Original Article

Dexamethasone dose-dependently prevents taxane-associated acute pain syndrome in breast cancer treatment

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ABSTRACT

Purpose

Taxane-associated acute pain syndrome (T-APS) is one of the most bothersome adverse effects caused by taxanes. We have previously reported the attenuating effect of dexamethasone (DEX) on T-APS and its risk factors under DEX prophylaxis. However, the appropriate DEX dosage administration remains unclear. Therefore, this study aimed to investigate whether DEX dose-dependently prevents T-APS in breast cancer patients.

Methods

We retrospectively evaluated patients with breast cancer who received docetaxel (75 mg/m^2)-containing chemotherapy without pegfilgrastim and regular non-steroidal anti-inflammatory drugs. The patients were divided into 4 mg/day and 8 mg/day DEX groups, with each DEX dosage on days 2–4 (n=68 for each group). Primary endpoint was the comparison of all-grade T-APS incidence between the groups. Propensity score-matching was performed to adjust the baseline factors between the groups, and outcomes in the matched-population were also assessed.

Results

The incidence of all-grade T-APS was 72.1% in 4 mg/day group and 48.5% in 8 mg/day group, which was significantly lowered by higher DEX dosage (P=0.008). The severity of T-APS was also significantly reduced in 8 mg/day group (P=0.02). These results were confirmed in the propensity score matching. Multivariate

logistic analysis showed that higher DEX dosage was an independent T-APS preventive factor, whereas age <55 years was a risk factor. Moreover, DEX-dosage-associated adverse effects similarly appeared in both groups.

Conclusion

Our study suggested that DEX dose-dependently prevents T-APS in breast cancer treatment. As understanding of the nature of T-APS and its appropriate management can significantly contribute to less onerous chemotherapy provision, further studies are required.

Key words: taxane-associated acute pain syndrome; docetaxel; dexamethasone; dose-dependent; arthralgia; myalgia.

Introduction

Taxane-associated acute pain syndrome (T-APS) is one of the most troublesome adverse effects caused by taxanes, such as docetaxel, paclitaxel, and nanoparticle albumin-bound paclitaxel [1–3], used in the treatment of breast cancer [4–9]. Symptoms such as arthralgia and myalgia appear 1 to 3 days after taxane administration and continue for a week in 60–90% of taxane-administered patients [1–3, 10–14], significantly reducing their quality of life (QOL) and activities of daily living (ADL).

Although the mechanisms associated with T-APS occurrence are still unclear, T-APS is thought to be related to nerve inflammation and injury, as well as nociceptor sensitization [1–3, 14]. Moreover, a recent study has described the association between T-APS and chemotherapy-induced peripheral neuropathy [15], suggesting that its mechanisms are quite complicated.

Factors such as high taxane dose, paclitaxel, metastatic setting, breast cancer, younger age, and co-administration of pegfilgrastim influence T-APS occurrence [3, 11, 16], whereas corticosteroids, Shakuyaku-Kanzo-To, and gabapentin have been suggested to have T-APS preventive or attenuating effects [1, 16–19]. Additionally, a recent study has shown the preventive effect of non-steroidal anti-inflammatory drugs (NSAIDs) against T-APS [20]. Even though we have previously shown that the additional administration of dexamethasone (DEX) on day 2 and day 3 of taxane-containing chemotherapy attenuates T-APS [1], the most suitable dose of DEX for T-APS prevention is still unknown. In our previous evaluation regarding T-APS-associated risk factors, DEX dosage (4 mg or 8 mg) was not associated with T-APS incidence; however, the patients who received pegfilgrastim and paclitaxel, which influence T-APS occurrence [3, 11], were significantly more included in the higher DEX dosage

group [3]. Therefore, the assessment of DEX dosage in the study was insufficient, considering the confounding factors and poor statistical power. As DEX administration can induce adverse effects such as blood sugar elevation, insomnia, reduced bone mineral densities, and increased susceptibility to infection, especially to pneumocystis pneumonia (PCP) [21, 22], additional evaluation regarding the appropriate DEX dosage administration is required.

