Regular Article

Effect of Obesity on Hematotoxicity Induced by Carboplatin and Paclitaxel Combination Therapy in Patients with Gynecological Cancer

Yosuke Ando,^a Takahiro Hayashi,^{*a,b} Hideyo Shiouchi,^b Chihiro Tanaka,^b Kaori Ito,^c Seira Nishibe,^a Nanaho Miyata,^a Ruri Horiba,^a Hisano Yanagi,^d Takuma Fujii,^e Kenji Kawada,^d Yoshiaki Ikeda,^b and Shigeki Yamada^a

^aDepartment of Clinical Pharmacy, Fujita Health University School of Medicine; 1–98 Dengakugakubo, Kutsukake-cho, Toyoake, Aichi 470–1192, Japan; ^bCollege of Pharmacy, Kinjo Gakuin University; 2–1723 Omori, Moriyama-ku, Nagoya 463–8521, Japan; ^cDepartment of Hematology, Fujita Health University School of Medicine; 1–98 Dengakugakubo, Kutsukake-cho, Toyoake, Aichi 470–1192, Japan; ^dDepartment of Medical Oncology, Fujita Health University School of Medicine; 1–98 Dengakugakubo, Kutsukake-cho, Toyoake, Aichi 470–1192, Japan; and ^eDepartment of Obstetrics and Gynecology, Fujita Health University School of Medicine; 1–98 Dengakugakubo, Kutsukake-cho, Toyoake, Aichi 470–1192, Japan.

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Despite *in vivo* studies suggesting that obesity increases carboplatin (CBDCA) bone marrow toxicity, the American Society of Clinical Oncology recommends that full weight-based cytotoxic chemotherapy doses be used to treat obese patients with cancer. Accordingly, the present study retrospectively investigated the effect of body mass index (BMI) on bone marrow toxicity in patients with gynecological cancer who underwent paclitaxel and carboplatin (TC) therapy after eliminating the effect of the target area under the curve (AUC). Risk factors for CBDCA bone marrow toxicity were also identified. A total of 110 patients with primary gynecological cancer or gynecological cancer of unknown primary origin who underwent TC therapy with a target AUC of 5–6 were included herein. Patients with a BMI of ≥ 25 and $< 25 \text{ kg/m}^2$ were assigned to the obesity and control groups, respectively, and evaluated according to changes in hematological test values (platelet, white blood cell, and hemoglobin counts) starting from initial TC therapy administration until 21 d after the second treatment course. The obesity group had a significantly higher thrombocytopenia rate than the control group. Risk factors for thrombocytopenia $\geq$ grade 2 included BMI $\geq 25 \text{ kg/m}^2$. Among patients with primary gynecological cancer or gynecological cancer of unknown primary origin who had a BMI of $\geq 25 \text{ kg/m}^2$, those receiving CBDCA may be at increased risk for thrombocytopenia $\geq$ grade 2 when the dosage is calculated using the Calvert formula with the creatinine clearance level.

Key words gynecological cancer; paclitaxel; carboplatin; body mass index; obesity

INTRODUCTION

The treatment of gynecological cancer generally includes surgery, chemotherapy, and radiotherapy, the choice of which differs depending on the type of cancer. Cisplatin (CDDP) has been used as the standard drug for treating ovarian cancer since 1980. Thereafter, studies have demonstrated the efficacy of paclitaxel (PTX) and CDDP combination therapy (TP therapy),¹⁾ which has led to its establishment as the standard treatment in recent years. In 2003, a comparison between PTX and carboplatin (CBDCA) combination therapy (TC therapy) and TP therapy demonstrated no difference in efficacy, although TC therapy caused fewer side effects and was simpler and easier to administer (including supportive therapy) compared to TP therapy.²⁾ As such, TC therapy was established as the standard treatment for ovarian cancer. Despite evidence showing poorer chemotherapy outcomes in cervical and uterine cancers than in ovarian cancer, TC therapy has been recommended for metastatic or recurrent cervical cancer.³⁾ On the other hand, doxorubicin (DXR) and CDDP combination therapy (AP therapy), docetaxel (DTX) and CBDCA combination therapy (DC therapy) or TC therapy has been recommended for uterine cancer.⁴⁾

