Chemosensitivity Testing of Paclitaxel *versus* Docetaxel in Human Gynecological Carcinomas: A Comparison with Carboplatin

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Abstract. *Background: The tetrazolium dye (MTT) assay is useful in predicting chemosensitivity. Materials and Methods: Using the MTT assay, an in vitro chemosensitivity test was designed for paclitaxel and docetaxel. The results were then compared with the sensitivity to carboplatin in 60 resected gynecological carcinomas. Results: The mean tumor inhibition rates [I.R.s; %] for paclitaxel, docetaxel and carboplatin were all higher in ovarian carcinomas than in endometrial carcinomas [74.3% vs. 47.3% ($p<0.01$), 57.2% vs. 21.9% ($p<0.001$), 71.3% vs. 50.1% ($p<0.01$), respectively]. In 28 ovarian carcinomas, the I.R.s for paclitaxel and carboplatin were higher than docetaxel [74.3% and 71.3% vs. 57.2%, respectively ($p<0.05$)]. In particular, the I.R. for paclitaxel was significantly higher than docetaxel [83.0% vs. 62.9% ($p<0.05$)] in serous adenocarcinomas. In clear cell adenocarcinomas, however, both the I.R.s for paclitaxel and docetaxel were significantly lower than carboplatin [27.8% and 23.3% vs. 58.5%, respectively ($p<0.01$)]. In 10 cervical carcinomas, the I.R. for docetaxel was significantly lower than paclitaxel and carboplatin [39.5% vs. 64.1% and 60.5%, respectively ($p<0.05$)]. In 22 endometrial carcinomas, the I.R. for docetaxel was also lower than paclitaxel and carboplatin [21.9% vs. 47.4% and 50.1% ($p<0.01$, $p<0.001$, respectively)]. Furthermore, the I.R. for docetaxel was significantly lower in G2 and G3 adenocarcinomas [16.9% vs. 45.8% and 52.8% ($p<0.05$, $p<0.01$, respectively)] [16.5% vs. 46.2% and 53.2% ($p<0.01$, $p<0.001$, respectively)]. Conclusion: The antitumor activity of both paclitaxel and docetaxel was higher in ovarian carcinomas than in endometrial carcinomas. In ovarian carcinomas, however, paclitaxel and carboplatin were superior to docetaxel. In cervical and endometrial carcinomas, docetaxel was significantly worse than paclitaxel and carboplatin.*

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Paclitaxel has been reported to be an active anticancer agent used to treat gynecological malignancies, such as ovarian (1-5), uterine cervical (6-8) and endometrial carcinomas (9). It acts by promoting the assembly of microtubules even in the presence of calcium chloride and at low temperatures, conditions that normally induce tubulin depolymerisation (10). In particular, paclitaxel and carboplatin have been accepted as "standard-chemotherapy" for first-line treatment of ovarian carcinomas. However, paclitaxel has been questioned for its effectiveness against uterine, cervical and endometrial carcinomas.

In vitro, another taxane drug called docetaxel binds to microtubules with a higher affinity compared to paclitaxel, and is capable of killing paclitaxel-resistant cell lines, suggesting a degree of non-cross resistance between these two drugs (11, 12). Therefore, one can select docetaxel as a second taxoid derivative against gynecological malignancies. Some reports of the clinical effectiveness of docetaxel in gynecological malignancies have appeared (13-18). At present, several clinical trials with paclitaxel and docetaxel in gynecological carcinomas are ongoing, but any comparison of the two drugs' antitumor effects would be premature, because this requires extensive examination with a large number of patients.

In the present study, a comparative examination was performed on the *in vitro* activity of paclitaxel, docetaxel and carboplatin against 60 human gynecological malignancies (28 ovarian, 10 cervical and 22 endometrial carcinomas) using the tetrazolium dye (MTT) assay in order to obtain chemotherapeutic indices of these substances against these malignancies.