Therefore, this study aimed to investigate whether DEX can be used dose-dependently to prevent T-APS in breast cancer patients.

Methods

1. Patients

Patients with breast cancer who received docetaxel (75 mg/m^2)-containing chemotherapy from November 2013 to August 2022 were enrolled in this retrospective study (Figure 1). All enrolled patients met the following baseline criteria: age ≥20 years; 0 to 1 Eastern Cooperative Oncology Group performance status (ECOG-PS); sufficient renal or liver function for treatment induction; and sufficient medical records. Based on previous reports [1, 3, 20], patients who were co-administered pegfilgrastim, regularly administered corticosteroids, analgesics, such as NSAIDs, acetaminophen, tramadol, or opioids, Shakuyaku-Kanzo-To, and gabapentin were excluded. The included patients were divided into two groups, namely: the 4 mg/day group, constituting patients who were administered oral 4 mg DEX on days 2–4 between November 2013 and April 2018, and the 8 mg/day group, constituting those who were dosed oral 8 mg DEX on days 2–4 between July 2017 and August 2022. We

hypothesized that all-grade T-APS incidence would be 70% in the 4 mg DEX group and 45% in the 8 mg DEX group, based on our previous evaluation and clinical experience [3]. To achieve 80% power with an alpha error of 5%, 68 patients who met the eligibility criteria were included per group.

This study was approved by the Ethical Review Board for Life Science and Medical Research of the Hokkaido University Hospital (approval number: 022-0139) and was performed in accordance with the Declaration of Helsinki and the STROBE statement. Owing to the retrospective nature of the study, informed consent was waived by the committee.

2. Treatment methods

Docetaxel 75 mg/m^2 was intravenously administered for 1 h. Trastuzumab (8 mg/kg at first administration and 6 mg/kg at subsequent administrations) ± pertuzumab (840 mg at first administration and 420 mg at subsequent administrations) were co-administered in patients with breast cancer having overexpressed human epidermal growth factor receptor-2 (HER2). Granisetron 3 mg with 6.6 mg of DEX for the 4 mg group or 9.9 mg for the 8 mg group were intravenously administered in the case of those receiving docetaxel + cyclophosphamide 600 mg/m^2 (TC), and DEX 6.6 mg was intravenously administered in patients receiving other docetaxel-containing regimens as premedication. Furthermore, oral DEX was administered on days 2–4, as previously described. Analgesic drugs such as NSAIDs, acetaminophen, and tramadol were administered to ameliorate T-APS, according to the attending physician's discretion.

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

All required information was extracted from patients' medical records. Myalgia and arthralgia appearing within a

week following docetaxel administration were defined as T-APS, and its incidence and severity in the first cycle were retrospectively evaluated in accordance with the Common Terminology Criteria for Adverse Events version 5.0, as well as our previous study [1, 3]. In the present study, the primary endpoint was the comparison of all-grade T-APS incidence between the groups, and the secondary endpoints included the assessment of T-APS severity, risk factor(s) for the incidence of all-grade T-APS, and safety. Propensity score-matching was performed to adjust the baseline factors between the two groups, and matched data were additionally analyzed to confirm the robustness of the all-patient population analysis.

4. Statistical analysis

The differences in baseline patient characteristics were compared using Fisher's exact probability test for the categorical outcome variables and the Mann-Whitney *U* test for the continuous parameters. The incidence of T-APS or other adverse effects was assessed using Fisher's exact probability method, and the severity of T-APS was evaluated using the Mann-Whitney *U* test. The univariate and multivariate analyses using logistic regression analysis were carried out to find the independent risk factor(s) for the incidence of all-grade T-APS, using the following covariates: age, sex, clinical staging, prior treatment existence, hormonal receptors expression, HER2 overexpression, body surface area (BSA), body mass index (BMI), liver dysfunction (grade 1 or higher aspartate aminotransferase, alanine aminotransferase, total bilirubin elevation), renal dysfunction (creatinine clearance [CCr] calculated by Cockcroft-Gault formula of less than 80 mL/min), hypoalbuminemia, regular alcohol intake (≥5 days in a week), smoking history at baseline, and DEX dose administered on days 2–4 by reference to previous reports [3, 11, 16]. Variables that demonstrated potential associations with the incidence in univariate

