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Biweekly administration of docetaxel and carboplatin for advanced or recurrent endometrial and ovarian carcinomas

D. Nakayama, H. Nishi, R. Kato, Y. Sagawa, F. Terauchi, K. Isaka

Department of Obstetrics and Gynecology, Tokyo Medical University, Shinjuku-ku, Tokyo (Japan)

Summary

Objective: To examine efficacy and safety of biweekly administration of docetaxel and carboplatin for advanced or recurrent endometrial and ovarian carcinomas. *Material and Methods*: The recommended doses were determined in the phase I study. In the phase II feasibility study, the primary end-point was safety, and the secondary end-point was response rate and progression-free survival (PFS). *Results*: The recommended doses of docetaxel and carboplatin were determined to be 45 mg/m^2 and AUC 3.0, respectively, in phase I study. In phase II feasibility study, no treatment-related death was observed. Most non-hematotoxicity cases were mild or moderate. Grade 4 neutropenia was confirmed in 13 patients (31.0%), whereas all cases showed tolerability with 2.6 days delay of anticancer drugs administration in both groups. Response rate was 55.0% in the ovarian carcinoma group, and average PFS was 8.7 months. In the endometrial carcinoma group, response rate was 50.0% and average PFS was 32.0 months. *Conclusion*: The present results showed that biweekly administration of docetaxel and carboplatin for advanced and recurrent endometrial and ovarian carcinomas results in acceptable side effects, response rate, and PFS.

Key words: Biweekly administration; Docetaxel; Carboplatin; Endometrial carcinoma; Ovarian carcinoma.

Introduction

Currently, taxane is widely used for treatment of a variety of malignant tumors throughout the world. The standard therapy for ovarian cancer is combined administration of paclitaxel with carboplatin every three weeks [1]. The response rate of paclitaxel and carboplatin administrated was 63-87% [2-4], and a high efficacy of the therapy has been shown in advanced or recurrent endometrial carcinoma. However, neurotoxicity, which is one of the side effects caused by paclitaxel, sometimes becomes severe and interferes with the treatment [5, 6].

Docetaxel exerts its anticancer effect by binding to microtubules and inhibiting depolymerization of the microtubules in the same manner as paclitaxel. In a comparative study of combined administration of paclitaxel with carboplatin and combined administration of docetaxel with carboplatin every three weeks as the first-line chemotherapy for patients with ovarian carcinoma, no significant differences were found in the progression-free survival (PFS) and response rate (58.7% *vs.* 59.5%) [7]. With regards to side effects of docetaxel and carboplatin administrated, however, notable strong myelosuppression and grade 3-4 neutropenia occurred (94% *vs.* 84%) compared to combined administration of paclitaxel with carboplatin. On the other hand, occurrence rates of neurotoxicity were 45% and 78% for neurosensory ($p < 0.001$) and 9% and 16% for neuromotor ($p < 0.001$), and were significantly mild [7].

Meanwhile, mitigation of side effects is expected with weekly administration of taxane and platinum, compared to a concomitant use of taxane and platinum with administration every three weeks, which is the standard administration. A number of clinical trials have been conducted to examine the efficacy of the weekly administration [8-11]. However, the weekly administration requires frequent office visits, which is inconvenience for patients and expected to increase healthcare costs. Results of some studies indicate that concomitant use of docetaxel and carboplatin by biweekly administration show favorable tolerability in patients with lung cancer [12, 13]. However, no study has been conducted to assess the efficacy and safety of biweekly administration of docetaxel and carboplatin for ovarian carcinoma and endometrial carcinoma, which would be very meaningful. Thus the present authors designed a phase I/II trial to examine efficacy and safety of biweekly administration of docetaxel and carboplatin for advanced or recurrent endometrial and ovarian carcinomas.

Materials and Methods

Patients

Twenty patients with ovarian carcinoma and 22 patients with endometrial carcinoma who gave their written agreement between April 2003 and October 2006 were included in this study. The median age of the patients with ovarian carcinoma and patients with endometrial carcinoma was 55.8 (35-69) years and 63.2 (49-74)

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years, respectively. ECOG Performance Status was 0 for seven patients, 1 for nine patients, and 2 for four4 patients in the ovarian carcinoma group and 0 for 11 patients, 1 for six patients, and 2 for five patients in the endometrial carcinoma group. According to the classification of International Federation of Gynecology and Obstetrics, two patients (10.0%) were classified as Stage IC, 16 patients (80.0%) as Stage IIIC, and two patients (10.0%) as Stage IV for advanced stages at the initial diagnosis in the ovarian carcinoma group, and eight patients (36.4%) were classified as Stage IB, five patients (22.7%) as Stage II, three patients (13.6%) as Stage IIIA, one patient (4.5%) as Stage IIIB, two patients (9.1%) as Stage IIIC1, and three patients (13.6%) as Stage IVB for advanced stages at the initial diagnosis in the endometrial carcinoma group. All of 20 patients with ovarian carcinoma were recurrent cases, four patients were determined as recurrent because the CA125 value became two times higher than the upper limit of the reference value, the others had measurable disease. Nineteen of 22 patients with endometrial carcinoma were recurrent cases, and all cases, included three advanced cases (Stage IVB), had measurable disease.

