nine cycles, was regressed on cohorts and covariates by logistic regression.

A dose-response relationship was studied by comparing Kaplan-Meier curves by cohort of those having an event of either being reduced or experiencing cessation due to neuropathy by increasing cycles of paclitaxel (dose). If a dose reduction occurred for reasons other than neuropathy, the patient was censored at that event. Further, the analysis of the occurrence of such events by dose was extended by applying Cox regression modelling to control for potential

confounders listed above of the relationship and to provide estimates of the effect of cryotherapy. Assumptions were verified, and inference was provided in terms of 95% confidence intervals (CI) and standard testing at 5% significance level. Analyses were conducted using statistical software STATA(7) and R(8).

Results

A total of 299 breast cancer patients were assessed for eligibility of whom 84 were excluded due to another chemotherapy regimen, no possibility of contacting the patient, patient declining participation, or death, leaving 215 patients available for analysis (Figure 1). The 2016-cohort included 119 patients who received cryotherapy when needed with 12 patients treated in the beginning of 2017 before prophylactic cryotherapy was implemented, and the 2017-cohort 96 patients with two patients receiving prophylactic cryotherapy in 2016. Patients in the 2016-cohort were older than in the 2017-cohort with median ages of 59 and 56 years at diagnosis respectively, and had more often HER-2-positive tumors, 25% versus 11%. Otherwise the two cohorts were similar in patient and disease characteristics, notably with respect to prior neuropathy and diabetes (Table 1).

In the 2017-cohort, all patients had cryotherapy for all cycles of paclitaxel while cryotherapy was needed due to symptoms of CIPN in 54 (45%) patients in the 2016-cohort (Table 2). After 9 cycles of paclitaxel, the mean cumulative dose reached was 645 mg/m^2 in the 2017-cohort and 603 mg/m^2 in the 2016-cohort, the difference being statistically significant, p=0.03. Significantly fewer patients (61%) completed nine cycles of paclitaxel in the 2016-cohort than in the 2017-cohort (74%). The dose of paclitaxel was reduced due to CIPN in 9% of the patients in the 2016-cohort and 3% in the 2017-cohort while paclitaxel was discontinued due to CIPN in 30% of patients in the 2016-cohort and 21% in the 2017-cohort. The Kaplan-Meier analysis (Figure 2) shows that the likelihood of completing the planned dose of 720 mg/m2 compared was significantly higher, 77%, in the 2017-cohort than in the 2016-cohort, 64%, p=0.017. The dose reductions or discontinuations due to CIPN began occurring from the 3rd cycle of paclitaxel. In a Cox proportional hazards model, we estimated the hazard ratio (HR) of a dose reduction or cessation due to CIPN. With the 2016-cohort as reference, the univariate HR was 0.54 (95 CI 0.32-0.90), p=0.019, and the

multivariate HR, adjusted for age and HER-2 status, 0.50 (95% CI 0.30-0.84), *p*=0.009, for the 2017-cohort.

Discussion

The present study demonstrates that prophylactic use of cryotherapy has the potential to reduce the risk of a dose-limiting toxicity due to CIPN and increases the proportion of patients who can complete the planned dose of paclitaxel for early-stage breast cancer in the adjuvant setting. In our study, the primary end-point was the cumulative dose of paclitaxel while others have evaluated the effect of cryotherapy on incidence of CIPN. Sato et al. (9) reported data from gynecological cancer patients who received three-weekly cycles of paclitaxel 150-175 mg/m^2 with 40 patients in the intervention group and 142 patients in the control group. Incidence of CIPN grade 2 or higher was significantly lower in the cooling group than in the control group, but there was no significant effect on dose reductions. In a pilot study, Sundar et al. (10) studied nerve conduction in 20 breast cancer patients receiving 12 cycles of weekly paclitaxel 80 mg/m^2 with cooling of one leg while the other served as a control. They observed a significant correlation between amount of skin cooling and motor nerve amplitude preservation at 6 months, but no statistically significant effect on sensory velocity and amplitude. Hanai et al. (3) performed a self-controlled clinical trial including 36 breast cancer patients treated with 12 cycles of weekly paclitaxel (80mg/m2) who received frozen gloves and socks on the dominant side while the non-dominant side acted as an untreated control. The incidence of objective and subjective CIPN signs was clinically and statistically significantly lower on the intervention side than on the control side. In a pilot phase II prospective trial 39 breast cancer patients scheduled to receive weekly paclitaxel at a dose of 80 mg/m2 for a planned course of 12 weeks were randomized to receive standard care versus topical cryotherapy with bags of crushed ice on the hands and feet (11). The CIPN20 sensory scores over 12 weeks of paclitaxel did not differ between the study arms, but when the cryotherapy arm was compared to a combined control arm from three trials, the cryotherapy arm had less neuropathy indicating limited statistical power.