CBDCA used in TC therapy is excreted predominantly by the kidneys, with approx. 70% being eliminated through

urine.⁵⁾ Furthermore, given the correlation between the tumor reduction effect of CBDCA and the unbound area under the curve (AUC),⁶⁾ the Calvert formula [$\text{dose (mg)} = \text{target AUC} \times \{\text{glomerular filtration rate (GFR)} + 25\}$] can be used to calculate the CBDCA dose as it considers individual differences in renal function.⁷⁾ This method has also been widely used for calculating the administered dose in studies involving Japanese patients.⁸⁾ Furthermore, when calculating the CBDCA dose using the aforementioned formula, reports have shown an advantage of substituting GFR with creatinine clearance (CCr) using the Cockcroft–Gault formula⁹⁾: $\text{CCr (mL/min)}: \{140 - \text{age (years)}\} \times \text{weight (kg)} \times 0.85 \text{ (in females)} / (\text{serum Cr} \times 72)$.^{10–12)} A survey of 112 Japanese medical institutions showed that 71.4% substituted GFR with CCr when calculating the CBDCA dose using the Calvert formula.¹³⁾

Several studies have reported on the effect of obesity on CBDCA therapy. According to a clinical study of patients who underwent a combination therapy of CBDCA and taxane antineoplastic agents (PTX or docetaxel) for ovarian cancer, differences in body mass index (BMI) had no effect on overall survival or progression-free survival (PFS) rates, which are indicators of therapeutic efficacy.¹⁴⁾ Furthermore, a previous survey of obese patients who received TC therapy for ovarian cancer revealed that among the group with a relative dose intensity (RDI) $< 85\%$, those with a BMI $\geq 30 \text{ kg/m}^2$ exhibited

*To whom correspondence should be addressed. e-mail: taka-h@fujita-hu.ac.jp

shorter PFS rates than those with a BMI $<25\text{ kg/m}^2$.¹⁵⁾ By contrast, a study involving rats reported that obesity increased CBDCA-induced bone marrow toxicity.^{16,17)} Moreover, a clinical study on female patients with lung cancer reported no association between BMI and the onset of myelosuppression,¹⁸⁾ while the American Society of Clinical Oncology (ASCO) Clinical Practice Guideline reported that concerns regarding toxicity or overdose in obese patients with cancer, based on the use of actual body weight, are unfounded.¹⁹⁾ However, another report showed that among patients with gynecological cancer, those with a BMI $\geq 27\text{ kg/m}^2$ had higher incidences of severe thrombocytopenia than those with a BMI $<27\text{ kg/m}^2$,²⁰⁾ which has led to different perspectives regarding the impact of obesity on myelosuppression. Therefore, the results of different clinical studies have led to various conclusions regarding the effect of BMI on CBDCA treatment. In addition, a clinical study examining the effect of CBDCA on patients with ovarian cancer reported that a high target *AUC* was associated with an increased incidence of leukopenia and thrombocytopenia.⁶⁾ Therefore, examining the effect of BMI on CBDCA therapy after removing the influence of the target *AUC* is imperative.

Considering the aforementioned points, the present study retrospectively examined the effect of BMI on bone marrow toxicity among patients with gynecological cancer who had undergone TC therapy after eliminating the influence of the target *AUC*. Risk factors for CBDCA bone marrow toxicity were also identified.

MATERIALS AND METHODS

Subjects The study sample included patients aged ≥ 20 years who underwent at least two courses of TC therapy for primary gynecological cancer (ovarian, cervical, and uterine cancer) or for gynecological cancer of unknown primary origin at the Department of Gynecology, Fujita Health University Hospital. Patients had a target *AUC* of 5–6 for the CBDCA dose calculated backward using the Calvert formula. Those who had received other forms of chemotherapy within the 2 years preceding the onset of TC therapy and those considered unsuitable by the principal investigator were excluded from the study.

