〔短　　報〕

An Analysis of Generic Drug Safety in Paclitaxel and Carboplatin Chemotherapy for Gynecologic Malignancies

婦人科悪性腫瘍におけるパクリタキセル・カルボプラチン療法での後発品製剤安全性の検討

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Summary：Generic drug substitution is encouraged in Japan, but one problem with substitution is that there is no requirement to include clinical testing in reports of equivalence. In the field of cancer chemotherapy, where safety margins are narrow, differences in adverse events with substitution are especially likely to affect treatment. This highlights the need for clinical assessment of these drugs. However, while comparative reports on generic drug substitution are available for individual generic drug formulations, few reports have dealt with regimens of multiple co-administered generic drugs, and treatment often proceeds without sufficient evidence.
In this study, we investigated differences in safety with generic substitution of paclitaxel and carboplatin chemotherapy, one of the main treatment regimens for gynecologic malignancies. As a result, an equivalence was suggested in hematologic toxicity, myalgia and arthralgia even after the substitution. For other non-hematologic toxicities, odds ratio showed a decreasing trend after the substitution, although equivalence was not guaranteed. In addition, there was no significant difference in the number of cases requiring dose reductions during treatment, which suggests that safety is guaranteed even after the substitution. It is necessary to increase the number of cases and to report with more scientific evidence.

Key words：generic drug, safety, paclitaxel, carboplatin

要旨：わが国では後発医薬品への切り替えが推進されているが，切り替え時の問題点として，臨床試験における同等性の報告が義務付けられていないことが挙げられる．安全域が狭いがん化学療法の分野において，切り替えによる有害事象発現の差異が治療に影響する可能性は高く，実臨床での薬剤評価が必要と考える．しかし，後発医薬品への切り替えに際し，製剤毎での比較報告はあるものの，後発医薬品を併用したレジメンとしての報告は少なく，十分なエビデンスが少ないなかで治療が行われているのが現状である．
本検討では婦人科悪性腫瘍における重要なレジメンである，パクリタキセル・カルボプラチン療法における切り替えによる安全性の差異を確認した．結果として，血液毒性，筋肉痛及び関節痛については，切り替え後も同等である可能性が示唆された．他の非血液毒性については，切り替えによりオッズ比は低下傾向であったが，同等性は保証され

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なかった．また，治療中に減量を必要とした症例数に有意な差は認められず，切り替え後も安全性が保たれていることが示唆された．今後も症例数を重ね，より科学的根拠のある報告をする必要がある．

キーワード：後発医薬品，安全性，パクリタキセル，カルボプラチン

Introduction

Generic drugs are considered equivalent to original drugs in quality, efficacy, and safety, and are generally less costly. In order to reduce the burden on patients and improve the health care insurance budget, the Japanese government encourages the use of generic drugs. Generic drug substitution can contribute greatly to the health economics of cancer therapy, where drug costs are particularly high. One drawback of generic drug substitution is that reports are not required to include clinical testing. Because of the narrow safety margins in the field of cancer chemotherapy, differences in adverse reactions with substitution are especially likely to affect treatment. This highlights the need for clinical assessment of these drugs.

Paclitaxel and carboplatin therapy (hereafter, TC therapy) is well established as one of the main chemotherapy regimens for the treatment of gynecologic malignancies. It is the first-line chemotherapy for ovarian cancer. In the GOG-0218 trial, it was shown to improve progression-free survival (PFS) in combination with bevacizumab [1], elevating it to an even more important position among treatment regimens. While there is no firm evidence for its use as a first-line therapy in recurrent or metastatic cervical cancer and uterine cancer, TC therapy is often chosen in clinical settings for its ease of administration and high tolerability. In the JCOG0505 trial, the main side effects of TC therapy were hematologic toxicities such as neutropenia (Grade 4, 45.2％) and anemia (Grade 4, 14.3％), as well as allergic reactions (Grade 2, 3.2％) and arthralgia (Grade 2, 20.6％) [2]. However, there are no similar published reports of the side effects in TC therapy using generic drugs. Because our hospital has been using generics for both paclitaxel and carboplatin since 2012, we investigated whether the therapy has remained safe after the substitution.