logistic regression analysis ($P<0.20$) were considered when building the multivariable model. Propensity score-matching was performed using the following variables: age, sex, clinical staging, prior treatment existence, hormonal receptors expression, HER2 overexpression, BSA, BMI, liver dysfunction, CCr, serum albumin, regular alcohol intake, smoking history, and the existence of bone metastasis. To reduce bias with these potential confounding factors, 1:1 matching (without replacement) in the two groups was performed using the nearest neighbor method with a 0.20-width caliper of the standard deviation of the logit of propensity scores.

All analyses were performed using JMP version 16.2 statistical software (SAS Institute Japan, Tokyo, Japan). *P*-values of <0.05 were considered to be statistically significant.

Results

1. Patient characteristics

The baseline patient characteristics are shown in Table 1. In the all-patient population, there were no significant differences between the two groups in sex, ECOG-PS, staging, presence of prior treatment, hormonal receptor expression, HER2 overexpression, Ki-67, existence of bone metastasis, BSA, BMI, liver dysfunction, regular alcohol intake, and smoking history. In contrast, patients in the 8 mg DEX group were significantly older; however, patients <55 years old, who were suggested to be at higher risk for T-APS development, showed no statistically significant difference between the groups. Furthermore, CCr and serum albumin levels were significantly lower in those who received 8 mg/day of DEX. Notably, no background differences were confirmed between the groups in the propensity score-matched population.

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

The incidence and severity of T-APS during the first docetaxel cycle are shown in Figure 2. The incidence of all-grade T-APS was 72.1% in the 4 mg/day group and 48.5% in the 8 mg/day group, showing that it was significantly lowered by higher DEX dosage (P=0.008). The severity of T-APS was also significantly attenuated in the 8 mg/day group. These results were also confirmed in the propensity score-matching population. On further evaluations, univariate and multivariate logistic regression analyses showed that age <55 years was an independent T-APS risk factor, whereas higher DEX dosage was an independent preventive factor (Table 2).

3. Adverse effects related to DEX dosage

The results of DEX-dosage-associated adverse effects are shown in Table 3. The incidence of nausea, anorexia, fatigue, insomnia and febrile neutropenia (FN) was not different between the groups. In addition, there were no patients with grade 3/4 symptoms except FN. Furthermore, none of the patients developed PCP.

Discussion

T-APS can significantly decrease the QOL and ADL of patients, sometimes leading to taxane dose reduction. Prophylaxis is the most important T-APS management strategy, as most taxane-containing treatments are conducted on an outpatient basis. In our previous study, the evaluation of DEX dosages was insufficient due to confounders and poor power analysis [3]. Furthermore, considering DEX-induced adverse effects, it is imperative to assess the most suitable DEX dosage administration for proper T-APS management. Therefore, this study aimed to investigate which DEX dosage between 4 mg and 8 mg is superior for the prevention of T-APS.

From our results, 8 mg DEX administration on days 2–4 significantly decreased all-grade T-APS incidence compared to 4 mg DEX administration in all and propensity score-matching population, which met the primary endpoint of this study. Previous studies have suggested that the main mechanism of T-APS could be due to inflammation [1–3], and a study has also demonstrated that interleukin-1b is a crucial factor in the pathogenesis of T-APS [23]. Therefore, we consider that the potent anti-inflammatory effect of DEX prevented T-APS incidence. Moreover, this is the first study to show DEX dose-dependent preventive effects against T-APS.