Materials and Methods

Tissues. The tumor specimens were obtained from patients during primary surgery at the Department of Obstetrics and Gynecology of Himeji Medical Center and Tenri Hospital, Japan. All tissues were obtained from untreated patients. Informed consent was obtained from each patient in advance. Twenty-eight ovarian

Table I. *The I.R.s for paclitaxel versus docetaxel in 28 ovarian carcinomas and their differences between the different histological subtypes, in comparison with carboplatin.*

		Carcinoma type			
	n=28	Serous (n=15)	Poorly diff.(n=5)	Clear cell (n=6)	Mucinous (n=2)
I.R. for paclitaxel (%)	74.3±25.2*	83.0±13.8**	90.5±3.2	27.8±9.1***	84.8±6.9
I.R. for docetaxel (%)	57.2±36.5	62.9±36.1	67.1±46.5	23.3±9.9***	82.4±16.9
I.R. for carboplatin (%)	71.3±20.0*	78.1±15.5	74.7±15.5	58.5±21.5	50.2±39.7

I.R.: inhibition rate.
*significantly higher than docetaxel ($p<0.05$);
**significantly higher than docetaxel ($p<0.05$);
***significantly lower than carboplatin ($p<0.01$).

carcinoma, 10 cervical carcinoma and 22 endometrial carcinoma samples were collected. The specimens were collected directly into tissue-culture medium for cell culture. According to the International Federation of Gynecology and Obstetrics (FIGO) classification, the 28 ovarian carcinomas consisted of 2 stage-1a, 4 stage-1c, 1 stage-2 , 15 stage-3 and 6 stage-4 specimens. Histologically, there were 15 serous cystadenocarcinomas, 2 mucinous cystadenocarcinomas, 6 clear cell adenocarcinomas and 5 poorly-differentiated adenocarcinomas. With respect to the 10 cervical carcinomas, 4 stage-1b, 3 stage-2b and 3 stage 3b specimens were found. Histologically, all 10 were squamous cell carcinomas. The 22 endometrial carcinomas consisted of 16 stage-1 and 6 stage-3 specimens. Histologically, all 22 endometrial carcinomas were of the endometrioid type of which 6 were well-differentiated (G1), 7 moderately-differentiated (G2) and 9 poorly-differentiated (G3) adenocarcinomas.

Drugs. The drugs used were paclitaxel (Taxol; Bristol-Myers Squibb Co., Tokyo, Japan), docetaxel (Taxotere; Sanofi-Aventis Co., Tokyo, Japan) and carboplatin (Paraplatin; Bristol-Myers Squibb Co.). The following reported peak plasma concentrations (PPC), corresponding to 100% PPC, were used in accordance with previously reported data: paclitaxel 6.7 μg/ml (clinical dosage 210 mg/m^2) (19), docetaxel 2.8 μg/ml (clinical dosage 90 mg/m^2) (20) and carboplatin 35.6 μg/ml (clinical dosage 375 mg/m^2, AUC 123.7 μg hr/ml) (21). We used 1PPC for each chemotherapeutic agent in the MTT assay.

MTT assay. Fresh surgical specimens of ovarian, cervical and endometrial carcinomas were obtained from women who underwent surgical resection. The tissues were minced by scissors in RPMI 1640 medium (Nissui corp., Tokyo, Japan) containing 20% fetal calf serum and 0.3 g/l glutamine. The tumor cells were then incubated at 37˚C for 30 min in an enzyme cocktail containing 0.02% deoxyribonuclease I (Sigma, St. Louis, USA), 0.05% pronase (Calbiochem, Dormstadt, Germany) and 0.02% collagenase. The tumor cell suspension (5x10^5 cells/ml) was then strained through a 150-μm stainless steel mesh. The cells were centrifuged at 1,000 rpm for 5 min, and after rinsing twice, the viable carcinoma cells were verified using 0.25% trypan blue dye exclusion (Sigma). The cell number was adjusted to 1-2x10^5 cells/ml, and a 180-μl aliquot of the tumor cell suspension was plated into each well of 96-well cell culture plates (Nunc Inc., Rochester, USA), followed by the addition of 20 μl of 1PPC of each chemotherapeutic agent. The cells were then incubated at 37˚C for 72 h in a 5% CO_2 incubator. After the cells were washed with phosphate-buffered saline, 25 μl of MTT (2 mg/ml) (Sigma) was added, and the mixture was allowed to incubate for 4 h at 37˚C. The plates were then centrifuged at 1,800 rpm for 10 min; the supernatant was then removed and the formazan was eluted with 150 μl of DMSO (Nakarai Tesque, Kyoto, Japan). The optical density (OD) was finally measured with an enzyme-linked immunosorbent assay (ELISA) reader (NJ-2000, Japanese Intermed.) at 540 nm. The tumor inhibition rate (I.R.) was calculated from the following equation:

