Original Article

Risk factor analysis for taxane-associated acute pain syndrome under the dexamethasone prophylaxis

Yoshitaka Saito[1], Yoh Takekuma[1], Masaki Kobayashi[2], Tatsuhiko Sakamoto[1], HirokoYamashita[3], Mitsuru Sugawara*[,1, 4]

[1]*Department of Pharmacy, Hokkaido University Hospital: Kita 14-jo, Nishi 5-chome, Kita-ku, Sapporo 060-8648, Japan*

[2]*Laboratory of Clinical Pharmaceutics & Therapeutics, Faculty of Pharmaceutical Sciences, Hokkaido University: Kita 12-jo, Nishi 6-chome, Kita-ku, Sapporo 060-0812, Japan*

[3]*Department of Breast Surgery, Hokkaido University Hospital: Kita 14-jo, Nishi 5-chome, Kita-ku, Sapporo 060-8648, Japan*

[4]*Laboratory of Pharmacokinetics, Faculty of Pharmaceutical Sciences, Hokkaido University: Kita 12-jo, Nishi 6-chome, Kita-ku, Sapporo 060-0812, Japan*

*Corresponding author:

Department of Pharmacy, Hokkaido University Hospital, Kita 14-jo, Nishi 5-chome, Kita-ku, Sapporo 060-8648, Japan. Tel/Fax: +81-11-706-5680 and +81-11-706-7616;

E-mail: msuga@med.hokudai.ac.jp

ABSTRACT

Purpose

Taxane-associated acute pain syndrome (T-APS) reportedly occurs in approximately 70% of patients undergoing therapy. We have previously reported that additional dexamethasone (DEX) administration attenuates T-APS. The aim of this study was to reveal risk factor(s) associated with the incidence of T-APS under prophylactic DEX administration.

Methods

In total, 143 patients with breast cancer who received a docetaxel (75 mg/m^2) or paclitaxel (175 mg/m^2)-containing treatment regimens were enrolled. DEX (4–8 mg) was orally administered on days 2–4. Risk factors for the incidence of ≥G2 and all-grade T-APS, as well as T-APS incidence between taxane-containing regimens in the first cycle, were retrospectively evaluated.

Results

Approximately 90% of the patients received taxanes for adjuvant or neoadjuvant chemotherapy. Overall, 55% of patients administered 4 mg DEX, whereas, 45% received 8 mg DEX. Pegfilgrastim was administered in 27% of patients. Incidence of ≥G2 and all-grade T-APS was 23.8%, and 69.2%, respectively. Univariate and multivariate analyses revealed that administration of pegfilgrastim is an independent

risk factor for the incidence of ≥G2 and all-grade T-APS; age younger than 55 years is also a risk factor for all-grade T-APS. Moreover, the incidence of ≥G2 and all-grade T-APS was 45.5% and 81.8% in a paclitaxel regimen, and 22.0% and 68.2% in docetaxel-including regimens, respectively, revealing increased tendency with paclitaxel administration, with no significant differences.

Conclusion

Pegfilgrastim co-administration is an independent risk factor for ≥G2 and all-grade T-APS, and age younger than 55 years is a risk factor of all-grade T-APS under prophylactic DEX administration.

Key words: taxane-associated acute pain syndrome (T-APS); paclitaxel; docetaxel; dexamethasone (DEX); arthralgia; myalgia;

Introduction

Taxanes are a class of chemotherapeutic agents that include paclitaxel, docetaxel, nanoparticle albumin-bound paclitaxel, and cabazitaxel, with the first three listed considered key drugs in the treatment of breast cancer in adjuvant, neoadjuvant, and metastatic settings [1-6].

Taxane-associated acute pain syndrome (T-APS) is one of the most frequently observed adverse effects, known to appear 1 to 3 days after administration in 60-90% of patients [7, 8]. Symptoms such as arthralgia and myalgia can occur within a week, significantly affecting the patient's quality of life (QOL) for several days [9-13]. Clinically, T-APS is known to be considerably distinct from chemotherapy-induced peripheral neuropathy (CIPN), with different mechanisms of action and temporal profiles [10]; in contrast, it has been reported that patients with worse T-APS severities appear to develop more CIPN [14]. Moreover, a recent study has indicated the complex association between T-APS and CIPN [15]. Although mechanisms underlying T-APS need to be comprehensively clarified, T-APS is considered to be associated with nerve inflammation and injury, as well as nociceptor sensitization [7, 8, 13, 16, 17]. Kanbayashi et al. have reported that T-APS appears in a taxane-dose dependent manner [18], and metastatic setting, breast cancer, and paclitaxel reportedly enhance the

incidence of T-APS [10]. Other factors such as age, sex, height, prior chemotherapy, renal or hepatic function, and the metastatic sites were not significantly correlated with T-APS [7, 11, 13, 18].

Moreover, corticosteroids [7, 19], Shakuyaku-Kanzo-To [20], and gabapentin [21] have been suggested to prevent or attenuate T-APS. We have previously reported that dexamethasone (DEX) administration at 8 mg, on days 2 and 3, attenuates T-APS, without reducing its incidence [7]. In contrast, risk factors for T-APS incidence or aggravation with preventive DEX administration remain unclear.

This study aimed to reveal risk factor(s) for T-APS incidence under prophylactic DEX administration.

Methods

1. Patients

In total, 143 patients with breast cancer who received chemotherapy including docetaxel (75 mg/m^2) or paclitaxel (175 mg/m^2) from November 2013 to August 2020 were enrolled in this retrospective study (Figure 1).

