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Micturition symptoms in gynecologic cancer patients receiving paclitaxel and platinum-based chemotherapy regimen: a prospective study

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Objective
To evaluate the effect of paclitaxel and platinum-based chemotherapy (PT) on micturition symptoms.

Methods
All gynecologic cancer patients who were assigned to receive the PT regimen and understood the Thai language were invited to participate in this study. The exclusion criteria were as follows: abnormal urinary symptoms, retained urinary catheter or percutaneous nephrostomy, anticholinergic drug use, or scheduled to receive radiation therapy after the completion of chemotherapy. The participants were interviewed using three Thai validated questionnaires, the incontinence impact questionnaire-short form, urogenital distress inventory short form, and Sandvik score, on the day before receiving the first cycle of chemotherapy (pre-treatment), on the day before receiving the 4th cycle (mid-treatment), and 46 weeks after completing 69 cycles (post-treatment). The scores at the three time points were compared. Patients who received less than three cycles were not included in the analysis.

Results
One hundred and ten patients were included in this study. There were significant differences in the median questionnaire scores at the three time points for both carboplatin plus paclitaxel and cisplatin plus paclitaxel. However, when using a pairwise difference between the two treatment protocols, there were no significant changes in the score from pre-treatment to post-treatment.

Conclusion
The PT regimen has an impact on micturition symptoms during chemotherapy which recover after treatment completion.

Keywords: Urinary symptoms; Paclitaxel; Urinary incontinence

Introduction

A principal treatment for gynecologic cancer, in addition to surgery and radiation, is chemotherapy, which is usually a paclitaxel and platinum-based regimen (PT) [1]. Paclitaxel is a microtubule-stabilizing agent that is highly toxic to the axonal microtubules of sensory neurons, which results in peripheral neuropathy in up to 30% of patients [2,3]. Cisplatin, a platinum-based drug, induces retrograde axonal degeneration in the distal portion of the long axon [4]. Peripheral neuropathies due to any cause, including chemotherapy such as paclitaxel, can present as clinical or subclinical autonomic dysfunction and manifest as cardiovascular, gastrointestinal, and urogenital system dysfunction. Paclitaxel produces

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several neurotoxic substances by altering calcium signaling, aggravating mitochondrial damage, and increasing the levels of neuropeptides, growth factors, reactive oxygen species, and matrix metalloproteinase-13. These toxic substances cause selective damage to small or unmyelinated fibers, ultimately causing neuropathy [2,5]. These substances are believed to affect the sympathetic and parasympathetic innervation of the bladder, causing an imbalance in the stimulatory and inhibitory signals innervating the detrusor, and finally causing abnormal micturition symptoms. To the best of our knowledge, only two studies have addressed this. One cross-sectional study carried out in Korea by Cho et al. [6] examined lower urinary tract symptoms in 158 patients with advanced gastric and lung cancers treated with at least one cycle of platinum-based drug and/or paclitaxel. They utilized self-reported questionnaires of international prostate symptom scores and found that 20.2% of patients reported severe lower urinary tract symptoms, which were related to the severity of peripheral neuropathy [6]. A prospective cohort study carried out by Strauchon et al. [7] in the United States of America investigated the urinary symptoms of 62 gynecologic cancer patients treated with carboplatin and paclitaxel after primary surgery for ovarian, fallopian tube, peritoneal, and endometrial cancers. They used five questionnaire types, incontinence impact questionnaires (IIQ-7), medical epidemiologic and social aspects of aging (MESA), urogenital distress inventory (UDI-6), Sandvik severity index, and functional assessment of cancer therapy/Gynecologic Oncology Ggroup-neurotoxicity (FACT/GOG-Ntx), at three time points: pre-chemotherapy, during the fifth chemotherapy cycle (mid-treatment) and 6-12 weeks post-chemotherapy. They found that carboplatin and paclitaxel impacted the urinary incontinence severity. As there is only a single publication on the micturition symptoms of gynecological cancer patients treated with platinum and paclitaxel, we conducted this study with the primary aim of evaluating the impact of this regimen on urinary symptoms. The results of this study may be beneficial in raising physicians' awareness of micturition symptoms in these patients.

Methods

1. Patient selection

This study was conducted between December 2020 and February 2022 after the study protocol was approved by the local Research Ethics Committee. The inclusion criteria were primary and recurrent gynecologic cancer patients who were assigned to receive chemotherapy with PT at Chiang Mai University Hospital. All recruited participants were required to understand Thai. The exclusion criteria were as follows: abnormal micturition symptoms, retained Foley's catheter or percutaneous nephrostomy, anticholinergic drug use, pelvic radiation after completion of chemotherapy, less than three PT regimen cycles received.