$$\text{I.R. } (\%) = (1 - T/C) \times 100\%$$

where T=OD540 of the treated cells and C=OD540 of the control cells. The drug was judged to be effective or ineffective when the I.R. was >50% or <50%, respectively.

Statistical analysis. The analyses of the chemosensitivity were performed using Student's *t*-test. $p<0.05$ was considered to be statistically significant.

Results

Tumor sensitivity to paclitaxel, docetaxel and carboplatin in ovarian carcinoma. A comparison of the sensitivities to paclitaxel, docetaxel and carboplatin in the 28 ovarian carcinomas and their differences among the different histological subtypes are listed in Table I. The mean I.R.s for paclitaxel, docetaxel and carboplatin were 74.3%, 57.2% and 71.3%. The I.R.s were all relatively high. In particular, the I.R.s for paclitaxel and carboplatin were greater than that for docetaxel ($p<0.05$). Among the different histological subtypes, there were different anti-tumor sensitivities. The I.R. for paclitaxel in serous adenocarcinomas was significantly higher than docetaxel [83.0% *vs.* 62.9%, $p<0.05$]. There were no significant differences between the I.R for paclitaxel and carboplatin [83.0% *vs.* 78.1%]. However, the I.R.s for both paclitaxel and docetaxel in clear cell adenocarcinomas were significantly lower than that for carboplatin [27.8% and 23.3% *vs.* 58.5%, respectively, $p<0.01$]. There were no significant differences in poorly-differentiated and mucinous adenocarcinomas [90.5%, 67.1%, 74.7% and 84.8%, 82.4%, 50.2%]. These rates were all relatively high.

Tumor sensitivity to paclitaxel, docetaxel and carboplatin in uterine cervical carcinoma. A comparison of the sensitivities to paclitaxel, docetaxel and carboplatin in the 10 cervical carcinomas is shown in Table II. The mean I.R.s for paclitaxel, docetaxel and carboplatin were 64.1%, 39.5% and 60.5% in cervical carcinomas. The I.R. for docetaxel was significantly lower than for paclitaxel and carboplatin ($p<0.05$%) (Table II).

Tumor sensitivity to paclitaxel, docetaxel and carboplatin in uterine endometrial carcinoma. A comparison of the sensitivities to paclitaxel, docetaxel and carboplatin in the 22 endometrial carcinomas and their differences between the various histological grades are listed in Table III. The mean I.R.s for paclitaxel, docetaxel and carboplatin were 47.4%, 21.9% and 50.1%. The I.R. for docetaxel was significantly lower than those for paclitaxel and carboplatin ($p<0.01$, $p<0.001$, respectively). Among the different histological grades, there were different anti-tumor sensitivities. In G2 and G3 adenocarcinomas, the I.R. for docetaxel was significantly lower than for paclitaxel and carboplatin [16.9% *vs.* 45.8% and 52.8%; 16.5% *vs.* 46.2% and 53.2%, ($p<0.05$, $p<0.01$; $p<0.01$, $p<0.001$, respectively). However, no statistically different sensitivities to paclitaxel, docetaxel and carboplatin were observed in the G1 adenocarcinomas [50.4%, 34.2%, 42.5%, respectively].