Methods

1. Subjects

Patients began receiving tri-weekly TC therapy for uterine, cervical, or ovarian cancer at Kindai University Hospital between January 2008 and December 2016. There were two subject groups: 1) the original drugs (hereafter, orig. TC) group: 47 patients who received Taxol® Injection (Bristol-Myers Squibb Company) and Paraplatin® Injection (Bristol-Myers Squibb Company), and 2) the generic drugs (hereafter, gx. TC) group: 53 patients who received Paclitaxel Injection "Sawai"® (Sawai Pharmaceutical Co., Ltd.) and Carboplatin Intravenous Infusion "NK"® (Nippon Kayaku Co., Ltd.). Patients with prior history of chemotherapy, and those who underwent surgery and cases with bevacizumab in combination during the observation were excluded. The observation period lasted for 6 treatment courses according to each clinical guideline. Our hospital's gynecology clinic administers tri-weekly TC therapy using paclitaxel at a dose of 180 mg/m^2 and carboplatin at target AUC=6 once every three weeks, regardless of cancer type (Table 1).

Table 1　Tri-weekly TC therapy

Drug	Dose	Administration
Rp.1		
Dexamethasone	16.5 mg	15 minutes
Famotidine	20 mg	
5-HT3 antagonists*		
(Diphenhydramine 50 mg p.o.)		
Rp.2		
Paclitaxel**	180 mg/m^2	3 hours
Rp.3		
Carboplatin***	AUC=6	1 hours

*Granisetron 3 mg, Ramosetron 0.3 mg, or Palonosetron 0.75 mg
** Taxol® Injection, or Paclitaxel Injection "Sawai"®
*** Paraplatin® Injection, or Carboplatin Intravenous Infusion "NK"®

2. Safety assessment

We performed a safety assessment which retrospectively investigated patient characteristics and manifestation of adverse events. Myelosuppression, febrile neutropenia, hypersensitivity, hepatotoxicity, nephrotoxicity, rash, myalgia and arthralgia, which have been generally reported in TC therapy and which could be retrospectively investigated, were evaluated as adverse event items. Adverse events were graded for assessment according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0-JCOG.

3. Statistical analysis

Student's t-test was used for comparisons between two sample means, and Fisher's exact test was used to analyze contingency tables. For all tests, a p-value of <0.05 was considered statistically significant. For each adverse event, clinical acceptance range of the odds ratio was set to [0, 2]. We admit that even rare adverse events will not exceed 2 times, and assumed that safety is equivalent within the range.

Results

1. Patient characteristics

Tables 2 and 3 show the characteristics of patients in the original and generic groups.

There was no difference in age, body surface area, liver function, renal function, and bone marrow function between the groups (Table 2). In addition, we compared aspects of treatment for each group, including the initial dose, relative treatment intensity, duration of treatment (measured in days until the final administration), number of treatment courses, number of cases with dose reductions during the 6 courses, and number of cases showing disease progression during the 6 courses. We found no differences between groups (Table 3).

2. Adverse events

Hematologic toxicity was a relatively frequent reported adverse event in tri-weekly TC therapy. In particular, we investigated occurrences of Grade 3 and higher anemia, neutropenia, thrombocytopenia,

Table 2　Background of patients studied

	orig. TC		gx. TC		p value [a)]
Characterstics	N	%	N	%	
No. of patients	47		53		
Age(y)	56.6(27-80)		56.6(34-76)		n.p
Original cancer					
ovarian	23	48.9	17	32.0	
cervix	10	21.3	9	17.0	
uterine	14	29.8	27	51.0	
Baseline					
Body Surface Area	1.501m^2		1.536m^2		0.226
Ccr(mL/min) *	89.75		94.48		0.465
AST(U/L)	20.6		20.9		0.874
ALT(U/L)	17.8		17.9		0.966
t-Bil(mg/dL)	0.47		0.46		0.824
WBC(/μL)	5786		5653		0.741
Neutrophil (/μL)	3477		3348		0.698
Platelet(× 10^4/μL)	24.7		25.1		0.656
Hemoglobin(g/dL)	13.5		13.3		0.685

Abbreviations :TC paclitaxel+carboplatin; orig. original drug; gx. generic drug; Ccr Creatinine Clearance; AST Aspartate Aminotransferase; ALT Alanine transaminase; t-Bil Total Bilirubin

a) student's t-test

*The creatinine clearance estimated by Cockcroft & Gault equation.