Patients who met the inclusion criteria were invited to participate in the study and they provided informed consent. All participants were interviewed by a well-trained medical team using three validated questionnaires to evaluate micturition symptoms at three time points: 1) the day before receiving the first chemotherapy cycle (pre-treatment), 2) the day before receiving the 4th cycle (mid-treatment), and 3) 4-6 weeks after completion of 6-9 cycles (post-treatment).

Three validated Thai versions of the IIQ-7-short form, UDI-6 short form, and Sandvik score (SS) were used in this study. IIQ-7 is a seven-item life impact questionnaire specific to urinary incontinence, covering four domains of physical activity, travel, social/relationships, and emotional health. UDI-6 is a 6-item inventory that is specific to irritation, stress, and obstructive/discomfort micturition symptoms. Both questionnaires were designed around a 4-point response scale: 0=not at all, 1=slightly, 2=moderately, and 3=greatly. The mean score of all items was multiplied by 33 1/3 to convert it to scores of 0-100 [8]. The SS is a severity index score that uses information about urine frequency (4 levels) and amount of urine leakage (3 levels). Both scores were multiplied, till an index value of 1-12 is reached [9]. In each case, a higher score represented more severe micturition-related symptoms.

The following clinical data were collected: age, body mass index (BMI), cancer type, International Federation of Gynecology and Obstetrics staging, recurrence status, previous operative procedure, parity, underlying disease, menopausal status, chemotherapy regimen, and response to treatment.

2. Sample size calculation

The prospective cohort study sample size was calculated using power analysis. In this study, a repeated-measures analysis of variance was used to compare the scores of the IIQ-7 questionnaire at different time intervals. The significance level (α) was set to 0.05, and the power of the test (1-β) was

0.80. According to previous research [6,7], it was necessary to convert the median (and interquartile range) to the mean (and standard deviation) using Hozo et al. [10] formula for calculating the pooled variance.

From the Supplementary Table 1, a variance of 1.632 was calculated for use with G*power (Düsseldorf University, Düsseldorf, North Rhine-Westphalia, Germany) to calculate the effect and sample sizes [11]. The estimated effect size was 0.403 and the minimum sample size was 63 patients. An expected dropout rate of 10% was added, finally resulting in a total of 70 patients.

3. Statistical analysis

Descriptive statistics are reported as mean and standard deviation for continuous variables and number and percentage for categorical variables. The data were tested for normal distribution using the Shapiro-Wilk test, and continuous data that were not normally distributed were reported using median and interquartile ranges. A generalized estimation equation with a gamma link transformation was used to compare the questionnaire scores between the three groups (pre-treatment, mid-treatment, and post-treatment) before multiple comparisons were performed using the Bonferroni correction. All analyses used a significance level of 0.05, and were performed using SPSS (ver. 22.0; IBM, Armonk, NY, USA).

Results

Of the 163 gynecologic cancer patients who were assigned to receive the PT regimen during the study period, 53 were excluded for the following reasons: percutaneous nephrostomy (n=4), retained urinary catheter (n=3), self-urinary catheter use (n=1), pelvic radiotherapy after completion of chemotherapy (n=11), and less than three cycles of PT regimen received (n=34). Finally, data from 110 cases were analyzed. Basic clinical data are shown in Table 1. The mean age of the patients was 57.6 years and 86% were menopausal. The mean BMI was 22.5 kg/m^2. Approximately a quarter of the patients were nulliparous. The three most common types of cancer were ovarian, uterine, and cervical. 72% of the study patients presented with advanced-stage disease. Nearly half of the patients had an underlying disease. Sixty-five patients underwent surgery; the most common procedure was performed in 61 patients. Ninteen patients had a suboptimally debulked tumor in the following locations: pelvis (n=9), abdomen (n=2), and pelvis & abdomen (n=8); five patients had bladder involvement.

Approximately 48.2% of patients received chemotherapy as the primary treatment, and 9% received chemotherapy as neoadjuvant treatment. The most common regimen was carboplatin plus paclitaxel (82.7%), followed by cisplatin plus paclitaxel (10.0%) and carboplatin, paclitaxel plus bevacizumab (7.3%). An objective response rate of 53.6% was achieved.