Investigations This retrospective study was based on patient data collected from electronic patient files available in the databases of Fujita Health University Hospital. Following BMI measurements prior to treatment initiation, patients with a BMI of ≥ 25 and $<25\text{ kg/m}^2$ were assigned to the obesity and control groups, respectively, according to the criteria stipulated by the Japan Society for the Study of Obesity.²¹⁾ Prior to treatment initiation, the following patient data were recorded: subject age, BMI, body weight, body surface area, serum creatinine (SCr) level, CCr, eGFR, cancer type, chemotherapy history, and hematological test results, including platelet (Plt), white blood cell (WBC), and hemoglobin (Hb) counts. The following drug administration data were also examined: initial PTX dose, initial CBDCA dose, and average relative dose intensity (ARDI) of PTX and CBDCA. The RDI (%) of PTX was calculated using the following formula: actual dose ($\text{mg/m}^2/\text{week}$)/planned dose ($=175\text{ mg/m}^2/\text{week}$) $\times 100$. Here, the administration period for the planned dose was set to 3 weeks. The RDI (%) of CBDCA was calculated backward from the actual administered dose using the following for-

mula: *AUC* (/week)/planned *AUC* ($=5.5$) $\times 100$. In the present study, GFR was calculated using the GFR predictive equation for Japanese women published in 2008 by the Japanese Society of Nephrology: $\text{eGFR (mL/min/1.73 m}^2\text{)} = 194 \times \text{Cr}^{-1.094} \times \text{age}^{-0.287}$ ($\times 0.739$ for women).²²⁾

Assessment The lowest blood tests values (Plt, WBC, and Hb) obtained starting from initial TC therapy administration until 21 d following the second treatment course were evaluated based on the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0.

Statistical Analysis Normally distributed variables were expressed as means $\pm$ standard deviations, whereas non-normally distributed variables were expressed as medians and interquartile ranges. The unpaired *t*-test and Mann–Whitney *U* test were used to compare normally and non-normally distributed variables between both groups, respectively. The χ^2 test was utilized for ratio comparisons between both groups. Univariate analysis was performed to identify factors influencing hematopenia, whereas multivariate logistic regression analysis was performed for items with a risk rate of $<20\%$. The Hosmer–Lemeshow statistical test was used to validate the goodness-of-fit of the developed model. The Statistical Package for the Social Sciences v. 22.0 (IBM Corporation, Armonk, NY, U.S.A.) was used for all statistical analyses, with $p < 0.05$ indicating statistical significance.

Ethics The present study was conducted according to the protocols approved by the Fujita Health University School of Medicine Epidemiological and Clinical Research Ethics Committee.

Ethical Approval All procedures performed in the present study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

RESULTS

Patients The study sample consisted of 110 patients, among whom 87 and 23 belonged to the control and obesity groups, respectively. Compared to the control group, the obesity group had a significantly higher body weight ($p < 0.001$), body surface area ($p < 0.001$), CCr level ($p = 0.0085$), and SCr level ($p = 0.035$). Furthermore, the obesity group tended to have a higher WBC count than the control group ($p = 0.050$). No significant differences in any of the other variables were observed between both groups (Table 1).

Dosage No difference in the initial dosage of PTX (mg/m^2) or CBDCA (*AUC*) was observed between both groups. However, the obesity group had a higher initial CBDCA dosage (mg/body unit) and total CBDCA dosage after two courses (mg/body unit) than the control group (Table 2).