Corticosteroid premedication reportedly prevents fluid retention caused by docetaxel, although the dosages and durations are varied (usually 8–16 mg/day of DEX for 3–5 days) [24–26]. The DEX dosage at our facility was increased from 4 mg/day to 8 mg/day in accordance with these aforementioned reports. We consider that an 8 mg dosage would be suitable for use because we are accustomed to the dosage used in antiemesis, and a higher dosage than 8 mg/day can induce stronger adverse effects, particularly infection. However, the suitable duration of prophylactic DEX administration remains unclear. Moreover, we also evaluated the incidence of DEX-associated adverse effects such as nausea, anorexia, fatigue, insomnia, FN, and PCP infection, which showed no difference between the groups. However, we could not evaluate these adverse effects in multiple administration cases, blood sugar elevation, and loss in bone density, as this was a short-term evaluation study. In addition, an association between T-APS and chemotherapy-induced peripheral neuropathy is reported, suggesting that its mechanisms are quite complicated [15]. Therefore, combination prophylaxis with other anti-inflammatory agents and/or anti-peripheral neuropathy medicines may be more effective. Likewise, the assessment of management methods used for breakthrough pain symptoms is also important. Consequently, further evaluations regarding suitable

DEX administration periods and multidirectional T-APS management strategies in longer assessment periods are needed.

The reported risk factors for T-APS include breast cancer, metastatic setting, and high taxane dose [11, 16]. Paclitaxel is known to substantially enhance T-APS when compared with other taxanes, which was in contrast with the findings of our previous study [3, 11]. Furthermore, we have also reported that patients whose ages are <55 years and with pegfilgrastim co-administration are at higher risk for T-APS development under DEX prophylaxis [3]. In this study, the factors related to docetaxel-induced T-APS were age <55 years and low DEX dosage. We have speculated that the results regarding younger patients might be due to pegfilgrastim co-administration [3]; however, the same result was obtained in the present study despite excluding pegfilgrastim-administered patients. Previous studies have reported a lower frequency and intensity of musculoskeletal-related pain symptoms in older adults compared with younger adults [27, 28], which might be due to the differential age-related changes in the structure and function of nociceptors sub-types and transmission pathways and a possible reduction in reaction time to mechanical stimuli [28]. Therefore, we should carefully monitor and prescribe analgesics for breakthrough pain with sufficient education for prompt T-APS treatment in younger patients.

This study has some limitations. First, this study was retrospective in nature and was conducted on a relatively small number of patients from a single institution. In addition, we assessed T-APS by referring to a treatment diary written by almost all the patients, although some of them listed the incidence of T-APS alone, and their individual complaints. Therefore, the severity of T-APS might not have been correctly evaluated. Consequently, it is

necessary to conduct a large-scale, randomized, prospective, multicenter study with subjective assessment by patients, such as the visual analog scale (VAS) or numerical rating scale (NRS), to confirm these results. Second, almost all patients in this study were female and relatively younger due to their breast cancer features. In fact, in our previous results in non-small cell lung cancer (NSCLC) patients receiving carboplatin + paclitaxel [1], 8 mg of DEX on days 2 and 3 did not affect the total T-APS incidence when compared with non-DEX administered patients, although it reduced ≥grade 2 symptoms, which was different from our present results. In this study, we consider primarily the breast cancer patient population, particularly the younger participant population than NSCLC, and the difference in targeted taxanes and DEX administration duration secondarily affected the difference [3, 11]. Third, in the all-patient population analysis, patients in the 8 mg/day group were significantly older than those in the 4 mg/day group, although those whose ages were <55 years showed no statistical difference between the groups. In addition, 8 mg/day DEX administered patients had significantly lower CCr and serum albumin levels than the 4 mg/day patients. However, the dose-dependent T-APS preventive effect by DEX was confirmed in the propensity score-matching population analysis. With regard to the above, evaluating well-balanced patients in an all-patient population analysis is desirable. Finally, we evaluated T-APS in the first cycle of 75 mg/m^2 docetaxel alone. Investigation with other taxanes, particularly paclitaxel, is necessary as it can induce more T-APS [11]. In addition, evaluation of DEX efficacy and safety in multiple administrations is needed for further clinical benefits.

