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Objective evaluation of the alleviating effects of Goshajinkigan on peripheral neuropathy induced by paclitaxel/carboplatin therapy: A multicenter collaborative study

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Abstract. Paclitaxel/carboplatin chemotherapy for cancer (TC therapy) exhibits neurotoxicity and causes peripheral neuropathy at a high frequency, which is difficult to cope with. In this study, we investigated the efficacy of Goshajinkigan, a traditional Japanese herbal medicine, for TC therapy-induced peripheral neuropathy. The subjects included in our study were patients with ovarian or endometrial cancer who underwent TC therapy and developed peripheral neuropathy. The patients were randomly divided into Group A, comprising of 14 patients (vitamin B12 treatment), and Group B, comprising of 15 patients (vitamin B12 + Goshajinkigan treatment). The observation period was 6 weeks following treatment initiation, and the evaluation items were as follows: i) the current perception threshold (CPT value) of the peripheral nerve, ii) visual analogue scale for numbness, iii) National Cancer Institute Common Terminology Criteria for Adverse Events v3.0 grade of neurotoxicity, and iv) a questionnaire on the subjective symptoms of peripheral neuropathy (functional assessment of cancer therapy-taxane). These were compared between the groups and no significant differences were noted in any item. However, CTCAE grade 3 neurotoxicity developed in 2 patients (14.3%) after 6 weeks of administration in Group A, whereas no neurotoxicity was observed in Group B. When the change in the frequency of abnormal CPT ratio at 6 weeks of administration from that before treatment was compared between the groups, the frequency of abnormal value was significantly lower in Group B than in Group A ($p<0.05$). This suggests that Goshajinkigan inhibits the progression of peripheral neuropathy.

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Introduction

For chemotherapy against gynecological cancer centering on ovarian cancer, platinum and taxane preparations are widely used. However, neurotoxicity, especially peripheral neuropathy appearing as an adverse reaction to a taxane preparation, paclitaxel, is a problem that remains to be solved. Several patients develop intractable nervous symptoms persisting for months after receiving the paclitaxel treatment, and this is one of the factors that cause deterioration of patient quality of life (QOL). Recently, it was reported that Goshajinkigan, a traditional Japanese herbal medicine, is useful for coping with chemotherapy-induced peripheral neuropathy (1).

However, in general, it is difficult to objectively evaluate the severity of peripheral neuropathy, and very few reports have referred to the objective electrophysiological evaluation of neuropathy. We tried to undertake objective evaluations of neuropathy, including the determination of current perception thresholds (CPT) in gynecological patients who underwent chemotherapy including paclitaxel, and developed peripheral neuropathy. Such patients were randomly assigned to two groups receiving and not receiving the Goshajinkigan treatment, and the efficacy of Goshajinkigan in alleviating peripheral neuropathy was investigated.

Patients and methods

Patients. This study was conducted under the approval of the Institutional Review Board (IRB) of each study center. The subjects were patients with ovarian or endometrial cancer who met all of the following inclusion criteria: i) histological diagnosis of ovarian or endometrial cancer, ii) having at least one cycle of paclitaxel and carboplatin combination therapy (TC therapy) conducted as the first chemotherapy and a National

Table I. Evaluation items.

Evaluation item	Range
Evaluation of current perception threshold (CPT) (evaluation of forefinger)	0-999 (100 = 1 mAmp)
Grade of numbness on visual analogue scale (VAS)	0-10
Motor and sensory neuropathy grade (NCI-CTCAE v3.0)	Grade 0 (no symptom) - Grade 5
Subjective neuropathy symptom questionnaire examination (FACT-Taxane)	0-64

The items were evaluated before the study treatment and after 3 and 6 weeks of the study treatment, and the changes were compared between the Goshajinkigan treatment group and the Goshajinkigan non-treatment group.

Cancer Institute Common Terminology Criteria for Adverse Events v3.0 (NCI-CTCAE) peripheral neuropathy grade of ≥1, iii) age of ≥20 and ≤70 years, and iv) having provided written consent to participate in this study. The exclusion criteria were as follows: i) previous use of Goshajinkigan or vitamin B12 within the past 4 weeks, ii) any schedule of using another anticancer agent during the study period, and iii) presence of severe peripheral neuropathy at the initiation of this study.

Methods. This study was conducted as a parallel group randomized controlled trial by central registration, and the registered patients were randomly assigned to the Goshajinkigan non-treatment group (control group, Group A) and the Goshajinkigan treatment group (Group B). In Group B, Tsumura Goshajinkigan Extract Granules® 7.5 g/day (t.i.d.) and vitamin B12 (Methycobal®) at 1,500 μg/day (t.i.d.) were administered, and in Group A, only vitamin B12 was administered. The registered patients received a maximum of 6 cycles of TC therapy (paclitaxel 175-180 mg/m^2, i.v. on Day 1; carboplatin AUC 5-6 , i.v. on Day 1; each cycle, 21 days).