Safety In the incidence of hematotoxicity $\geq$ grade 2, the obesity group had a significantly higher thrombocytopenia rate than the control group ($p = 0.0027$). No differences in leukopenia ($p = 0.63$) or Hb reduction ($p = 0.12$) were observed between the two groups (Table 3). Furthermore, the obesity group had significantly higher maximum decreases in blood cell counts for ΔPlt and ΔWBC than those of the control group. No significant difference in ΔHb levels was observed between the groups ($p = 0.098$) (Table 3).

Risk Factors Risk factors for thrombocytopenia $\geq$ grade

Table 1. Patient Background (before Chemotherapy)

	Control group (<i>n</i> = 87)	Obesity group (<i>n</i> = 23)	<i>p</i> -Value
Age (years)	61.0 (47.0–68.5)	59.0 (47.0–70.5)	0.76
BMI (kg/ m ²)	20.06 (18.81–22.76)	27.31 (26.20–28.09)	<0.001
Weight (kg)	48.5 (44.7–54.1)	63.2 (59.8–70.8)	<0.001
BSA (m ²)	1.64 ± 0.13	1.84 ± 0.16	<0.001
SCr (mg/dL)	0.59 (0.54–0.66)	0.64 (0.59–0.71)	0.035
Ccr (mL/min)	82.36 ± 24.20	99.14 ± 31.64	0.0085
GFR (mL/min/1.73 m ²)	82.15 ± 16.76	73.52 ± 19.24	0.080
Type of cancer			0.62
Ovarian cancer	47	9	
Cervical cancer	4	10	
Endometrial cancer	23	8	
Cancer of unknown primary	13	5	
Plt (×10 ⁴ /μL)	28.1 (23.9–34.4)	30.9 (25.6–44.0)	0.13
WBC (×10 ³ /μL)	5.0 (4.1–6.7)	5.9 (5.5–7.5)	0.050
Hb (g/dL)	11.87 ± 1.17	12.18 ± 1.36	0.37

BSA, body surface area; Ccr, creatinine clearance.

Table 2. Anticancer Drug Dosages

	Control group (<i>n</i> = 87)	Obesity group (<i>n</i> = 23)	<i>p</i> -Value
PTX initial dosage (mg/m ²)	153.68 (151.73–155.53)	153.43 (151.27–155.69)	0.95
CBDCA initial dosage (<i>AUC</i>)	5.51 (5.44–5.65)	5.48 (5.33–5.55)	0.22
CBDCA initial dosage (mg/body)	592.07 ± 135.78	674.78 ± 173.48	0.013
CBDCA total dosage in 2 courses (mg/body)	1175.73 ± 259.69	1322.39 ± 344.14	0.024

PTX, paclitaxel; CBDCA, carboplatin; *AUC*, area under the concentration–time curve.

Table 3. Incidence of Haematotoxicity

	Control group (<i>n</i> = 87)	Obesity group (<i>n</i> = 23)	<i>p</i> -Value
Incidence of haematotoxicity ≥ grade 2 (%)			
Thrombocytopenia	3.4	21.7	0.0027
Leukopenia	82.8	87.0	0.63
Anaemia	23.0	39.1	0.12
Maximum blood count change between both courses			
ΔPlt (×10 ⁴ /μL)	−11.9 (−18.6–−8.0)	−14.9 (−26.1–−12.0)	0.010
ΔWBC (×10 ³ /μL)	−3.0 (−4.3–−2.0)	−4.0 (−4.6–−2.2)	0.035
ΔHb (g/dL)	−1.2 (−1.6–−0.8)	−1.5 (−2.1–−1.0)	0.098

2 were examined. Univariate analysis revealed significant differences in BMI ≥25 kg/m² and eGFR (mL/min/1.73 m²), but not in age, Plt count, initial PTX dosage (mg/m²) or initial CBDCA dosage (*AUC*). After performing multivariate analysis on the two aforementioned factors having a risk rate <20% and a BMI ≥25 kg/m² were subsequently identified as only risk factor (Table 4).