In conclusion, our study suggested that DEX dose-dependently prevents T-APS in breast cancer treatment. Further studies on T-APS such as validation of our study results by a randomized trial should be encouraged, as

understanding the nature of T-APS and its appropriate management can significantly contribute to better chemotherapy provision with fewer and milder adverse effects.

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 and YT.

Conducted experiments: YS.

Performed data analysis: YS.

Wrote or contributed to the writing of the manuscript: YS, YT, TT, TO, and MS.

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Table 1. Patient characteristics

	All-patient analysis			Propensity-matched analysis		
	4 mg group	8 mg group	*P*-value	4 mg group	8 mg group	*P*-value
No. of patients	68	68		48	48	
Age (median, range)	51 (30–68)	55 (27–73)	0.01*	52 (32–67)	51 (27–73)	0.82
Patients <55 years old (n, %)	39 (57.4%)	31 (45.6%)	0.23	26 (54.2%)	31 (64.6%)	0.41
Sex (male/female)	1/67	2/66	1.00	0/48	1/47	1.00
Performance status 0-1	68	68	1.00	48	48	1.00
Staging (n, %)						
1-3	64 (94.1%)	58 (85.3%)		44 (91.7%)	46 (95.8%)	
4 or Recurrence	4 (5.9%)	10 (14.7%)	0.16	4 (8.3%)	2 (4.2%)	0.68
Prior treatment existence (n, %)	49 (72.1%)	55 (80.9%)	0.31	37 (77.1%)	39 (81.3%)	0.80
Histology (n, %)						
ER-positive, PR-positive, or both	36 (52.9%)	39 (57.4%)	0.73	22 (45.8%)	26 (54.2%)	0.54
HER2 overexpression	19 (27.9%)	23 (33.8%)	0.58	16 (33.3%)	15 (31.3%)	1.00
Ki-67 (%) (median, range)	40.2 (1.5–97.6)	45.2 (4.7–95.9)	0.81	44.1 (1.5–97.6)	44.8 (4.7–95.9)	0.98
Bone metastasis (n, %)	0 (0%)	3 (4.4%)	0.24	0 (0%)	0 (0%)	1.00
BSA (m^2) (median, range)	1.55 (1.31–1.96)	1.54 (1.30–2.00)	0.64	1.54 (1.36–1.96)	1.55 (1.30–2.00)	0.58
BMI (kg/m^2) (median, range)	22.0 (17.9–37.5)	23.5 (16.3–36.6)	0.13	21.6 (17.9–37.5)	23.2 (16.3–36.6)	0.21
Liver dysfunction (n, %)	37 (54.4%)	32 (47.1%)	0.49	24 (50.0%)	25 (52.1%)	1.00
CCr (mL/min) (median, range)	100.5 (49.7–211.4)	92.3 (60.2–223.2)	0.02*	94.8 (49.7–168.3)	96.8 (64.9–223.2)	0.92
Serum albumin (g/dL) (median, range)	4.1 (3.6–4.9)	4.0 (3.2 –4.9)	0.003**	4.1 (3.6–4.9)	4.1 (3.4 –4.9)	0.68
Patients with hypoalbuminemia (n, %)	17 (25.0%)	27 (39.7%)	0.10	16 (33.3%)	13 (27.1%)	0.66

Alcohol intake (≥5 days in a week) (n, %)	16 (23.5%)	8 (11.8%)	0.11	8 (16.7%)	6 (12.5%)	0.77
Smoking history (Former/Current) (n, %)	31 (45.6%)	34 (50.0%)	0.73	21 (43.8%)	21 (43.8%)	1.00
Current smoker	11 (16.2%)	14 (20.6%)	0.66	7 (14.6%)	10 (20.8%)	0.59
Treatment regimen (n, %)						
Docetaxel	42 (61.8%)	42 (61.8%)		28 (58.3%)	30 (62.5%)	
Docetaxel + trastuzumab	17 (25.0%)	5 (7.4%)		14 (29.2%)	4 (8.3%)	
Docetaxel + cyclophosphamide	7 (10.3%)	3 (4.4%)		4 (8.3%)	3 (6.3%)	
Docetaxel + trastuzumab + pertuzumab	2 (2.9%)	18 (26.5%)		2 (4.2%)	11 (22.9%)	

*$P<0.05$, **$P<0.01$

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

Liver dysfunction: grade 1 or higher aspartate aminotransferase, alanine aminotransferase, total bilirubin elevation.