All enrolled patients presented sufficient renal or liver function, with an Eastern Cooperative Oncology Group performance status (ECOG-PS) of 0 to 1. Patients

experiencing uncontrolled pain at baseline or those who were regularly administered corticosteroids, opioids, Shakuyaku-Kanzo-To, and gabapentin at baseline were excluded. Patients with inadequate medical records were also excluded. We calculated the number of patients to be approximately 140, as the incidence of ≥G2 T-APS, which is the primary endpoint of this study, was estimated to be 20% based on a previous report [7]; we attempted to include approximately three covariates in the multivariate analysis.

The present study was approved by the Institutional Review Board of the Hokkaido University Hospital (approval number: 020-0255) and was performed in accordance with the Declaration of Helsinki. Owing to the retrospective nature of the study, informed consent from subjects was not mandated.

2. Treatment methods

Docetaxel 75 mg/m^2 dissolved in 5% glucose (250 mL) was intravenously administered for 1 h, and paclitaxel 175 mg/m^2 dissolved in 5% glucose (500 mL) was intravenously administered over for 3 h. Trastuzumab (8 mg/kg at first administration, 6 mg/kg at subsequent administration) ± pertuzumab (840 mg at first administration, 420 mg at subsequent administration) were co-administered in cases of human epidermal growth factor receptor-2 (HER 2) overexpressed breast cancer. DEX 9.9 mg and

granisetron 3 mg were intravenously administered in the case of docetaxel + cyclophosphamide 600 mg/m^2 (TC), and DEX 6.6 mg was administered with other docetaxel-containing regimens for premedication. DEX 16.5 mg, famotidine 20 mg, and chlorpheniramine 10 mg were administered to prevent nausea or **hypersensitivity reactions** following paclitaxel administration. Furthermore, all patients orally administered 4–8 mg of DEX on days 2–4. Pegfilgrastim was administered in all cases of dose-dense paclitaxel therapy and depending on the physician's discretion during docetaxel administration. Analgesic drugs such as non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, tramadol, and opioids were administered to ameliorate T-APS at the physician's discretion.

3. Survey of the incidence and severity of T-APS

All required information was obtained from patients' medical records. We considered arthralgia and myalgia appearing within a week following taxane administration as T-APS, and its incidence and severity in the whole first cycle were retrospectively evaluated. The severity was graded in accordance with the Common Terminology Criteria for Adverse Events version 5.0.

In the present study, the primary endpoint was defined to reveal the risk factor(s) for the incidence of ≥G2 T-APS, as it could significantly reduce QOL of the patients and

necessitate taxane dose reduction. Secondary endpoints were elucidation of the risk factor(s) for the incidence of all-grade T-APS, and comparison of T-APS incidence between docetaxel and paclitaxel-containing regimens.

4. Statistical analysis

Univariate and multivariate analyses were performed using the logistic analysis to reveal the independent risk factor(s) regarding the ≥G2 and all-grade T-APS incidence, using the following covariates: age, treatment setting, treatment line, hormonal receptors expression, HER2 overexpression, body mass index (BMI), liver dysfunction (grade 2 or higher aspartate aminotransferase, alanine aminotransferase, γ-glutamyltransferase, total bilirubin elevation), renal dysfunction (grade 1 or higher serum creatinine elevation), the dose of DEX on days 2–4, and co-administration of pegfilgrastim. Variables that demonstrated potential associations with incidence in univariate logistic regression analysis ($P \leq 0.10$) were considered when building the multivariable model. The incidence of T-APS between docetaxel- and paclitaxel-containing regimens were compared using Fisher's exact probability method. All analyses were performed using JMP version 14.0 statistical software (SAS Institute Japan, Tokyo, Japan). Differences were considered statistically significant when *P*-values were less than 0.05.

Results

1. Patient characteristics

The baseline patient characteristics are shown in Table 1. Approximately 90% of patients received taxanes as adjuvant or neoadjuvant chemotherapy. Overall, 78% of patients received prior chemotherapy before taxanes. In total, 55% of patients were administered DEX 4 mg on days 2–4, while 45% received 8 mg DEX. Pegfilgrastim was administered to 27% of the patients, whereas other granulocyte colony-stimulating factor (G-CSF) medicines were not administered to the patients.

2. Incidence, severity, and risk analyses of T-APS

Data on the incidence and severity of T-APS during the first taxane treatment cycle are shown in Figure 2. The incidence of ≥G2 T-APS was 23.8%, and that of all-grade T-APS was 69.2%. The results of the univariate and multivariate analyses to identify risk factors for T-APS are shown in Table 2. Administration of pegfilgrastim was found to be an independent risk factor for the incidence of ≥G2 T-APS (Table 2A). Regarding all-grade T-APS, pegfilgrastim administration and patients aged < 55 years were identified as risk factors (Table 2B). Furthermore, patients with a BMI of ≥ 18.5 tend to experience higher levels of all-grade T-APS, but with no statistical significance

established.

3. Incidence and severity of T-APS between taxane-containing regimens

Additionally, we evaluated the incidence and severity of T-APS between docetaxel-containing regimens and a paclitaxel-containing regimen (Table 3). Accordingly, the incidence of ≥G2 and all-grade T-APS were 22.0% and 68.2% in docetaxel-including regimens, and 45.5% and 81.8% in dose-dense paclitaxel, respectively, tending to be higher in paclitaxel therapy, with no statistically significant differences detected. Furthermore, as all paclitaxel-administered patients received pegfilgrastim, we also assessed the incidence of pain between both taxane-containing regimens in pegfilgrastim administered patients. Incidence of ≥G2 and all-grade T-APS was 33.3% and 85.2% in docetaxel-containing regimens, and 45.5% and 81.8% in a paclitaxel regimen, respectively, with no statistically significant differences.