The micturition symptoms were assessed for in 110 patients at pre-treatment, 90 at mid-treatment, and 67 at post-treatment. The reasons for dropout for each time point are summarized in the footnotes of Table 2; the most common reason being having received the 3rd or 6th course of chemotherapy. The mean interval between chemotherapy completion and the post-treatment interview was 35.1 days. The questionnaire results for patients administered carboplatin plus paclitaxel and cisplatin plus paclitaxel are shown in Tables 2 and 3. All questionnaires (IIQ-7, UDI-6, and SS) showed statistically significant differences between the three time points (P<0.001) for both carboplatin plus paclitaxel and cisplatin plus paclitaxel. Although the median was zero, there was a difference in the interquartile range.

When examining the pairwise difference between the two time-points of the carboplatin plus paclitaxel regimen, all questionnaires achieved significantly worse scores between pre-treatment and mid-treatment; however, the IIQ-7 and UDI-6 scores improved significantly between mid-treatment to post-treatment. The changes in the scores from pre-treatment to post-treatment were not significant.

In the cisplatin plus paclitaxel regimen, IIQ-7 and UDI-6 scores were significantly worse between pre-treatment and mid-treatment; however, there was a tendency for an improvement in scores from mid-treatment to post-treatment. The SS score significantly improved from mid-treatment to post-treatment. However, the changes in all scores from pre-treatment to post-treatment were not significant.

The maximum scores of IIQ-7, UDI-6, and SS for carboplatin plus paclitaxel were 9.52,16.66, and 0.5, respectively, and that for cisplatin plus paclitaxel were 9.52, 11.11, and 0.0, respectively. All the scores indicated mild symptoms of urinary incontinence. None of the individuals developed loss of urination or overflow incontinence.

Table 1. Clinical data (n=110)

Variable	Value
Age (yr)	57.6±10.1
Median age (yr)	58 (29-76)
BMI (kg/m^2)	22.5 (3.7)
Location of cancer	
Cervix	34 (30.9)
Ovary	37 (33.6)
Uterine	18 (16.4)
Fallopian tube	15 (13.6)
Primary peritoneal cancer	3 (2.7)
Vulva	1 (0.9)
Stage	
I	20 (18.2)
II	11 (10.0)
III	44 (40.0)
IV	35 (31.8)
Nulliparity	28 (25.5)
Underlying disease	53 (48.2)
HT	10
DLP	9
DM	3
Other[a)]	31
Menopause	86 (78.2)
Hormonal replacement therapy	3 (2.7)
Surgery	
None	39 (35.5)
TAH and BSO	31 (28.2)
TAH and BSO and complete surgical staging	34 (30.9)
Radical hysterectomy and pelvic lymphadenectomy	2 (1.8)
Wide local excision and bilateral groin node dissection	2 (1.8)
Other[b)]	2 (1.8)
Residual tumor	
None	29 (26.4)
Optimal	11 (10.0)
Suboptimal	19 (17.3)
Unknown	12 (10.9)
No surgery	39 (35.5)
Primary treatment[c)]	53 (48.2)
Recurrent treatment	57 (51.8)
Regimen	
Carboplatin and paclitaxel	91 (82.7)
Cisplatin and paclitaxel	11 (10.0)

Table 1. Clinical data (n=110) (Continued)

Variable	Value
Carboplatin and paclitaxel and bevacizumab	8 (7.3)
Chemotherapy setting	
Systemic chemotherapy	99 (81.8)
Neoadjuvant chemotherapy	11 (9.1)
Number of total chemotherapy cycles	
3	11 (10.0)
4	4 (3.6)
5	7 (6.4)
6	79 (71.8)
8	1 (0.9)
9	8 (7.3)
Response	
Complete/partial response	59 (53.6)
Stable disease	28 (25.5)
Progression	18 (16.4)
Could not evaluate[d]	5 (4.5)

Values are presented as mean±standard deviation, median (range), or number (%).
BMI, body mass index; HT, hypertension; DLP, dyslipidemia; DM, diabetes mellitus; TAH, total abdominal hysterectomy; BSO, bilateral salpingo-oophorectomy.
[a]Asthma (n=1); human immunodeficiency viral infection (HIV) (n=3); breast cancer (n=1); stroke and HT (n=1); DM and DLP (n=2); DM and HT (n=4); DM, HT, and DLP (n=3); DM, HT, DLP, and HIV (n=1); DM, HT, and hypothyroidism (n=1); HT and HIV (n=1); HT and lung cancer (n=1); HT and DLP (n=7); HT, DLP, and rheumatoid arthritis (n=1); ischemic stroke (n=1); HT and old cerebrovascular accident (n=1); thyrotoxicosis (n=2).
[b]Left salpingo-oophorectomy (SO) and colostomy (n=1); bilateral groin node dissection (n=1).
[c]No surgery (n=14), TAH & BSO (n=20); TAH and BSO and complete surgical staging (n=18); left SO and colostomy (n=1). The median interval between surgery and the start of chemotherapy was 18.0 days (4-56 days).
[d]Anaphylaxis (n=2), lost to follow-up (n=3).