DISCUSSION

The present study examined the effects of obesity on hematotoxicity in patients with primary gynecological cancer or gynecological cancer of unknown primary origin who underwent TC therapy. After examining differences between the two TC therapy courses, the obesity group showed a

greater reduction in Plt count than the control group. The occurrence of thrombocytopenia in CBDCA toxicity was known to be dose limited, and thrombocytopenia occurred more frequently than leukopenia at any given CBDCA *AUC*, namely CBDCA dosage.²³⁾ In this study, the CBDCA dose was calculated using the aforementioned formula, and reports have shown an advantage in substituting GFR with CCr using the Cockcroft–Gault formula.^{10–12)} Accordingly, the real dose based on the aforementioned formula in the obesity group might exceed the appropriate dose for treatment. Furthermore, after comparing the incidence of hematotoxicity between both therapy courses, the obesity group had a higher incidence of thrombocytopenia ≥ grade 2 compared to the control group. In addition, a BMI ≥25 kg/m² was identified as only risk factor for thrombocytopenia ≥ grade 2. Kashiwabara *et al.*¹⁸⁾ com-

Table 4. Risk Factors for Thrombocytopenia $\geq$ Grade 2

	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	<i>p</i> -Value	Odds ratio (95% CI)	<i>p</i> -Value
Age (years)	1.013 (0.95–1.08)	0.67		
BMI (kg/m^2) ≥ 25	7.78 (1.70–35.53)	0.008	6.59 (1.38–31.50)	0.018
GFR ($\text{mL}/\text{min}/1.73\text{m}^2$)	0.967 (0.93–1.01)	0.135	0.98 (0.94–1.024)	0.362
PLT ($\times 10^4/\mu\text{L}$)	0.95 (0.88–1.04)	0.26		
Dosage of PTX (mg/m^2)	1.03 (0.85–1.25)	0.78		
Dosage of CBDCA (<i>AUC</i>)	7.35 (0.31–172.19)	0.22		

Predictive ability of the final model was quantified using the Hosmer–Lemeshow test for goodness of fit; $p = 0.186$.

pared the onset of hematotoxicity in patients with lung cancer who were categorized into BMI < 25 and $\geq 25\text{kg}/\text{m}^2$ groups. Although they found no difference in the incidence of thrombocytopenia, several patients in the BMI $\geq 25\text{kg}/\text{m}^2$ group required a reduction in CBDCA dose due to grade 4 neutropenia that developed during the second treatment course. Furthermore, Gutierrez *et al.*,²⁰⁾ who examined 52 patients with gynecological cancer, reported that the incidence of thrombocytopenia $\geq$ grade 3 was higher among patients with a BMI $\geq 27\text{kg}/\text{m}^2$ than among those with a BMI $< 27\text{kg}/\text{m}^2$. Accordingly, the aforementioned reports consider BMI and the onset of hematotoxicity to be closely associated with TC therapy. After examining the effects of obesity on the incidence of cytopenia $\geq$ grade 2 according to Plt, WBC, and Hb counts, the present study revealed that obesity only affected Plt count. This result was consistent with that provided in a study by Gutierrez *et al.*,²⁰⁾ which showed that although BMI varied, obese patients were more prone to thrombocytopenia. The ASCO recommends that full weight-based cytotoxic chemotherapy doses be used to treat obese patients with cancer considering that most data indicate myelosuppression to be similarly or less pronounced among obese than among non-obese patients receiving full weight-based doses.¹⁹⁾ However, our results do not support the recommendations of the ASCO.