Discussion

The management of T-APS is an important therapeutic goal as T-APS significantly decreases the patient's QOL, and could result in dose reduction during taxane therapy. Owing to substantially complicated underlying mechanisms, multidirectional strategies in the prevention or handling of breakthrough symptoms are necessary. We have

previously reported that prophylaxis with DEX is an effective strategy to attenuate T-APS [7]. Herein, we evaluated the risk factor(s) for T-APS incidence under prophylactic DEX administration.

In the present study, the incidence of all-grade T-APS was confirmed in approximately 70% of patients, whereas ≥G2 T-APS was observed in 23.8% of patients. The reported incidence of T-APS varied between taxanes: paclitaxel (median 13.1 %, range 0.9–86%), docetaxel (median 10.5 %, range 3.6–70%), and nab-paclitaxel (26 %, range 14–43%) [10]. The underlying reasons for the observed variability in incidence are considered to be multi-factorial and reflect differences between taxanes, doses employed, combination regimens, patient populations, variability in the co-administered supportive care treatments that can themselves cause myalgias (e.g., G-CSF), and endpoints. In previous investigations that evaluated T-APS as the primary endpoint, the incidence of T-APS is reported as approximately 60–90% [7, 8, 18, 20, 22, 23], and that of ≥G2 T-APS is 33–65% [7, 18, 20]. As T-APS also appears to be more frequent in patients with breast cancer than in those with prostate, lung, or ovarian cancer [10], the results obtained in the current study seem to be similar in incidence, and milder in severity when compared with these reports. The results of our previous study revealed an attenuating effect of DEX administration on T-APS, and this study supports these results.

Reportedly, risk factors for T-APS include the drug dose [18], metastatic setting, and breast cancer [10]. Additionally, paclitaxel is known to substantially enhance T-APS when compared with other taxanes [10]. In this study, co-administration of pegfilgrastim was revealed as an independent risk factor of ≥G2 and all-grade T-APS incidence with DEX prophylaxis. Pegfilgrastim is frequently used for primary prophylaxis against febrile neutropenia (FN) [24–27]. The American Society of Clinical Oncology (ASCO) guidelines recommend its routine administration from the first cycle of myelosuppressive chemotherapy, in which the risk of developing FN is approximately 20% or higher [28]. TC and dose-dense paclitaxel therapy absolutely, as well as docetaxel after anthracycline-containing regimens depending on patient's risk, meet the definition of preventive pegfilgrastim therapy [29–31]. Its typical adverse effect is pain, which appears in 20–70% of the patients [32, 33]. Kosaka et al. have reported that patients experience 24.9% arthralgia, 12.1% myalgia, and 14.5% back pain following pegfilgrastim administration in TC therapy [34]. Moreover, the appearance of this pain syndrome is greatly increased during the first chemotherapy cycle and decreases in subsequent cycles [32, 33], with independent risk factors reported as younger patients, breast cancer, previous history of bone pain, and taxane co-administration [35–37]. In contrast, Gavioli et al. have reported no factors involving

pegfilgrastim-induced pain [38]. Therefore, a uniform consensus remains to be established [33].

The mechanism underlying pegfilgrastim-induced pain has not been comprehensively elucidated but could be attributed to bone marrow quantitative and qualitative expansion similar to that observed during some pathological conditions [32, 39]. It is speculated that T-APS and G-CSF-induced pain can potently interact additively and synergistically owing to their differing mechanisms. Effective management of G-CSF-induced pain involves the administration of NSAIDs, antihistamines, and opioids [32, 33], which is similar to T-APS management. In particular, management using NSAIDs has effectively reduced the incidence and duration of pegfilgrastim-induced bone pain, and it has been employed in clinical settings [40]. G-CSF may enhance the inflammatory response, resulting in an increased histamine level [32]. The increase in the histamine level can cause nociceptive pain mediated by c-fibers and neuropathic pain, as well as increased edema formation within bone, which leads to the pain [32]. Therefore, prophylaxis using NSAIDs and/or antihistamines in addition to DEX administration may attenuate these symptoms; however, further studies are needed to analyze this.

Younger age was also detected as a risk factor of all-grade T-APS incidence. This is the first report indicating that younger patients are at a greater risk to develop T-APS, and

this result is consistent with previous reports regarding pegfilgrastim-induced pain [35-37]. Xu et al. have postulated that the underlying reason for this observation, although unclear, may be related to the differences in bone and bone marrow architecture (e.g., with aging, red marrow is increasingly converted to fatty marrow), with younger patients experiencing more pain secondary to acute bone marrow expansion. Furthermore, a review of studies evaluating age-related differences in pain perception and complaints has revealed a lower frequency and intensity of musculoskeletal-related pain symptoms in older adults when compared with younger adults [32, 36, 41]; this result might partially be attributed to pegfilgrastim-induced pain.

We should remain cautious of the risks of T-APS development in the patients with risk factors described above, as almost all taxane treatments are conducted on an outpatient basis. Furthermore, it is necessary to consider the site, duration, and severity of symptoms in patients according to a previous report [15]. Moreover, medication support by additional per-request analgesic drugs, apart from prophylaxis using corticosteroids, Shakuyaku-Kanzo-To, and gabapentin, would be effective.

As paclitaxel is reportedly associated with a higher incidence of T-APS when compared with other taxanes [10], we additionally evaluated the incidence of T-APS

between docetaxel-containing and paclitaxel-including regimens. Accordingly, the incidence of ≥G2 and all-grade T-APS did not statistically differ between the regimens. Moreover, T-APS similarly occurred in both taxane-including treatments as in pegfilgrastim administered patients. Based on these results, we could speculate that both taxanes can induce nearly equivalent T-APS, although further comparative study is needed to verify this.