Evaluation items. Patients were observed for 6 weeks, and they underwent CPT determination of the bilateral forefingers, visual analogue scale (VAS) determination for numbness, grade classification of motor and sensory neuropathy according to CTCAE and examination with the subjective neuropathy symptom questionnaire using modified functional assessment of cancer therapy-taxane (FACT-Taxane) (2) before the study treatment, after 3 weeks, and after 6 weeks of the study treatment to compare the changes in neuropathy symptoms between the two groups (Tables I and II).

CPT test. The CPT examination has been reported to be useful for the detection, screening, diagnosis and management of diseases of peripheral neuropathy (3-5). The principle and method of CPT determination are shown below. The nerve diameter differs depending on the nerve type, and each nerve has a specific frequency suitable for depolarization depending on its diameter. It is therefore possible to undertake selective quantitative evaluation of both large fibers and small fibers by stimulating at different frequencies. The sine-wave current is gradually increased from a low level (0-9.99 mA) at three different frequencies of 5, 250 and 2,000 Hz at the region of measurement. The minimum current perceived is the CPT

Table II. Subjective neuropathy symptom questionnaire using modified FACT-Taxane.

Upper limb symptoms
Hand numbness or tingling pain
Other uncomfortable hand sensation
Bilateral hand swelling
Sore fingertips
Trouble in buttoning
Difficulty in feeling the shape of a small object grasped in the hand
Lower limb symptoms
Foot numbness or tingling pain
Other uncomfortable foot sensation
Bilateral foot swelling
Difficulty in walking
Other symptoms
Joint pain or muscle convulsion
Whole body swelling
Feeling of whole body weakness
Worsened hearing acuity
Noise in the ear
Very concerned about unusual appearance of hands and nails

Self-entry questionnaire about upper/lower limb symptoms and other symptoms; each response was scored depending on severity (0 points, not applicable at all; 1 point, slightly applicable; 2 points, somewhat applicable; 3 points, considerably applicable; 4 points, very applicable).

Table III. Normative data for median nerve (100 CPT = 1 mAmp).

	Min	Max	Mean	SD
Ranges (Hz)				
2,000	120	398	226	80
250	22	180	81	42
5	16	101	46	27
Within-site ratio				
2 kHz/5 Hz	2.03	14.7	6.2	4.2
2 kHz/250 Hz	1.53	5.80	3.2	2.1
250 Hz/5 Hz	0.83	4.38	2.0	1.1

Sources: Neuval® Database II - Normative Data, Neurotron, Inc., Baltimore, MD, USA, 2001. These normative data were obtained primarily from the following institutions: Johns Hopkins Medical Institution, University of Maryland School of Pharmacology, Creighton University School of Medicine, New York Medical College, New York University Medical Center, Palmer College of Chiropractic and the University of New Mexico School of Medicine.

Table IV. Patient background.

	Group A (not administered Goshajinkigan; n=14)	Group B (administered Goshajinkigan; n=15)	Wilcoxon's rank sum test
Age (years)	59.7	55.6	
Performance status			
0	9	9	
1	5	4	
2	0	2	
Disease			
Ovarian cancer	12	12	
Endometrial cancer	2	2	
Multiple cancer	0	1	
Vas score	3.1±2.2	2.5±1.6	p=0.827
CTCAE neuropathy grade			
Motor	0.6±0.7	0.5±0.7	p=0.760
Sensory	1.3±0.5	1.1±0.4	p=0.404
FACT-Taxane	8.5±5.5	8.3±8.1	p=0.896
CPT range (5 Hz)			
Right	113±68.3	98±46.6	p=0.535
Left	120±62.6	121±117.9	p=0.451
CPT range (250 Hz)			
Right	156±73.3	168±92.1	p=0.947
Left	167±63.4	163±105.1	p=0.385
CPT range (2 kHz)			
Right	346±140.8	375±127.2	p=0.537
Left	366±138.8	341±133.6	p=0.354

Patient backgrounds at the time of registration in this study. The patients were randomly assigned to the Goshajinkigan non-treatment group (Group A) or the Goshajinkigan treatment group (Group B). There were no significant inter-group differences in patient backgrounds.

of each subject. The CPT at 2,000 Hz corresponds to a large myelinated fiber (Aβ), and the CPT at 250 Hz corresponds to a small myelinated fiber (Aδ), while the CPT at 5 Hz corresponds to an unmyelinated nerve (C) (6).

CPT was measured using the Neurometer NervScan NS3000®. CPT range and within-site CPT ratio analyses of the bilateral second fingers controlled by the median nerves were performed.

The CPT Range Analysis compares raw CPT measures to the normative ranges. CPT values below the minimum CPT normative range qualify as hyperesthesia and indicate that the nerve fibers are suffering from inflammation or are under regeneration, and values above the maximum CPT normative range indicate hypoesthesia associated with loss of function or neuropathy.

The within-site CPT ratio analysis is an analytical method for measureing the ratio within the measurement region (2,000 Hz/5 Hz; 2,000 Hz/250 Hz; 250 Hz/5 Hz). Ratios outside the healthy ranges indicate very mild sensory abnormalities. The normative data are displayed in Table III.