Table 2. Questionnaire scores comparing each chemotherapy time point

Regimen questionnaire	Pretreatment	Mid-treatment	Post-treatment[a]	*P*-value
Carboplatin and paclitaxel	99	81[b]	59[b]	
IIQ-7	0.00 (0.00-0.00)	0.00 (0.00-9.52)	0.00 (0.00-0.00)	0.003[c]
UDI-6	0.00 (0.00-5.55)	5.55 (5.55-16.66)	0.00 (0.00-5.55)	<0.001[c]
SS	0.00 (0.00-0.00)	0.00 (0.00-0.50)	0.00 (0.00-0.00)	0.003[c]
Cisplatin and paclitaxel	11	9[b]	8[b]	
IIQ-7	0.00 (0.00-9.52)	0.00 (0.00-14.28)	0.00 (0.00-9.52)	0.039[c]
UDI-6	5.55 (0.00-16.66)	5.55 (0.00-33.33)	5.55 (0.00-16.66)	0.012[c]
SS	0.00 (0.00-1.00)	0.00 (0.00-1.00)	0.00 (0.00-0.50)	0.044[c]

Values are presented as median (25th to 75th percentiles) or number.
IIQ-7, incontinence impact questionnaire-short form; UDI-6, urogenital distress inventory short form; SS, Sandvik score.
[a]Mean±standard deviation of post-treatment days=35.1±7.1 days from completion of chemotherapy.
[b]Reasons for dropping out from treatment regimen. Carboplatin and paclitaxel: mid-treatment (n=18): lost to follow-up (n=1), allergy to paclitaxel (n=2), progression (n=4), just received the 3rd course (n=11); post-treatment (n=22): lost to follow-up (n=1), progression (n=5), just received the 6th course (n=16). Cisplatin and paclitaxel: mid-treatment (n=2), change in treatment (n=2); post-treatment (n=1): progression (n=1).
[c]Generalized estimating equations significant at 0.05.

Table 3. Comparisons of the questionnaire scores between each time point

Regimen questionnaire	Change from pretreatment to mid-treatment		Change from mid-treatment to post-treatment		Change from pretreatment to post-treatment	
	Value	*P*-value	Value	*P*-value	Value	*P*-value
Carboplatin and paclitaxel	81		59		59	
IIQ-7	0.00 (0.00 to 9.52)	0.008[a)]	0.00 (-9.52 to 0.00)	0.014[a)]	0.00 (0.00 to 0.00)	>0.999
UDI-6	5.55 (0.00 to 5.56)	<0.001[a)]	-5.55 (-11.11 to 0.00)	0.001[a)]	0.00 (0.00 to 0.00)	>0.999
SS	0.00 (0.00 to 0.00)	0.002[a)]	0.00 (0.00 to 0.00)	0.141	0.00 (0.00 to 0.00)	0.930
Cisplatin and paclitaxel	9		8		8	
IIQ-7	0.00 (0.00 to 9.52)	0.033[a)]	0.00 (-4.76 to 4.76)	0.813	0.00 (0.00 to 7.14)	0.572
UDI-6	5.55 (0.00 to 11.11)	0.015[a)]	0.00 (-11.11 to 0.00)	0.082	0.00 (-2.78 to 2.78)	>0.999
SS	0.00 (0.00 to 0.00)	>0.999	0.00 (-0.50 to 0.00)	0.047[a)]	0.00 (-1.00 to 0.00)	0.191

Values are presented as median (25th to 75th percentiles) or number.
IIQ-7, incontinence impact questionnaire-short form; UDI-6, urogenital distress inventory short form; SS, Sandvik score.
[a)]Multiple comparisons using Bonferroni corrections; statistically significant at 0.05.