We have previously reported that DEX administration (8 mg) on days 2 and 3 attenuated T-APS [7]. However, in the present study, no difference in ≥G2 and all-grade T-APS incidence was observed between 4 mg and 8 mg of DEX on days 2-4. As high-dose steroid therapy induces adverse effects such as blood glucose elevation or insomnia, lower-dose and/or shorter-duration DEX administration for prophylaxis is suitable. Further studies are needed to elucidate the ideal DEX dosing for T-APS prevention.

There are some limitations in evaluating risk factors for T-APS under prophylactic DEX administration. First, this study was retrospective in nature and employed a relatively small patient population from a single institution. Although we tried to exclude the patients with inadequate medical records, the accuracy of the T-APS incidence and severity may be decreased, as it has been reported that symptom

evaluation by medical personnel differs from that by patients suffering from chemotherapy-induced nausea and vomiting [42, 43]. Therefore, it is necessary to conduct a large-scale, randomized, prospective, multicenter study to confirm these results. Moreover, it is better to use a subjective assessment by patients, such as the visual analogue scale (VAS) or numerical rating scale (NRS) rather than a physician-based or pharmacist-based evaluation. Second, as almost all patients in this study were female, a study including more-balanced patient groups will provide further benefits. Finally, we evaluated the risk factors for T-APS during the first chemotherapy course, but it is crucial to evaluate these factors throughout multiple chemotherapy courses.

In conclusion, the results of our study suggest that pegfilgrastim co-administration is an independent risk factor of ≥G2 and all-grade T-APS, and age younger than 55 years is a risk factor of all-grade T-APS during prophylactic DEX administration. Understanding the nature of T-APS and further prophylaxis could significantly contribute to its management; therefore, further studies are warranted for improved T-APS management.

Compliance with Ethical Standards

Disclosure of potential conflicts of interest

Funding: None.

Conflict of Interest: The authors have no conflict of interest.

Ethical approval: All the procedures performed in studies involving human participants were carried out in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

Consent to participate: For this type of study, formal consent is not required.

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' contributions:

Participated in research design: YS, TY, TS, and MK.

Conducted experiments: YS and TS.

Performed data analysis: YS and TS.

Wrote or contributed to the writing of the manuscript: YS, TY, MK, TS, HY, and MS.

References

1. Peto R, Davies C, Godwin J, Gray R, Pan HC, Clarke M, et al (2012) Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. *Lancet* **379**:432–444
2. De Laurentiis M, Cancello G, D'Agostino D, Giuliano M, Giordano A, Montagna E et al (2008) Taxane-based combinations as adjuvant chemotherapy of early breast cancer: a meta-analysis of randomized trials. *J Clin Oncol* **26**:44–53
3. Kramer JA, Curran D, Piccart M, de Haes JC, Bruning PF, Klijn JG et al (2000) Randomised trial of paclitaxel versus doxorubicin as first-line chemotherapy for advanced breast cancer: quality of life evaluation using the EORTC QLQ-C30 and the Rotterdam symptom checklist. *Eur J Cancer* **36**:1488–1497
4. Katsumata N, Watanabe T, Minami H, Aogi K, Tabei T, Sano M et al (2009) Phase III trial of doxorubicin plus cyclophosphamide (AC), docetaxel, and alternating AC and docetaxel as front-line chemotherapy for metastatic breast cancer: Japan Clinical Oncology Group trial (JCOG9802). *Ann Oncol* **20**:1210–1215
5. Sledge GW, Neuberg D, Bernardo P, Ingle JN, Martino S, Rowinsky EK et al (2003) Phase III trial of doxorubicin, paclitaxel, and the combination of doxorubicin and

paclitaxel as front-line chemotherapy for metastatic breast cancer: an intergroup trial (E1193). *J Clin Oncol* **21**:588–592

6. Megerdichian C, Olimpiadi Y, Hurvitz SA (2014) nab-Paclitaxel in combination with biologically targeted agents for early and metastatic breast cancer. *Cancer Treat Rev* **40**:614–625

7. Saito Y, Kobayashi M, Yamada T, Sakakibara-Konishi J, Shinagawa N, Kinoshita I et al (2020) Efficacy of additional dexamethasone administration for the attenuation of paclitaxel-associated acute pain syndrome. *Support Care Cancer* **28**:221–227

8. Chiu N, Zhang L, Dent R, Giotis A, van Draanen J, Gallo-Hershberg D et al (2018) A prospective study of docetaxel-associated pain syndrome. *Support Care Cancer* **26**:203–211

9. Fernandes R, Mazzarello S, Majeed H, Smith S, Shorr R, Hutton B et al (2016) Treatment of taxane acute pain syndrome (TAPS) in cancer patients receiving taxane-based chemotherapy-a systematic review. *Support Care Cancer* **24**:1583–1594

10. Fernandes R, Mazzarello S, Hutton B, Shorr R, Majeed H, Ibrahim MF et al (2016) Taxane acute pain syndrome (TAPS) in patients receiving taxane-based chemotherapy for breast cancer-a systematic review. *Support Care Cancer*

24:3633–3650

11. Kunitoh H, Saijo N, Furuse K, Noda K, Ogawa M (1998) Neuromuscular toxicities of paclitaxel 210 mg m(-2) by 3-hour infusion. *Br J Cancer* **77**:1686–1688

12. Rowinsky EK, Eisenhauer EA, Chaudhry V, Arbuck SG, Donehower RC (1993) Clinical toxicities encountered with paclitaxel (Taxol). *Semin Oncol* **20**:1–15