Cryotherapy was introduced to reduce nail toxicity and uses the basic principle that vasoconstriction can limit the local effects of cytotoxic therapies(12). Generally, the frozen gloves

and socks were well tolerated with just one to two patients per cohort discontinuing to use them due to discomfort. We observed no serious side effects such as frostbites. Though the exact mechanism behind CIPN remains unknown, symptoms include sensory loss in a “glove-and-stocking”–type distribution thought to arise from damage to the dorsal root ganglion extending to the distal axon. Taxanes may cause disruption of microtubules of the mitotic spindle that interferes with the axonal transport and thereby affects the sensory neurons as well as the axons(13).

Our results also show that even with prophylactic cryotherapy, CIPN is still a dose-limiting toxicity since only 77% of the 2017-cohort were able to complete the planned dose. However, the question remains how much the cumulative dose matters in terms of efficacy of paclitaxel. The meta-analysis from the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG)(14) suggests that increasing the dose intensity of paclitaxel is likely to enhance efficacy, but no trials were identified assessing dose-intensification of taxane regimens without anthracyclines. For these, there is evidence that dose reductions and delays are associated with a poorer survival(15). In the metastatic setting, however, dose escalation of paclitaxel beyond 175 mg/m2 every three weeks, does not seem to improve survival but increase the toxicity, in particular neuropathy, considerably(16).

The E1199 trial compared two regimens of paclitaxel, 80 mg/m^2 weekly for 12 cycles and 175 mg/m^2 every 3 weeks for 4 cycles, and two regimens of docetaxel, docetaxel 35 mg/m^2 weekly for 12 cycles and 100 mg/m^2 every 3 weeks for 4 cycles, but found no association between taxane-induced neuropathy and outcomes such as overall survival, disease-free survival or recurrence-free survival(4, 17). Our results differ from those of the E1199 trial which reported no significant difference between the proportion of patients who required a dose reduction for any reason among patients who developed CIPN compared with those who did not in any arm, and a similar median relative dose intensity in patients who did and who did not develop CIPN in any arm(17). However, our results agree with those from a US single institution study of 488 women receiving adjuvant or neo-adjuvant paclitaxel or docetaxel, where the cumulative dose delivered was significantly lower than the planned cumulative dose among women who had a dose reduction or

treatment termination attributed to CIPN(18). One of the reasons for this discrepancy may be the difference between clinician-reported and patient-reported toxicity outcomes used in this study. Nyrop et al.(19) have demonstrated minimal agreement between patient-reported and clinician-assessed CIPN toxicity scores which varied by grade of CIPN. For grade 0, the agreement was 87% while it decreased to 46-48% for grades 1 to 2.

In this study, 25% of patients in the 2016-cohort and 11% in the 2017-cohort had HER-2 positive tumors (Table 1). Probably due to chance, these figures differ slightly from the Danish national average of 14%(20). We adjusted the effect of cryotherapy for HER-2 status, but the estimate did not change much, suggesting no major confounding effect of HER-2 status. Neuropathy is not a commonly reported side effect to trastuzumab(21), but higher rates of peripheral neuropathy have been reported when patients with metastatic breast cancer were randomized to paclitaxel plus trastuzumab versus paclitaxel alone(22).

The strength of this study is that it used patient-reported toxicity outcome measures which were registered prospectively, though collected retrospectively. The data reflect a real world setting of an unselected patient group. This may also be regarded as a limitation since a randomized trial can be considered the gold standard. However, a randomized trial could not be conducted at our institution, since it would be considered unethical to withhold cryotherapy from patients who present with symptoms of CIPN. Originating from a single center can also limit the generalizability of the results. It was a limitation that we did not manage to obtain informed consent from 34 (11%) of the potentially eligible patients, due to patients not being followed any longer, patients changing their appointments or doctors not being aware of this project. We did not ask patients to come into our clinic solely for the purpose of giving informed consent to participate.

Conclusion

Prophylactic cryotherapy has the potential to reduce the risk of a dose-limiting event due to CIPN and increases the proportion of patients completing the planned dose of paclitaxel in adjuvant treatment of early- stage breast cancer. Despite this, CIPN remains to be an important dose-limiting toxicity of paclitaxel.