Finally, we compared the I.R.s for paclitaxel, docetaxel and carboplatin among ovarian, cervical and endometrial carcinomas. The I.R.s for both paclitaxel and docetaxel in ovarian carcinomas were significantly higher than in endometrial carcinomas [74.3% *vs.* 47.4%, $p<0.01$; 57.2% *vs.* 21.9%, $p<0.001$, respectively]. The same tendency was found with respect to carboplatin [71.3% *vs.* 50.1%, $p<0.01$] (Table IV).

Table II. *The I.R.s for paclitaxel versus docetaxel in 10 cervical carcinomas, in comparison with carboplatin. All 10 were squamous cell carcinomas.*

	n=10
I.R. for paclitaxel (%)	64.1±18.7
I.R. for docetaxel (%)	39.5±31.2*
I.R. for carboplatin (%)	60.5±13.5

I.R.: inhibition rate.
*significantly lower than paclitaxel and carboplatin ($p<0.05$, respectively).

Discussion

We previously reported high accuracy rates for the MTT assay (81.3%) in 16 gynecological carcinomas (22). Furthermore, the overall accuracy of the MTT assay in predicting the clinical efficacy has been reported to be 78% in 45 patients with advanced gastric cancers (23). These results support the usefulness of the MTT assay for the *in vitro* chemosensitivity testing of fresh surgical specimens. Therefore, we used the MTT assay as a chemotherapeutic index.

Paclitaxel and cisplatin are the most active drugs against ovarian carcinoma. Since these two drugs have different mechanisms of action and toxicity profiles, they have been used in combination against advanced ovarian carcinomas or recurrent carcinomas as a first-line chemotherapy. Gronlund *et al.* (2) treated 43 patients who received carboplatin and paclitaxel as their first-line chemotherapy. The overall response rate was found to be 84% (complete recovery (CR) rate of 57%) in the 37 evaluable patients. Rose *et al.* (1) also found an overall response rate of 90% (CR rate of 70%) among 20 evaluable patients treated with carboplatin and paclitaxel. These high anti-tumor response rates against ovarian carcinomas are consistent with our present data with the I.R.s for paclitaxel and carboplatin of 74.3% and 71.3 %, respectively. This combination chemotherapy has been widely used as first-line chemotherapy against ovarian carcinomas throughout the world. Our present study also showed high rates of antitumor effect for both paclitaxel and docetaxel [74.3% *vs.* 57.2%] against ovarian carcinomas. However, there were statistically significant differences between them ($p<0.05$). Clinically, the overall response rates of docetaxel and platinum combined chemotherapy against ovarian carcinomas have been reported to be around 58-73% (14, 15). These rates were thought to be high, but slightly inferior to paclitaxel combined chemotherapy. However, neurotoxicity of docetaxel combined chemotherapy was less severe than that seen with paclitaxel combined chemotherapy (14). Therefore, docetaxel combined with cisplatin or carboplatin is now indicated as part of the first-line therapy against ovarian carcinoma (13). This requires further clinical examination and development of their means of administration. Histologically, against serous adenocarcinomas of the ovary, paclitaxel was more effective than docetaxel [83.0% *vs.* 62.9%, $p<0.05$]. Of the many kinds of ovarian carcinomas, we would choose paclitaxel combined chemotherapy against this histological subtype. Against clear cell adenocarcinoma of the ovary, however, we should recognize the very low rates of antitumor efficacy for both paclitaxel and docetaxel [27.8% and 23.3%]. In brief, there is difficulty in using taxane-combined chemotherapy against clear cell adenocarcinoma of the ovary.