13. Loprinzi CL, Reeves BN, Dakhil SR, Sloan JA, Wolf SL, Burger KN et al (2011) Natural history of paclitaxel-associated acute pain syndrome: prospective cohort study NCCTG N08C1. *J Clin Oncol* **29**:1472–1478

14. Reeves BN, Dakhil SR, Sloan JA, Wolf SL, Burger KN, Kamal A et al (2012) Further data supporting that paclitaxel-associated acute pain syndrome is associated with development of peripheral neuropathy: North Central Cancer Treatment Group trial N08C1. *Cancer* **118**:5171–5178

15. Asthana R, Zhang L, Wan BA, Gallo-Hershberg D, Giotis A, Pasetka M et al (2020) Pain descriptors of taxane acute pain syndrome (TAPS) in breast cancer patients-a prospective clinical study. *Support Care Cancer* **28**:589–598

16. Ren K, Dubner R (2010) Interactions between the immune and nervous systems in pain. *Nat Med* **16**:1267–1276

17. Ueda H (2006) Molecular mechanisms of neuropathic painphenotypic switch and

initiation mechanisms. *Pharmacol Ther* **109**:57–77

18. Kanbayashi Y, Sakaguchi K, Nakatsukasa K, Ouchi Y, Tabuchi Y, Yoshioka T et al (2019) Predictive factors for taxane acute pain syndrome determined by ordered logistic regression analysis. *Support Care Cancer* **27**:2673–2677

19. Markman M, Kennedy A, Webster K, Kulp B, Peterson G, Belinson J (1999) Use of low-dose oral prednisone to prevent paclitaxel-induced arthralgias and myalgias. *Gynecol Oncol* **72**:100–101

20. Yoshida T, Sawa T, Ishiguro T, Horiba A, Minatoguchi S, Fujiwara H (2009) The efficacy of prophylactic Shakuyaku-Kanzo-to for myalgia and arthralgia following carboplatin and paclitaxel combination chemotherapy for non-small cell lung cancer. *Support Care Cancer* **17**:315–320

21. Nguyen VH, Lawrence HJ (2004) Use of gabapentin in the prevention of taxane-induced arthralgias and myalgias. *J Clin Oncol* **22**:1767–1769

22. Chiu N, Chiu L, Chow R, Lam H, Verma S, Pasetka M et al (2017) Taxane-induced arthralgia and myalgia: a literature review. *J Oncol Pharm Pract* **23**:56–67

23. Jacobson SD, Loprinzi CL, Sloan JA, Wilke JL, Novotny PJ, Okuno SH et al (2003) Glutamine does not prevent paclitaxel-associated myalgias and arthralgias. *J Support Oncol* **1**:274–278

24. Vogel CL, Wojtukiewicz MZ, Carroll RR, Tjulandin SA, Barajas-Figueroa LJ, Wiens BL et al (2005) First and subsequent cycle use of pegfilgrastim prevents febrile neutropenia in patients with breast cancer: a multicenter, double-blind, placebo-controlled phase III study. *J Clin Oncol* **23**:1178–1184

25. Balducci L, Al-Halawani H, Charu V, Tam J, Shahin S, Dreiling L et al (2007) Elderly cancer patients receiving chemotherapy benefit from first-cycle pegfilgrastim. *Oncologist* **12**:1416–1424

26. Pinto L, Liu Z, Doan Q, Bernal M, Dubois R, Lyman G (2007) Comparison of pegfilgrastim with filgrastim on febrile neutropenia, grade IV neutropenia and bone pain: a meta-analysis of randomized controlled trials. *Curr Med Res Opin* **23**:2283–2295

27. Cooper KL, Madan J, Whyte S, Stevenson MD, Akehurst RL (2011) Granulocyte colony-stimulating factors for febrile neutropenia prophylaxis following chemotherapy: systematic review and meta-analysis. *BMC Cancer* **11**:404

28. Smith TJ, Bohlke K, Lyman GH, Carson KR, Crawford J, Cross SJ et al (2015) Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol* **33**:3199–3212

29. Sparano JA, Wang M, Martino S, Jones V, Perez EA, Saphner T et al (2008)

Weekly paclitaxel in the adjuvant treatment of breast cancer. *N Engl J Med* **358**:1663–1671

30. Citron ML, Berry DA, Cirrincione C, Hudis C, Winer EP, Gradishar WJ et al (2003) Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. *J Clin Oncol* **21**:1431–1439
31. Jones SE, Savin MA, Holmes FA, O'Shaughnessy JA, Blum JL, Vukelja S et al (2006) Phase III trial comparing doxorubicin plus cyclophosphamide with docetaxel plus cyclophosphamide as adjuvant therapy for operable breast cancer. *J Clin Oncol* **24**:5381–5387
32. Lambertini M, Del Mastro L, Bellodi A, Pronzato P (2014) The five "Ws" for bone pain due to the administration of granulocyte-colony stimulating factors (G-CSFs). *Crit Rev Oncol Hematol* **89**:112–128
33. Moore DC, Pellegrino AE (2017) Pegfilgrastim-Induced Bone Pain: A Review on Incidence, Risk Factors, and Evidence-Based Management. *Ann Pharmacother* **51**:797–803
34. Kosaka Y, Rai Y, Masuda N, Takano T, Saeki T, Nakamura S et al (2015) Phase III

placebo-controlled, double-blind, randomized trial of pegfilgrastim to reduce the risk of febrile neutropenia in breast cancer patients receiving docetaxel/cyclophosphamide chemotherapy. *Support Care Cancer* **23**:1137–4311