Table 3　Therapy parameters in patients

Parameters	orig. TC (N=47)		gx. TC (N=53)		p value
	N	%	N	%	
No. of treatment days	97.3		101.4		0.530 a)
No. of treatment cycles	5.21		5.38		0.541 a)
Dose reduction for any reason					
yes	12	25.5	13	24.5	0.947 b)
no	35	74.5	40	75.5	
Progression of disease by 6 cycles	1	2.1	2	3.8	0.947 b)
PTX					
Initial dose (mg/body)	274.8		276.7		0.749 a)
Relative dose intensity (%)	92.4		94.6		0.105 a)
CBDCA					
Initial dose (mg/body)	592.9		614.1		0.330 a)
Relative dose intensity (%)	91.0		88.8		0.349 a)

Abbreviations :TC paclitaxel+carboplatin; orig. original drug; gx. generic drug; PTX paclitaxel; CBDCA carboplatin
Data show therapy parameters in patients.
a) student's t-test
b) Fisher's exact test

etc., which often lead to difficulties such as dose restriction or discontinuation of treatment in performing medical care. As a result, equivalence was suggested, although there was a trend toward these events being somewhat more frequent in the original group. For febrile neutropenia, odds ratio showed a decreasing trend of 0.575 (95% CI: 0.092 to 3.600), although equivalence was not guaranteed (Table 4).

For non-hematologic toxicities, we analyzed Grade 2 and higher adverse events, which are relatively likely to affect activities of daily living (ADL). We analyzed allergic reactions because they are a particularly important adverse event to consider for both paclitaxel and carboplatin, with major implications for continuation of treatment. However, the odds ratio was 0.432 (95％ CI: 0.037 to 4.931) and equivalency was not guaranteed. For myalgia and arthralgia, the odds ratio was 0.839 (95% CI: 0.365 to 1.926) and thus equivalency was suggested. Although other items including nephrotoxicity and hepatotoxicity were investigated, equivalency was not guaranteed (Table 4).

Discussion

The biggest advantage of switching from original drugs to generics is the reduction in treatment costs. The pressure put on the medical economy by high treatment costs is becoming an issue, particularly in the field of cancer drugs where generic substitution can produce large economic benefits. Generic drugs are assessed based on data from bioequivalence, dissolution, and safety testing. However, they may use different additives, and there is no requirement to report clinical data. In addition, there are a few reports of generic drug substitution leading to an increase in adverse events[3] which, while extremely rare, leave concerns about the safety of generic drugs. Several previous studies have reported on generic versions of Paclitaxel. Yamamoto *et al*[4], focused on differences in additive composition between Paclitaxel [NK]® and Taxol® in a retrospective investigation into differences in side effects, although they used a different formulation from that used here. They reported no major effects on safety between the treatments; however, because there were no reports on the

Table 4　Occurrence of adverse events

	orig.TC (N=47)	gx.TC (N=53)	OR of non-AE (95% CI)	p value [a)]
	Number (%)			
Hematologic toxicities(grade 3-4)				
Anemia	14(29.8%)	10(18.9%)	0.548(0.216-1.389)	0.244
Neutropenia	45(95.7%)	47(88.7%)	0.348(0.066-1.815)	0.276
Thrombocytopenia	11(23.4%)	8(15.1%)	0.582(0.211-1.589)	0.290
Febrile Neutropenia	3(6.4%)	2(3.8%)	0.575(0.092-3.600)	0.664
Non-hematologic toxicities(grade 2-4)				
Acute kidney injury	1(2.1%)	1(1.9%)	0.885(0.053-14.548)	1.000
AST increased	3(6.4%)	3(5.7%)	0.880(0.169-4.586)	1.000
ALT increased	6(12.7%)	6(11.3%)	0.872(0.261-2.915)	0.824
Blood t-Bil increased	1(2.1%)	1(1.9%)	0.885(0.053-14.548)	1.000
Hypersensitivity/allergy				
PTX	2(4.3%)	1(1.9%)	0.432(0.037-4.931)	0.600
CBDCA	0	0	—	—
Pain (myalgia/arthralgia)	32(68.1%)	34(64.2%)	0.839(0.365-1.926)	0.833
Rash	0	0	—	—