Table 2. Univariate and multivariate analyses for risk factors associated with all-grade T-APS

	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	*P*-value	Odds ratio (95% CI)	*P*-value
Age (years)				
<55/≥55	2.52 (1.24–5.12)	0.01*	2.67 (1.24–5.76)	0.01*
Sex				
Male/Female	1.33 (0.12–14.98)	0.82	Excluded	-
Staging				
Stage IV or Metastatic/Others	1.21 (0.38–3.82)	0.75	Excluded	-
Prior treatment existence				
Present/Absent	0.55 (0.23–1.30)	0.17	0.78 (0.30–2.01)	0.61
Hormonal receptors				
ER, PR-positive or both/Negative	1.10 (0.55–2.20)	0.78	Excluded	-
HER2 overexpression				
Positive/Negative	0.85 (0.40–1.80)	0.67	Excluded	-
BSA (m^2)				
≥1.5/<1.5	0.61 (0.28–1.29)	0.19	0.75 (0.33–1.68)	0.48
BMI (kg/m^2)				
≥25/<25	0.71 (0.35–1.46)	0.35	Excluded	-
Liver dysfunction				
Present/Absent	0.62 (0.31–1.25)	0.18	0.50 (0.22–1.11)	0.09

Renal dysfunction				
Present/Absent	0.82 (0.36–1.87)	0.65	Excluded	-
Hypoalbuminemia				
Present/Absent	0.76 (0.37–1.59)	0.47	Excluded	-
Alcohol intake (≥5 days in a week)				
Yes/No	0.91 (0.37–2.22)	0.83	Excluded	-
Smoking history				
Current or former/Never	1.25 (0.63–2.49)	0.53	Excluded	-
Dexamethasone dosage				
8 mg/4 mg	0.37 (0.18–0.75)	0.006**	0.36 (0.17–0.76)	0.007**

*$P<0.05$, **$P<0.01$

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

Liver dysfunction: grade 1 or higher aspartate aminotransferase, alanine aminotransferase, total bilirubin elevation

Renal dysfunction: creatinine clearance of less than 80 mL/min

The cutoff of the serum albumin levels is 4.1 g/dL at our facility.

Table 3. Comparison of adverse effects associated with docetaxel and DEX

	All-patient analysis			Propensity-matched analysis		
	4 mg group (n=68)	8 mg group (n=68)	*P*-value	4 mg group (n=48)	8 mg group (n=48)	*P*-value
Nausea						
Grade 1/2	23.5%	25.0%	1.00	20.8%	27.1%	0.63
Anorexia						
Grade 1/2	25.0%	27.9%	0.85	25.0%	25.0%	1.00
Fatigue						
Grade 1/2	35.4%	50.0%	0.11	39.1%	41.7%	0.84
Insomnia						
Grade 1/2	38.0%	39.7%	1.00	47.1%	35.4%	0.36
FN						
Grade 3	27.9%	26.5%	1.00	25.0%	29.2%	0.82