35. Gregory SA, Schwartzberg LS, Mo M, Sierra J, Vogel C (2010) Evaluation of reported bone pain in cancer patients receiving chemotherapy in pegfilgrastim clinical trials: a retrospective analysis. *Comm Oncol* **7**:297–308
36. Xu H, Gong Q, Vogl FD, Reiner M, Page JH (2016) Risk factors for bone pain among patients with cancer receiving myelosuppressive chemotherapy and pegfilgrastim. *Support Care Cancer* **24**:723–730
37. Moukharskaya J, Abrams DM, Ashikaga T, Khan F, Schwartz J, Wilson K et al (2016) Randomized phase II study of loratadine for the prevention of bone pain caused by pegfilgrastim. *Support Care Cancer* **24**:3085–3093
38. Gavioli E, Abrams M (2017) Prevention of granulocyte-colony stimulating factor (G-CSF) induced bone pain using double histamine blockade. *Support Care Cancer* **25**:817–822
39. Metcalf D (2010) The colony-stimulating factors and cancer. *Nat Rev Cancer* **10**:425–434
40. Kirshner JJ, Heckler CE, Janelsins MC, Dakhil SR, Hopkins JO, Coles C et al

(2012) Prevention of pegfilgrastim-induced bone pain: a phase III double-blind placebo-controlled randomized clinical trial of the university of rochester cancer center clinical community oncology program research base. *J Clin Oncol* **30**:1974–1979

41. Gibson SJ, Helme RD (2001) Age-related differences in pain perception and report. *Clin Geriatr Med* **17**:433–456

42. Tamura K, Aiba K, Saeki T, Nakanishi Y, Kamura T, Baba H et al (2015) Testing the effectiveness of antiemetic guidelines: results of a prospective registry by the CINV Study Group of Japan. *Int J Clin Oncol* **20**: 855-865

43. Majem M, Moreno ME, Calvo N, Feliu A, Pérez J, Mangues MA (2011) Perception of healthcare providers versus patient reported incidence of chemotherapy-induced nausea and vomiting after the addition of NK-1 receptor antagonists. *Support Care Cancer* **19**:1983-1990

Table 1 Patient characteristics

Sex (male/female)	1/142
Age (median, range)	52 (21–71)
Performance status	
0-1	143
Staging	
1-3	131
4	8
Recurrence	4
Treatment setting	
Adjuvant	67
Neoadjuvant	65
Metastatic	11
Treatment line	
First-line	32
Second or later line	111
Histology	
ER-positive, PR-positive, or both	80
HER2 overexpression	47
Ki-67 (%) (median, range)	39.3 (1.3–97.6)
Bone metastasis	3
BSA (m^2) (median, range)	1.55 (1.31–2.00)
BMI (kg/m^2) (median, range)	22.7 (16.3–37.5)
Liver dysfunction	6
Renal dysfunction	6
Treatment regimen	
Docetaxel	78
Docetaxel + trastuzumab	26
Docetaxel + cyclophosphamide	16
Docetaxel + trastuzumab + pertuzumab	12
Dose-dense paclitaxel	11
Dose of oral dexamethasone on days 2–4	
4 mg	79
8 mg	64
Administration of pegfilgrastim	38

Liver dysfunction: grade 2 or higher aspartate aminotransferase, alanine aminotransferase, γ-glutamyltransferase, total bilirubin elevation.
Renal dysfunction: grade 1 or higher serum creatinine elevation.

ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; BSA, body surface area; BMI, body mass index.

Table 2 Univariate and multivariate analyses for risk factors associated with the frequency of (A) ≥G2 T-APS and (B) all-grade T-APS

(A)		Univariate analysis		Multivariate analysis	
	≥G2 T-APS frequency (n, %)	Odds ratio (95% CI)	*P*-value	Odds ratio (95% CI)	*P*-value
Age (years)					
≥ 55	11 (18.3%)				
< 55	23 (27.7%)	0.59 (0.26–1.32)	0.20	Excluded	-
Treatment setting					
Metastatic	2 (18.2%)				
Others	32 (24.2%)	0.69 (0.14–3.38)	0.65	Excluded	-
Treatment line					
First-line	4 (12.5%)				
Second or later line	30 (27.0%)	0.39 (0.12–1.19)	0.10	0.40 (0.13–1.25)	0.11
Hormonal receptors					
ER, PR-positive or both	21 (26.3%)				
Negative	13 (20.6%)	1.37 (0.62–3.01)	0.43	Excluded	-
HER2 overexpression					
Positive	12 (25.5%)				
Negative	22 (22.9%)	1.15 (0.51–2.59)	0.73	Excluded	-
BMI (kg/m^2)					
≥ 18.5	33 (25.0%)				

< 18.5	1 (9.1%)	3.33 (0.41–27.0)	0.26	Excluded	-
Liver dysfunction					
Present	3 (50.0%)				
Absent	31 (22.6%)	3.42 (0.66–17.80)	0.14	Excluded	-
Renal dysfunction					
Present	2 (33.3%)				
Absent	32 (23.4%)	1.64 (0.29–9.37)	0.58	Excluded	-
Dexamethasone dose					
4 mg	20 (25.3%)				
8 mg	14 (21.9%)	1.21 (0.55–2.64)	0.63	Excluded	-
Administration of pegfilgrastim					
Present	14 (36.8%)				
Absent	20 (19.0%)	2.45 (1.09–5.63)	0.03*	2.42 (1.06–5.54)	0.04*

*P <0.05

ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; BMI, body mass index.