Abbreviations: TC paclitaxel+carboplatin; orig. original drug; gx. generic drug; PTX paclitaxel; CBDCA carboplatin; OR Odds ratio; AST Aspartate Aminotransferase; ALT Alanine transaminase; t-Bil Total Bilirubin
Data show number of patients experiencing adverse events.
a) Fisher's exact test

paclitaxel formulation used by our hospital, we felt the need to perform a similar investigation. This paclitaxel formulation also includes the additive cremophor, which can reportedly contain impurities linked to liver damage[5)]. Because additives are not required to be equivalent to those in the original drug, differences in the cremophor could affect the drugs' clinical use. In addition, while there have been separate comparative reports on generic substitution of paclitaxel and carboplatin, there are few reports on the safety of administering both generic drugs together. Patients are currently being treated with generic regimens despite a lack of sufficient evidence for the long-term performance and pharmacokinetics of the two-drug combination.

We limited this study to ovarian cancer, where TC therapy is the first-line therapy, and cervical and uterine cancer, where it is often used as a first-line therapy due to factors such as convenience. This enabled us to investigate a relatively uniform population in terms of sex, starting dose, and other patient characteristics. Because of this and the fact that we saw no significant differences in relative treatment intensity, we believe that the two groups can be consistently compared.

When comparing adverse events, we were concerned about differences in supportive care. In particular, treatment days, relative dose intensity, and febrile neutropenia may be affected by G-CSF and transfusions. Unfortunately, it is difficult to evaluate how much it was affected; however, there was no significant difference in treatment days and relative dose intensity in this study.

A number of adverse events have been reported in TC therapy. In this study, we paid particular attention to Grade 3 and higher hematologic toxicities as well as allergic reactions, which often lead to discontinuation of treatment or dose reductions. As a result, hematologic toxicity was suggested to be equivalent, although it was highly observed in the original group. The odds ratio of allergic reactions,

an important evaluation item in this study, was 0.432 (95% CI: 0.037 to 4.931). Approximately 150 cases are required in each group to guarantee the equivalency at an odds ratio of 0.432. In addition, about 1250 cases are necessary if the power is 0.9 in order to prove statistically equivalent in allergy. This report is a preliminary investigation because the number of cases was insufficient, and the study was conducted in a single institution. Note that we would normally analyze peripheral neuropathy as well, as it is a characteristic adverse event for tri-weekly TC therapy, but ultimately chose not to in this study because 1) it is usually caused by paclitaxel itself, 2) supportive care for peripheral neuropathy has increased, 3) it is a pharmacological adverse event, and the effects of additives are expected to be comparatively less than for events like allergies, and 4) previous studies have already reported on peripheral neuropathy in generic formulations of paclitaxel, and concluded that there is no significant difference [6, 7].

We also saw no significant difference between groups in the proportion of dose decreases or discontinuation, or in disease progression during treatment. In this study, the number of cases is insufficient, and it is not possible to prove equivalence. However, the treatment intensity was suggested to be maintained even after the substitution. It is necessary to prove equivalence by focusing only on adverse effects that do not affect blood concentrations like allergic reactions and by increasing the number of cases.

Study approval and conflict of interest declaration

This study was conducted with the approval of the Kindai University Hospital Ethics Committee and the Kindai University Faculty of Pharmacy Ethics Committee. None of the authors have any corporate conflicts of interest to declare.

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