Methods

To examine efficacy and safety of biweekly administration of docetaxel with carboplatin therapy, recommended dose were determined in the phase I study; in the phase II feasibility study, the primary end-point was safety, and the secondary end-point was response rate and PFS. Of recurrent and advanced epithelial ovarian carcinoma and recurrent and advanced endometrial carcinoma cases, patients who were 20 years and older and below 75 years of age, whose ECOG Performance Status was 0-2, who maintained major organ functions, and who gave written agreement were included in the study. Intravenous drip infusion was conducted biweekly, and dose-limiting toxicity (DLT) was grade 4 hematotoxicity and Grade 3 non-hematotoxicity. As premedication, eight mg of dexamethasone and antiemetic agent (5HT3 antagonist) were dissolved into 100 ml of saline and administered by intravenous drip infusion 30 minutes before the docetaxel administration. Docetaxel was dissolved into 250 ml of 5% glucose solution or saline, and administered by intravenous drip infusion over 60 minutes. Carboplatin was dissolved into 100 ml of saline, and administered by intravenous drip infusion over 60 minutes.

Initial dose was 40 mg/m^2 for docetaxel and AUC 3.0 for carboplatin (level 1). Docetaxel and carboplatin were 35 mg/m^2 and AUC 3.0 for level 0, 45 mg/m^2 and AUC 3.0 for level 2, and 50 mg/m^2 and AUC 3.0 for level 3, respectively. Table 1 shows dose-escalation scheme. First, one cycle of level 1 administration was given to three patients, and the presence or absence of adverse drug reaction in each patient at each administration level was observed. The adverse reaction was evaluated according to the National Cancer Institute - Common Toxicity Criteria (NCI-CTC Version 3.0) [14]. Anticancer drugs at a dose determined at level 1 were administered in three patients, and the incidence of side effects was observed. The level was increased one level when no DLT occurred, and maximum-tolerated dose (MTD) was determined as the dose one level lower than the level at which DLT occurred in all three patients. When DLT occurred only in one or two of three patients, the same amount was administered in three new patients again, and the level was further increased if DLT occurred in two patients or less in six patients. If DLT occurred in at least three patients, MTD was determined as the dose one level lower.

Phase II feasibility study was conducted based on the recommended dose obtained in phase I. Toxicity was evaluated in all patients who received the treatment at every cycle. NCI-CTC Version 3.0 was used for the evaluation [14]. Response evaluation was conducted as follows for patients with a lesion available for two-dimensional measurement. The evaluation was conducted two times with at least four week intervals. Complete response (CR) was defined as CR of all measurable lesions and evaluable lesions determined by two separately conducted determinations. Partial response (PR) was defined as at least 50% decrease in the sum of the product of the vertical diameter of an evaluable lesion. Progressive disease (PD) was defined as a 25% or greater increase in the sum of the product of the vertical diameter of an evaluable lesion or appearance of new lesions. NE was defined as changes was not evaluable. Stable disease (SD) was defined as changes that do neither correspond to CR, PR, PD nor not evaluable (NE).

When no evaluable pathological changes were observed and recurrence was determined because of increase of CA125 value over the upper limit of the reference value or at least two times increase of the nadir level, efficacy was determined according to the CA125 criteria [15].

Table 1. — *Dose-escalation scheme.*

	DOC (mg/m2)	CBDCA AUC
Level 0	35	3.0
Level 1	40	3.0
Level 2	45	3.0
Level 3	50	3.0

Table 2. — *Hematologic toxicity of ovarian cancer group.*

Hematologic	G3	G4	Grade 4 (%)
Neutropenia	3	6	6 (30.0)
Febrile neutropenia	0	0	0
Anemia	3	1	1 (5.0)
Thrombocytopenia	2	0	0

Table 3. — *Hematologic toxicity of endometrial cancer group*

Hematologic	G3	G4	Grade 4 (%)
Neutropenia	4	7	7 (31.8)
Febrile neutropenia	0	0	0
Anemia	3	0	0
Thrombocytopenia	3	0	0

Results

Determination of recommended dose

No DLT was observed in three cases at level 1 or level 2. The recommended doses of docetaxel and carboplatin were determined to be 45 mg/m^2 and AUC 3.0 at level 2, respectively, in phase I study, because DLT was observed in all three cases at level 3.