Liver dysfunction: grade 2 or higher aspartate aminotransferase, alanine aminotransferase, γ-glutamyltransferase, total bilirubin elevation

Renal dysfunction: grade 1 or higher serum creatinine elevation

(B)		Univariate analysis		Multivariate analysis	
	T-APS frequency (n, %)	Odds ratio (95% CI)	*P*-value	Odds ratio (95% CI)	*P*-value
Age (years)					
< 55	64 (77.1%)				
≥ 55	35 (58.3%)	2.41 (1.17–4.97)	0.018*	2.41 (1.13–5.10)	0.02*
Treatment setting					
Metastatic	8 (72.7%)				
Others	91 (68.9%)	1.20 (0.30–4.76)	0.79	Excluded	-
Treatment line					
First-line	25 (78.1%)				
Second or later line	74 (66.7%)	1.79 (0.71–4.51)	0.22	Excluded	-
Hormonal receptors					
ER, PR-positive or both	58 (72.5%)				
Negative	41 (65.1%)	1.41 (0.69–2.89)	0.34	Excluded	-
HER2 overexpression					
Positive	32 (68.1%)				
Negative	67 (69.8%)	0.92 (0.44–1.96)	0.84	Excluded	-
BMI (kg/m^2)					
≥ 18.5	94 (71.2%)				
< 18.5	5 (45.5%)	2.97 (0.85–10.30)	0.09	3.52 (0.94–13.14)	0.06
Liver dysfunction					
Present	5 (83.3%)				
Absent	94 (68.6%)	2.29 (0.26–20.20)	0.46	Excluded	-

Renal dysfunction					
Present	4 (66.7%)				
Absent	95 (69.3%)	0.88 (0.16–5.02)	0.89	Excluded	-
Dexamethasone dose					
4 mg	56 (70.9%)				
8 mg	43 (67.2%)	1.19 (0.58–2.42)	0.63	Excluded	-
Administration of pegfilgrastim					
Present	32 (84.2%)				
Absent	67 (63.8%)	3.02 (1.16–7.89)	0.02*	2.96 (1.10–7.94)	0.03*

*P <0.05

ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; BMI, body mass index.

Liver dysfunction: grade 2 or higher aspartate aminotransferase, alanine aminotransferase, γ-glutamyltransferase, total bilirubin elevation

Renal dysfunction: grade 1 or higher serum creatinine elevation

Table 3 Comparison of T-APS incidence between docetaxel and paclitaxel-containing regimens

	Docetaxel-containing regimens	Paclitaxel-containing regimen	*P*-value
All patients			
Patient number	132	11	
Incidence of ≥G2 T-APS	29 (22.0%)	5 (45.5%)	0.13
Incidence of all-grade T-APS	90 (68.2%)	9 (81.8%)	0.50
Patients administered pegfilgrastim			
Patient number	27	11	
Incidence of ≥G2 T-APS	9 (33.3%)	5 (45.5%)	0.71
Incidence of all-grade T-APS	23 (85.2%)	9 (81.8%)	1.00

T-APS, Taxane-associated acute pain syndrome.