With regard to cervical carcinomas, the antitumor activity rates of paclitaxel and docetaxel in our data were 64.1% and 39.5% ($p<0.05$). In Japan, clinical reports of taxanes have not been produced. On a worldwide level, however, a few clinical reports of paclitaxel against cervical carcinomas can be found. The overall clinical response rates of paclitaxel and platinum combined chemotherapies against cervical carcinomas have been reported to be 36% (8), 60% (7) and 90.7% (6). This

Table III. *The I.R.s for paclitaxel versus docetaxel in 22 endometrial carcinomas and their differences between the various histological grades, in comparison with carboplatin.*

	n=22	G1	G2	G3
I.R. for paclitaxel (%)	47.4±33.4	50.4±38.1	45.8±29.9	46.2±35.5
I.R. for docetaxel (%)	21.9±23.3*	34.2±37.2	16.9±16.1**	16.5±12.8***
I.R. for carboplatin (%)	50.1±25.1	42.5±31.5	52.8±24.7	53.2±22.7

I.R.: inhibition rate.
*significantly lower than paclitaxel and carboplatin ($p<0.01$, $p<0.001$, respectively);
**significantly lower than paclitaxel and carboplatin ($p<0.05$, $p<0.01$, respectively);
***significantly lower than paclitaxel and carboplatin ($p<0.01$, $p<0.001$, respectively).

Table VI. *Relationship between the I.R.s for paclitaxel, docetaxel and carboplatin in 28 ovarian, 10 cervical and 22 endometrial carcinomas.*

	Ovarian carcinoma	Cervical carcinoma	Endometrial carcinoma
I.R. for paclitaxel (%)	74.3±25.2*	64.1±18.7	47.4±33.4
I.R. for docetaxel (%)	57.2±36.5**	39.5±31.2	21.9±23.3
I.R. for carboplatin (%)	71.3±20.0*	60.5±13.5	50.1±25.1

I.R.: inhibition rate.
*,**Significantly higher in ovarian carcinomas than in endometrial carcinomas. ($p<0.01$, $p<0.001$, respectively).

seems to represent a wide range, and the remains unexplained. Platinum drugs are the most active and widely used option in the treatment of squamous cell carcinoma of the cervix. We previously reported that the *in vitro* I.R. for a novel platinum analog, nedaplatin (254-S), was 70.7% and it was equal or superior to cisplatin in cervical carcinomas (24). Other drugs shown to have considerable activity are the camptothecin derivatives irinotecan and topotecan (25), and vinorelbine (26). The clinical effectiveness of paclitaxel and platinum in the treatment of cervical carcinomas has not been established yet. However, this combined chemotherapy will be anticipated for the treatment of carcinomas as a first or second line chemotherapy in the near future, because their clinical response rates and *in vitro* activity are relatively high. On the other hand, trials with docetaxel are ongoing. Only one report showed a 13% (two patients) clinical response rate for a single docetaxel therapy (16). On the basis of our *in vitro* data, we hypothesize that docetaxel may not have superior antitumor activity against all cervical carcinomas. Considering our data, we should devise more effective docetaxel-combined chemotherapies against cervical carcinomas.

With regard to endometrial carcinomas, the *in vitro* antitumor activity of paclitaxel and docetaxel was lower (47.4 % and 21.9%, respectively). Histologically, the I.R. for docetaxel in G2 and G3 adenocarcinomas was significantly lower than paclitaxel and carboplatin (16.9% and 16.5%). This result was the reverse of nedaplatin (24) and irinotecan (25) in our previous reports. Trials for the clinical administration of taxanes are ongoing. A few of these trials have been reported, and a single infusion of paclitaxel has been reported in Japan by Hirai *et al.* (9). They reported that the overall response rate was 30.4%. Another report from the Gynecologic Oncology Group (GOG) showed a 27% response rate for a single paclitaxel infusion (27). These rates may be relatively low. In Japan, paclitaxel and carboplatin combined chemotherapy are currently being used. Recently, the GOG tried doxorubicin plus cisplatin plus paclitaxel chemotherapy. They obtained a response rate of 57% for that regimen (28). To our knowledge, there has been no research into docetaxel administration against endometrial carcinomas. A few case reports in the treatment of metastatic or recurrent endometrial carcinoma were found (17, 18). On the basis of our *in vitro* data, we cannot suggest the sole use of docetaxel against endometrial carcinomas.

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