Toxicity

No treatment-related death was observed. Hematotoxicity results of ovarian carcinoma group and endometrial carcinoma group are summarized in Tables 2 and 3, respectively.

Table 4. — *Non-hematologic toxicity of ovarian cancer group*

Non-hematologic	G1	G2	G3	G4	Grade 3-4 (%)
Anorexia	1	2	0	0	0 (0)
Nausea/vomiting	3	4	0	0	0 (0)
Fatigue	4	2	0	0	0 (0)
Diarrhea	2	1	0	0	0 (0)
Alopecia	3	1	0	0	0 (0)
Neuropathy	2	1	0	0	0 (0)
Dysgeusia	4	0	0	0	0 (0)
Myalgia	1	0	0	0	0 (0)
ALT/AST	2	1	0	0	0 (0)
Nail change	4	1	0	0	0 (0)
Stomatitis	1	1	0	0	0 (0)
Allergic reaction	2	0	0	0	0 (0)

Table 5. — *Non-hematologic toxicity of endometrial cancer group*

Non-hematologic	G1	G2	G3	G4	Grade 3-4 (%)
Anorexia	2	2	0	0	0 (0)
Nausea/vomiting	4	4	0	0	0 (0)
Fatigue	5	2	0	0	0 (0)
Diarrhea	1	1	1	0	1 (4.5)
Alopecia	4	1	0	0	0 (0)
Neuropathy	1	1	0	0	0 (0)
Dysgeusia	3	0	0	0	0 (0)
Myalgia	2	0	0	0	0 (0)
ALT/AST	3	1	0	0	0 (0)
Nail change	4	0	0	0	0 (0)
Stomatitis	1	2	0	0	0 (0)
Allergic reaction	1	0	0	1	1 (4.5)

Anemia caused as a side effect of the treatment was confirmed in three patients (15.0%) for grade 3 and one patient (5.0%) for grade 4 in the ovarian carcinoma group. Anemia in either patient was improved by blood transfusion, but anticancer drug administration was delayed for three days and dose was reduced to the amount of level 1 for the latter patient. On the other hand, in the endometrial carcinoma group, anemia was confirmed in three patients (15.0%) for grade 3. Neutropenia was confirmed in seven patients (16.7%) for grade 3 and 13 patients (31.0%) for grade 4; however, administration of anticancer drugs was conducted after an average of 2.6 days of postponement because of administration of recombinant human granulocyte colony-stimulating factor (rhG-CSF). No patient developed febrile neutropenia in both groups. Non-hematotoxicity results of ovarian carcinoma group and endometrial carcinoma group are summarized in Tables 4 and 5, respectively. Most non-hematotoxicity cases were mild or moderate, and were transient with the exception of one case of endometrial carcinoma in which the treatment was discontinued because of anaphylactic shock during the third course of the treatment and one case of frequent diarrhea. In addition, the color of the nails of nine patients changed into dark brown (grade 1), and one patient experienced deformation and loss of nails (grade 2). Neuropathy was observed in three patients at grade 1 and in two patients at grade 2.

Response and survival

On average, administration was conducted 8.3 times (ovarian carcinoma group, 7.8 (1-15) times; endometrial carcinoma group, 8.6 (4-12) times). Response rate was 55.0% in the ovarian carcinoma group (CR: eight cases, PR: three cases, SD: one case, PD: three cases, NE: one case), and average PFS was 8.7 months. In the endometrial carcinoma group, response rate was 50.0% (CR: five cases, PR: six cases, SD: one case, PD: three cases, NE: three cases) and average PFS was 32.0 months. Table 6 shows the response rate.

Table 6. — *Response rate.*

	CR	PR	SD	PD	NE	Response rate (%)
Ovarian cancer (n=20)	8	3	1	3	1	55.0
Endometrial cancer (n=22)	5	6	1	3	3	50.0

Discussion

Taxane anticancer agents have previously indicated efficacy against ovarian and endometrial carcinomas. It is reported that the response rate of paclitaxel alone for advanced or recurrent endometrial carcinoma is 27-36% [16, 17], and 21-34% for docetaxel [18-20]. Doxorubicin plus cisplatin therapy (AP) and cyclophosphamide, doxorubicin, and cisplatin therapy (CAP) have been used for endometrial carcinomas since the 1980s [21, 22]. It was shown that AP therapy is superior to doxorubicin alone for advanced or recurrent endometrial carcinoma by two randomized controlled trials of European Organization for Research and Treatment of Cancer and Gynecologic Oncology Group [23, 24].