Discussion

Owing to the neurotoxic consequences of paclitaxel, it is possible that the urinary system may be affected, resulting in micturition symptoms such as urinary incontinence. This could potentially disturb the quality of life and possibly require surgical correction [12]. The present study revealed that though the PT regimen might worsen urinary incontinence in gynecologic patients, the symptoms were mild and transient. Some of our results differed from those of a previous study. Strauchon et al. [7] studied urinary incontinence in 62 women with ovarian, fallopian, peritoneal, and endometrial cancers who received carboplatin plus paclitaxel after primary surgery. Patients treated with radiation were excluded from the study. The authors used four validated questionnaires as follows: IIQ-7, UDI-6, SS, the medical, epidemiologic, and social aspects of aging: stress urinary incontinence (MESA-SUI), and medical, epidemiologic, and social aspects of aging: urge urinary incontinence (MESA-UUI). Neurotoxicity was also evaluated using the FACT/GOG-Ntx. All questionnaires were self-reported by the patients at three time points: the start day of chemotherapy (pre-treatment), during the 5th chemotherapy cycle (mid-treatment), and during their 6-12 weeks post-chemotherapy visit (post-treatment). They found a significant difference in the IIQ-7, MESA-UUI, MESA-SUI, and total FACT/GOG-Ntx scores at all three time points, but not for the UDI-6 and SS scores. Furthermore, significant differences were found between the pre-treatment and mid-treatment MESA-UUI, MESA-SUI, and FACT/GOG-Ntx scores. Only the IIQ-7 scores showed a significant improvement from mid-treatment to post-treatment. Finally, only the FACT/GOG-NTx questionnaire showed a significant change to worse neurotoxic symptoms; there were no significant changes in the other urinary symptom questionnaires. The authors mentioned the transient nature of urinary incontinence. However, because a quarter of the study patients dropped out, the authors were concerned about the power of their study to show significant results.

The explanation for the differing results between our study and that by Strauchon et al. [7] is probably due to differences in the methodology. Our study recruited all patients with primary and recurrence cancers at different time points. The mid-treatment time point in our study was the day after completion of three cycles of chemotherapy; however, in the Strauchon el al. [7] study, it was after the fifth cycle. At the post-treatment time point, there were no significant difference in the micturition symptoms in either study, especially urinary incontinence. This may be explained by the recovery from chemotherapy agent toxicity.

In our study, 11 patients received cisplatin instead of carboplatin during the PT regimen. Due to the greater neurotoxicity of cisplatin compared to carboplatin [4], we stratified the the questionnaire result analyses according to those who received carboplatin plus paclitaxel or cisplatin plus paclitaxel, which showed significant differences at all time points. In addition, the pairwise differences between the two time points of each regimen tended to be in the same direction; the urinary symptoms worsened when comparing pre-treat-

ment and mid-treatment, with a tendency for improvement between mid-treatment and post-treatment. There is a possibility that no level of significance was achieved due to the dropout of some patients between the mid- and post-treatment times for various reasons such as disease progression, change in treatment, or non-attendance at the interview.

In this study, eight patients received bevacizumab in the PT regimen. This drug is a humanized monoclonal immunoglobulin G1 antibody that reacts with vascular endothelial growth factors, resulting in adverse urinary system events and proteinuria [13]. All eight patients underwent urinary analysis before receiving the next course of chemotherapy, and the results were within normal limits. Thus, this treatment may not affect urinary symptoms.

The mild and transient effects of paclitaxel on micturition-related symptoms might be explained by the neurotoxic nature of paclitaxel, which commonly affects the distal sensory system more than the motor and autonomic systems. Therefore, the primary symptoms in patients are frequently described as numbness, pain, and tingling [14]. In addition, after the discontinuation of paclitaxel, the toxicity reduces, the process of damaging neurons ceases, and some neuronal fibers recover [2].

The other confounding factor that might explain the improvement of urinary symptoms at the post-treatment time point might be the improved response to chemotherapy treatment. However, only 53% of patients responded to treatment and therefore, might not explain the main effect.

In this study, 39 patients underwent surgery in the primary setting. The median time between the date of surgery and the first day of chemotherapy was 18 days. None of the patients developed intraoperative urinary tract complications or abnormal urinary symptoms in the perioperative period. Therefore, abnormal symptoms after chemotherapy were primarily due to chemotherapy.

A strength of this study was that it was a prospective study conducted at a single center; therefore, data were collected by a standardized team. Additionally, we used interviewers instead of patient self-reports, which probably increased the accuracy of the scoring, as the interviewers could explain the details of each questionnaire before the patients responded. However, there were two main limitations: 1) fewer questionnaires were used compared to the previous study due to the limited number of validated Thai versions of the questionnaires on urinary incontinence; and 2) the short follow-up time post-treatment, which might have overlooked some long-term side effects.

In conclusion, gynecologic cancer patients who received paclitaxel plus platinum-based chemotherapy demonstrated significantly worse scores for urinary incontinence which recovered after the completion of chemotherapy.

Conflict of interest

The authors declare no potential conflicts of interest.

Ethical approval

This study was approved by the Chiang Mai University Ethics Committee (Research ID: 07764; Study Code: OBG-2563-07764).

Patient consent

All the participants provided written informed consent.

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