A previous study found that although CBDCA therapy caused less nausea, neuropathy, and renal toxicity than CDDP therapy, it promoted a higher incidence of hematotoxicity, primarily thrombocytopenia.²⁴⁾ Hematotoxicity has also been observed in PTX therapy, with a particular tendency for neutropenia to occur 8–11d following administration.²⁴⁾ A comparison between the characteristics of the two agents shows that CBDCA may be more associated with thrombocytopenia. In addition, a clinical study examining the effects of CBDCA in patients with ovarian cancer revealed that a high target *AUC* was associated with increased incidence of leukopenia and thrombocytopenia.⁶⁾ Therefore, the effect of BMI on CBDCA therapy should be examined after accounting for the effect of the target *AUC*. After investigating risk factors for thrombocytopenia $\geq$ grade 3, Gutierrez *et al.*²⁰⁾ confirmed this finding through multivariate analysis controlling for age and ECOG performance status. The present study found no age differences between both groups, although patients with

low levels of consciousness were excluded. Furthermore, our analysis identified BMI $\geq 25\text{kg}/\text{m}^2$ as only risk factor for thrombocytopenia $\geq$ grade 2. In addition, we examined other risk factors that are reportedly associated with thrombocytopenia but are not dependent on the target *AUC* of CBDCA: age, Plt, dosage of anticancer drug and eGFR, which were all corrected according to the body surface. Also, when corrected for body surface, patient background for the obesity group showed an aggravation tendency in SCr and eGFR which was not observed in the control group. This finding was expected because the tendency for renal function aggravation has already been reported for patients with obesity.²⁵⁾

CBDCA dose was calculated using the Calvert formula wherein GFR was substituted with CCr, which has been used widely in Japan. In such cases, the CBDCA dosage may have been overcalculated for obese patients. This supports our result, which showed that the obesity group had a higher initial CBDCA dose and total CBDCA dose after two courses. Accordingly, a higher incidence of thrombocytopenia in obesity suggests that calculating the dosage for obese patients using the aforementioned method increases the risk of side effects. By contrast, the risk factors identified herein differed from those reported by Gutierrez *et al.*²⁰⁾ This may be attributed to the fact that our target *AUC* was limited to 5–6 in order to minimize any bias and maximize the number of subjects included.

The results of the present study revealed that using the Calvert formula to calculate the CBDCA dose and substituting GFR with CCr in patients with BMI $\geq 25\text{kg}/\text{m}^2$ increased the incidence of thrombocytopenia $\geq$ grade 2 due to overdosing. Therefore, appropriate attention should be paid to the onset of thrombocytopenia $\geq$ grade 2 when planning treatment for obese patients, particularly when calculating the CBDCA dose using CCr.

Uterine cancers have been categorized as either estrogen-dependent with a relatively good prognosis (type 1) or estrogen-nondependent with a poor prognosis (type 2) often found among elderly individuals. In certain type 1 cancers, visceral fat obesity induces ovulation disorders,²⁶⁾ which lead to progesterone inactivation. Accordingly, one study showed that the risk of uterine cancer among patients with a BMI $\geq 24\text{kg}/\text{m}^2$ was 2.73 times higher than that in patients with a BMI of

21–24 kg/m².²⁷⁾ Furthermore, another study showed that patients with a BMI of 30–34 and ≥ 40 kg/m² had a 2.5 and 6.3 times higher risk of mortality from uterine cancer compared to those with a BMI of 18.5–24.9 kg/m², respectively.²⁸⁾ By contrast, a clinical study on the effect of obesity on ovarian cancer in Western women showed that premenopausal women with a BMI ≥ 30 kg/m² had a 1.7 times higher risk for cancer onset than those with a BMI of 18.5–23 kg/m²,²⁹⁾ suggesting an association between BMI and the onset of ovarian cancer. This indicates a strong relationship between obesity and the onset of gynecological cancer.

Based on the aforementioned epidemiological background, the results of the present study suggest the significance of considering the appropriate anticancer agent dosage for the treatment of obese patients.

CONCLUSION

The present study found that when administering CBDCA therapy for patients with a BMI ≥ 25 kg/m² who present with primary gynecological cancer or gynecological cancer of unknown primary origin, utilizing the Calvert formula for dosage calculation and substituting GFR with CCr according to the Cockcroft–Gault formula may increase the incidence of thrombocytopenia $\geq$ grade 2.

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Conflict of Interest The authors declare no conflict of interest.

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