Recently, TAP therapy (concomitant use of paclitaxel 160 mg/m^2, doxorubicin 45 mg/m^2, and cisplatin 50 mg/m^2, G-CFS), which is a three-drug combination-chemotherapy including paclitaxel in addition to AP therapy, was examined in a randomized controlled trial (GOG 177). Response rate, PFS and OS of the TAP therapy were all significantly superior, but toxicity of TAP therapy, especially neuropathy, was more severe than that of AP therapy [25]. Based on these results, AP therapy is used as the first-line therapy for endometrial carcinoma in general community hospitals. However, doxorubicin has cardiotoxicity. It is reported that administration of doxorubicin at 550 mg/m^2 or higher caused significantly higher rate of congested heart failure [26]. Therefore, administration of doxorubicin at 550 mg/m^2 or higher was associated with a great risk even if the patient was determined as doxorubicin sensitive. Combination therapies of plat-

inum-based chemotherapy and paclitaxel are also used as front-line treatment for endometrial carcinoma in many facilities; however, only few therapies are effective for patients with these therapies-resistance.

It is hoped that docetaxel will be an alternative anticancer drug to paclitaxel. This is because docetaxel has 2.5 times higher effect on microtubules than paclitaxel [27]. Of 15 patients with paclitaxel-resistance ovarian carcinoma, CR was observed in five cases (33.3%), and PR in three cases (20.0%) in the present study. In addition, patients that previously received paclitaxel were excluded in a study previously reported on advanced or recurrent endometrial carcinoma [18-20]. In the present study, CR and PR respectively were observed in two patients (28.6%), respectively that previously received paclitaxel in endometrial carcinoma. Therefore, the present authors consider that a better effect can be expected from concomitant use of docetaxel and carboplatin.

In the present study, concomitant use of docetaxel and carboplatin by biweekly administration for advanced or recurrent ovarian carcinoma obtained 55.0% of CR and PR. There is a phase II trial that administered docetaxel (75 mg/m^2) and carboplatin (AUC: 5) every three weeks for recurrent ovarian, peritoneal, and tubal carcinoma as docetaxel plus carboplatin therapy [28]. Subjects of this trial were 25 patients with platinum sensitive recurrent ovarian carcinoma who experienced carboplatin alone or combination therapy of carboplatin and other anticancer drug as 9 first line chemotherapy; a high response rate of 72% was reported. Of these 25 cases, 21 cases received a combination therapy of paclitaxel and carboplatin; thus, it is considered that docetaxel will be an effective anticancer drug for recurrent ovarian carcinoma after therapy of paclitaxel and carboplatin.

Docetaxel has toxicity characteristics different from paclitaxel, although both are taxane agents [27]. Neutropenia is the most common toxicity of docetaxel. In the present study, grade 4 neutropenia was found in nine cases (45.0%) of ovarian carcinomas, and ten cases (45.5%) of endometrial carcinomas. Strauss *et al.* reported that grade 3 or worse neutropenia was observed in 60% of patients in their study that administered docetaxel (75 mg/m^2) and carboplatin (AUC: 5) every three weeks in recurrent ovarian carcinomas [28]. Moreover, grade 3 or worse neutropenia were observed in 94% of patients in every three-week administration of docetaxel (60 mg/m^2) plus carboplatin (AUC: 5), as well as febrile neutropenia, which required postponement of treatment for at least seven days, was observed in 14% of patients in a phase III trial that compared docetaxel plus carboplatin and paclitaxel and carboplatin as a first-line chemotherapy for ovarian carcinomas [7]. Also, in a comparison study of three arms including every three-week administration of docetaxel plus cisplatin, docetaxel plus carboplatin, and paclitaxel plus carboplatin for advanced recurrent ovarian carcinomas, grade 3 or worse neutropenia was observed in 90% of patients and febrile neutropenia was observed 6.7% of patients in the docetaxel plus carboplatin group [29]. For neurotoxicity, grade 3 motor neuropathy (6.7%) and grade 3 sensory neuropathy (1.3%) were observed in paclitaxel plus carboplatin group. On the other hand, neuropathy of grade 3 or worse was not observed in the docetaxel plus carboplatin group [29]. No neuropathy case of grade 3 or worse was found in the present study.

The present results showed that biweekly administration of docetaxel or carboplatin for advanced and recurrent endometrial and ovarian carcinomas results in acceptable side effects, favorable response rate, and PFS. It is suggested that biweekly administration of docetaxel and carboplatin maybe a front-line chemotherapy for advanced or recurrent endometrial and ovarian carcinomas. However, a further randomized phase III study would be required to evaluate risks and benefits of biweekly administration of docetaxel and carboplatin.

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Address reprint requests to:
H. NISHI, M.D.
Department of Obstetrics and Gynecology
Tokyo Medical University
Nishi-shinjuku 6-7-1, Shinjuku-ku
Tokyo, 160-0023 (Japan)
e-mail: nishih@tokyo-med.ac.jp