References

1. Hershman DL, Lacchetti C, Loprinzi CL. Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline Summary. J Oncol Pract. 2014;10(6):e421-e4.
2. Eckhoff L, Knoop AS, Jensen MB, Ejlertsen B, Ewertz M. Risk of docetaxel-induced peripheral neuropathy among 1,725 Danish patients with early stage breast cancer. Breast Cancer Res Treat. 2013;142(1):109-18.
3. Hanai A, Ishiguro H, Sozu T, Tsuda M, Yano I, Nakagawa T, et al. Effects of Cryotherapy on Objective and Subjective Symptoms of Paclitaxel-Induced Neuropathy: Prospective Self-Controlled Trial. Journal of the National Cancer Institute. 2018;110(2):141-8.
4. Sparano JA, Zhao F, Martino S, Ligibel JA, Perez EA, Saphner T, et al. Long-Term Follow-Up of the E1199 Phase III Trial Evaluating the Role of Taxane and Schedule in Operable Breast Cancer. J Clin Oncol. 2015;33(21):2353-60.
5. Ejlertsen B, Tuxen MK, Jakobsen EH, Jensen MB, Knoop AS, Hojris I, et al. Adjuvant Cyclophosphamide and Docetaxel With or Without Epirubicin for Early TOP2A-Normal Breast Cancer: DBCG 07-READ, an Open-Label, Phase III, Randomized Trial. J Clin Oncol. 2017;35(23):2639-46.
6. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377-81.
7. StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX. StataCorp LLC.
8. R Core Team. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing. Vienna, Austria, 2019 (https://www.r-project.org/).
9. Sato J, Mori M, Nihei S, Kumagai M, Takeuchi S, Kashiwaba M, et al. The effectiveness of regional cooling for paclitaxel-induced peripheral neuropathy. J Pharm Health Care Sci. 2016;2:33.
10. Sundar R, Bandla A, Tan SS, Liao LD, Kumarakulasinghe NB, Jeyasekharan AD, et al. Limb Hypothermia for Preventing Paclitaxel-Induced Peripheral Neuropathy in Breast Cancer Patients: A Pilot Study. Front Oncol. 2016;6:274.
11. Ruddy KJ, Le-Rademacher J, Lacouture ME, Wilkinson M, Onitilo AA, Vander Woude AC, et al. Randomized controlled trial of cryotherapy to prevent paclitaxel-induced peripheral neuropathy (RU221511I); an ACCRU trial. Breast. 2019;48:89-97.
12. Kadakia KC, Rozell SA, Butala AA, Loprinzi CL. Supportive cryotherapy: a review from head to toe. J Pain Symptom Manage. 2014;47(6):1100-15.
13. Park SB, Goldstein D, Krishnan AV, Lin CS, Friedlander ML, Cassidy J, et al. Chemotherapy-induced peripheral neurotoxicity: a critical analysis. CA Cancer J Clin. 2013;63(6):419-37.
14. Increasing the dose intensity of chemotherapy by more frequent administration or sequential scheduling: a patient-level meta-analysis of 37 298 women with early breast cancer in 26 randomised trials. Lancet. 2019;393(10179):1440-52.

15. Chirivella I, Bermejo B, Insa A, Perez-Fidalgo A, Magro A, Rosello S, et al. Optimal delivery of anthracycline-based chemotherapy in the adjuvant setting improves outcome of breast cancer patients. Breast Cancer Res Treat. 2009;114(3):479-84.
16. Winer EP, Berry DA, Woolf S, Duggan D, Kornblith A, Harris LN, et al. Failure of higher-dose paclitaxel to improve outcome in patients with metastatic breast cancer: cancer and leukemia group B trial 9342. J Clin Oncol. 2004;22(11):2061-8.
17. Schneider BP, Zhao F, Wang M, Stearns V, Martino S, Jones V, et al. Neuropathy Is Not Associated With Clinical Outcomes in Patients Receiving Adjuvant Taxane-Containing Therapy for Operable Breast Cancer. Journal of Clinical Oncology. 2012;30(25):3051-7.
18. Speck RM, Sammel MD, Farrar JT, Hennessy S, Mao JJ, Stineman MG, et al. Impact of chemotherapy-induced peripheral neuropathy on treatment delivery in nonmetastatic breast cancer. J Oncol Pract. 2013;9(5):e234-40.
19. Nyrop KA, Deal AM, Reeder-Hayes KE, Shachar SS, Reeve BB, Basch E, et al. Patient-reported and clinician-reported chemotherapy-induced peripheral neuropathy in patients with early breast cancer: Current clinical practice. Cancer. 2019;125(17):2945-54.
20. Jensen MB, Ejlertsen B, Mouridsen HT, Christiansen P. Improvements in breast cancer survival between 1995 and 2012 in Denmark: The importance of earlier diagnosis and adjuvant treatment. Acta Oncol. 2016;55 Suppl 2:24-35.
21. Sodergren SC, Copson E, White A, Efficace F, Sprangers M, Fitzsimmons D, et al. Systematic Review of the Side Effects Associated With Anti-HER2-Targeted Therapies Used in the Treatment of Breast Cancer, on Behalf of the EORTC Quality of Life Group. Target Oncol. 2016;11(3):277-92.
22. Gasparini G, Gion M, Mariani L, Papaldo P, Crivellari D, Filippelli G, et al. Randomized Phase II Trial of weekly paclitaxel alone versus trastuzumab plus weekly paclitaxel as first-line therapy of patients with Her-2 positive advanced breast cancer. Breast Cancer Res Treat. 2007;101(3):355-65.

Figure legends:

Figure 1: Flow chart of the study population.

Figure 2: Cumulative dose of paclitaxel in 119 Danish breast cancer patients (cohort 2016) and 96 patients (cohort 2017)