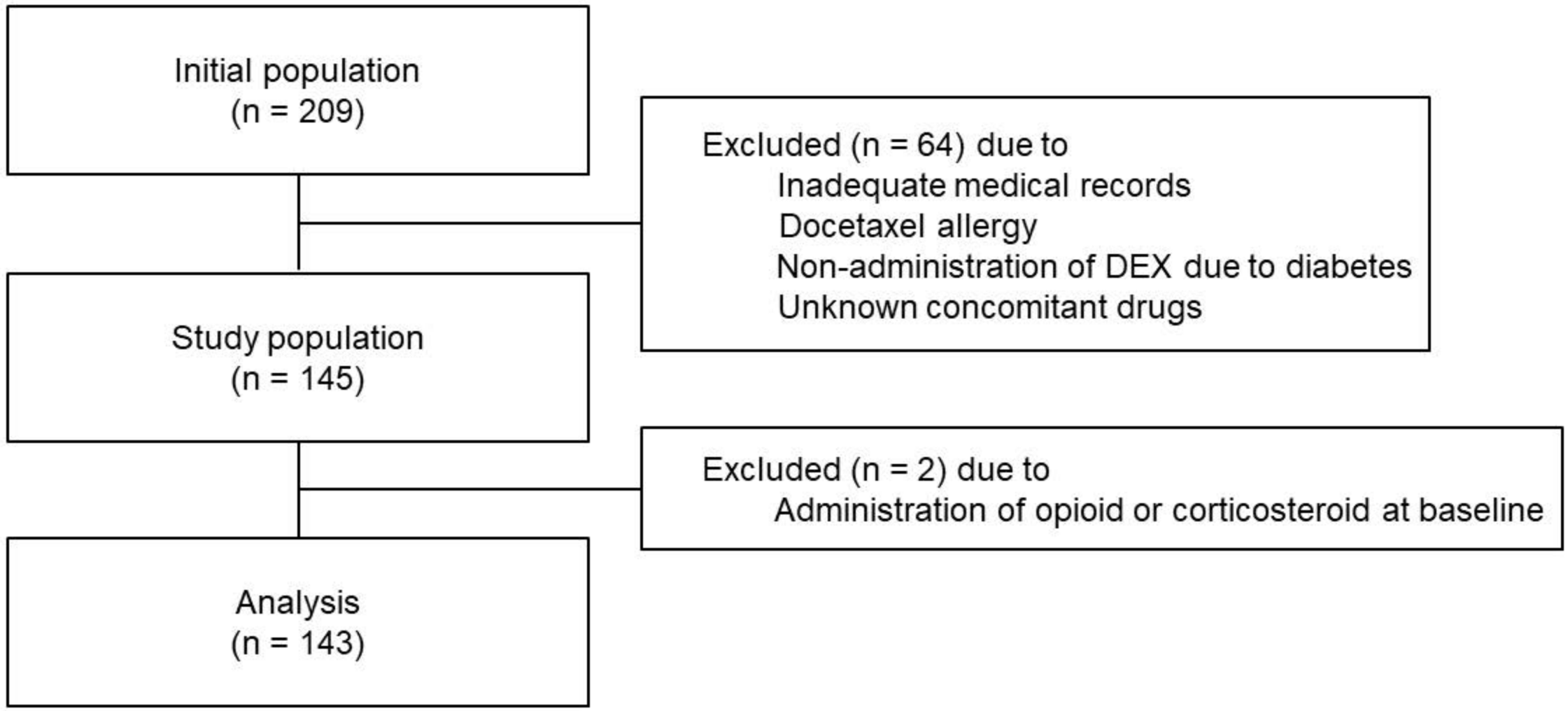
Figure captions

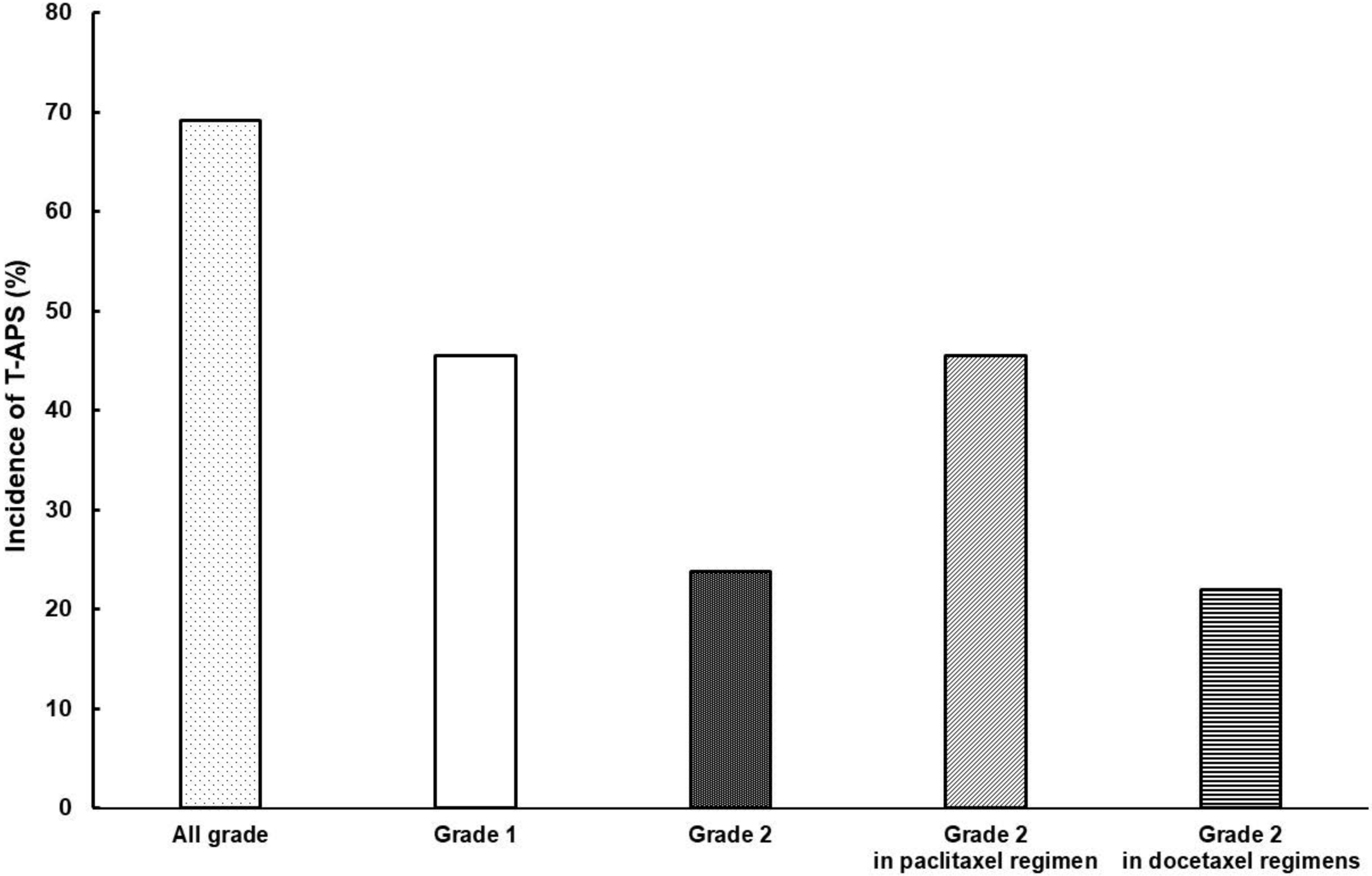
Fig. 1. Study design

DEX, dexamethasone.

Fig. 2. Incidence and severity of T-APS

T-APS, taxane-associated acute pain syndrome.


Initial population
(n = 209)
Excluded (n = 64) due to
Inadequate medical records
Docetaxel allergy
Non-administration of DEX due to diabetes
Unknown concomitant drugs
Study population
(n = 145)
Excluded (n = 2) due to
Administration of opioid or corticosteroid at baseline
Analysis
(n = 143)


80
70
60
50
40
30
20
10
0
Incidence of T-APS (%)
All grade
Grade 1
Grade 2
Grade 2
in paclitaxel regimen
Grade 2
in docetaxel regimens