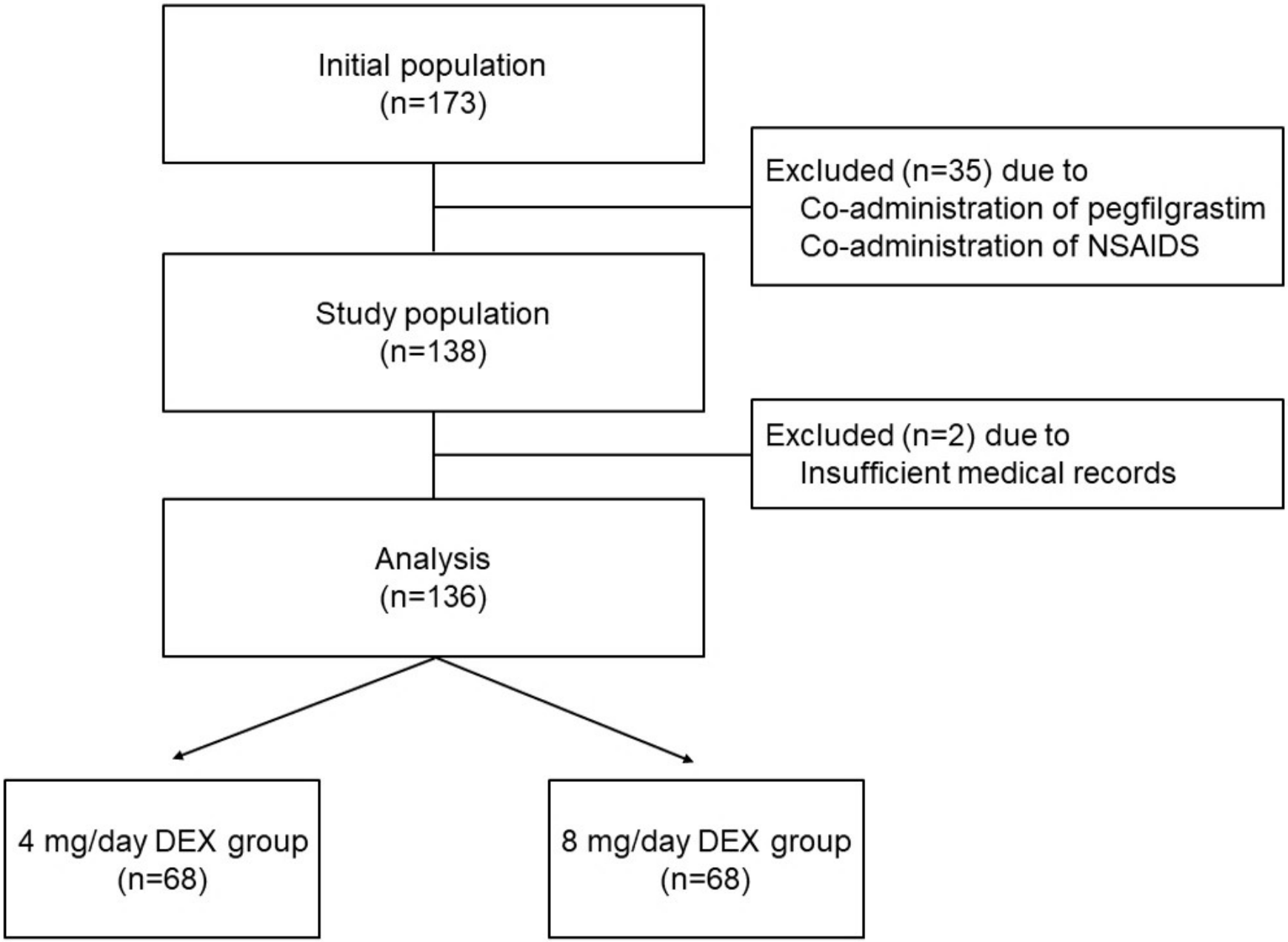
FN, febrile neutropenia

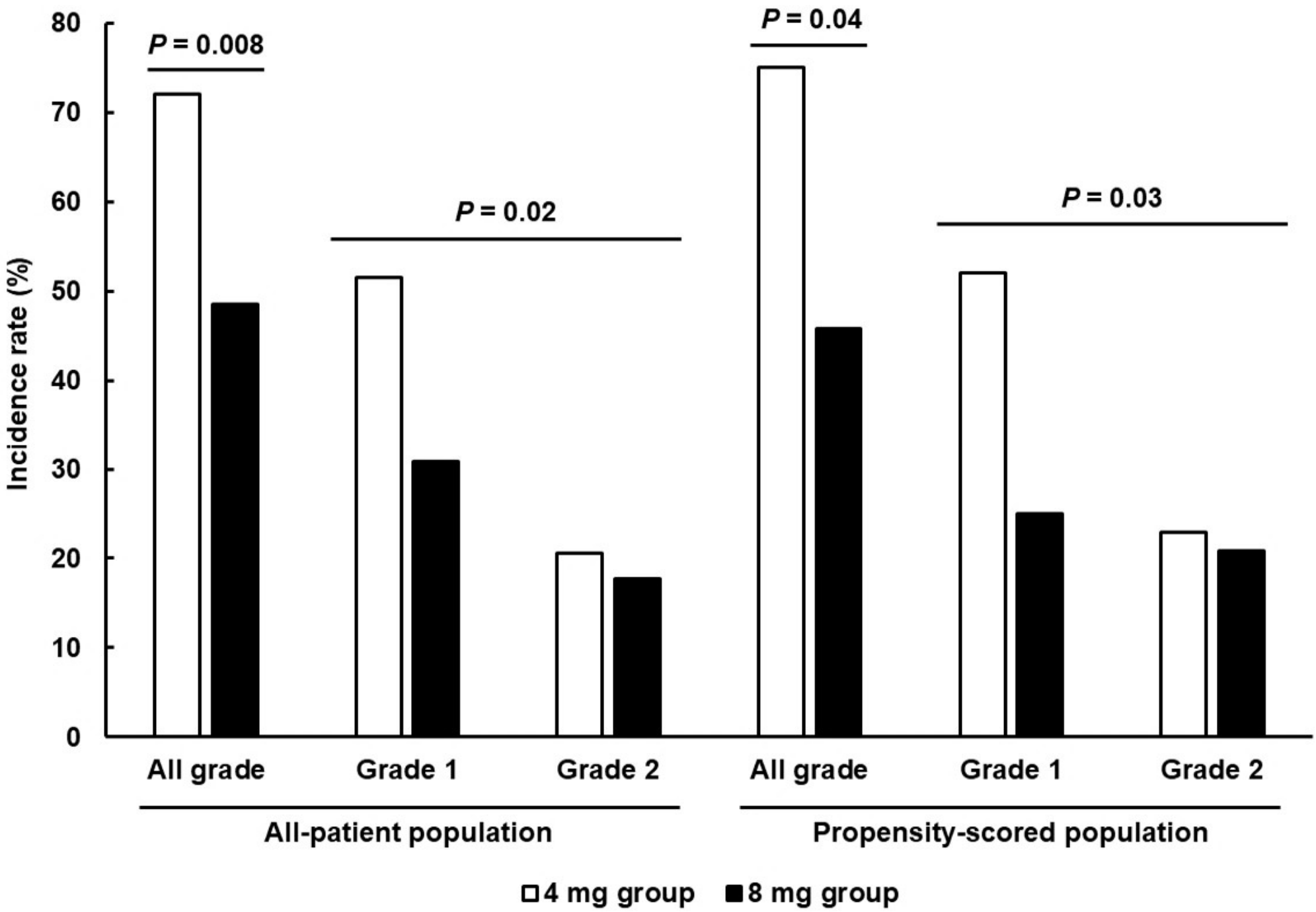
Figure captions

Fig. 1 Study design

NSAIDs, non-steroidal anti-inflammatory drugs; DEX, dexamethasone

Fig. 2 Comparison of all-grade T-APS incidence and its severity between the two groups in all and propensity score-matched population


Initial population
(n=173)
Excluded (n=35) due to
Co-administration of pegfilgrastim
Co-administration of NSAIDS
Study population
(n=138)
Excluded (n=2) due to
Insufficient medical records
Analysis
(n=136)
4 mg/day DEX group
(n=68)
8 mg/day DEX group
(n=68)


80
70
60
50
40
30
20
10
0
Incidence rate (%)
P = 0.008
P = 0.02
P = 0.04
P = 0.03
All grade
Grade 1
Grade 2
All grade
Grade 1
Grade 2
All-patient population
Propensity-scored population
4 mg group
8 mg group