Statistical analysis. Statistical analysis was performed using statistical analysis software, SAS release 9.13 (SAS Institute Japan). The VAS value, FACT-Taxane score, CTCAE neuropathy grade and therapeutic effect on CPT (2,000, 250 or 5 Hz) were evaluated at each time-point in each group employing Wilcoxon's signed rank test. Wilcoxon's rank sum test was employed for the comparison of the frequencies of the abnormal values of the above evaluation items and the CPT test between Group A and B. Since this was an exploratory study, multiplicity was not considered in any test. A value of $p<0.05$ was regarded as significant for all data.

Results

In the period from March 8, 2007, to March 31, 2009, 31 patients were registered at the four study centers (Iwate Medical University Hospital, Tottori University Hospital, Kitasato University Hospital and Keio University Hospital). All the patients met the inclusion criteria, although 2 patients dropped out of this study since they developed deep vein thrombosis in the lower limb during the TC therapy. Therefore, 29 valid patients (Group A, 15 patients; Group B, 14 patients) were included in the analysis. The patient background factors did not differ between the two groups (Table IV).

Table V. Changes in the outcome.

	Group A (not administered Goshajinkigan; n=14)			Group B (administered Goshajinkigan; n=15)			Wilcoxon's rank sum test[a]
	0 weeks	3 weeks	6 weeks	0 weeks	3 weeks	6 weeks	
VAS	3.1±2.2	2.9±3.3	3.7±3.4	2.5±1.6	3.8±2.7	3.4±2.7	p=0.827
CTCAE grade							
Motor neuropathy	0.6±0.7	0.6±1.0	0.8±1.1	0.5±0.7	0.6±0.7	0.8±0.9	p=0.760
Sensory neuropathy	1.3±0.5	1.0±1.0	1.3±1.0	1.1±0.4	1.3±0.5	1.4±0.5	p=0.404
FACT-Taxane	8.5±5.5	6.8±6.9	8.9±8.4	8.3±8.1	9.9±7.1	8.2±7.0	p=0.896
CPT range (5 Hz)							
Right	113±68.3	119±59.6	137±171.1	98±46.6	110±94.4	95±41.1	p=0.793
Left	120±62.6	141±84.4	154±147.6	121±117.9	112±87.2	119±66.3	p=0.948
CPT range (250 Hz)							
Right	156±73.3	141±67.6	140±80.7	168±92.1	151±122.9	148±30.6	p=0.982
Left	167±63.4	164±76.7	159±127.0	163±105.1	169±93.0	164±57.8	p=0.444
CPT range (2,000 Hz)							
Right	346±140.8	360±63.3	340±96.6	375±127.2	347±103.5	347±109.7	p=0.611
Left	366±138.8	393±147.7	355±155.5	341±133.6	334±90.6	358±106.3	p=0.743

[a]0 vs. 6 weeks. The duration of observation was 6 weeks. There were no significant differences in the VAS score, CTCAE grade, FACT-Taxane or CTP grade between the groups.

Table VI. Changes in CTCAE (sensory neuropathy) grade.

CTCAE sensory neuropathy	Before study treatment (no.)	After 3 weeks of study treatment (no.)	After 6 weeks of study treatment (no.)
Group A (not administered Goshajinkigan)			
No symptom	0	5	3
Grade 1	10	5	6
Grade 2	4	3	3
Grade 3	0	1	2
Grade 4	0	0	0
Grade 5	0	0	0
Group B (administered Goshajinkigan)			
No symptom	0	0	0
Grade 1	13	11	9
Grade 2	2	4	6
Grade 3	0	0	0
Grade 4	0	0	0
Grade 5	0	0	0

When limited to grade classification of sensory neuropathy, an event of ≥ Grade 3 was noted in 2 patients (14.3%) of the Goshajinkigan non-treatment group (Group A), but no events were noted in the Goshajinkigan treatment group (Group B).

There were no significant differences between Group A and Group B in terms of changes in VAS score, CTCAE neuropathy grade, FACT-Taxane and CPT ranges in the period from before the study treatment to Week 6 of study treatment (Table V). However, when limited to the grade of sensory neuropathy, symptoms of Grade ≥3 were noted in Group A at Week 3 or later (Week 6, 14.3%), but not in Group B (Table VI).

The change in the frequency of abnormal CPT range at 6 weeks of administration from that before treatment was compared between the groups employing Wilcoxon's rank

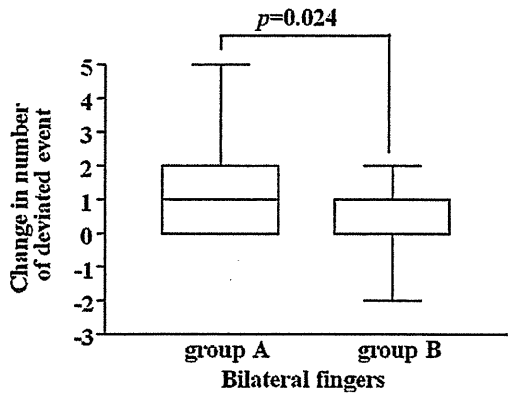

Figure 1. The change in the number of incidences of abnormal CPT ratio at 6 weeks of administration from that before treatment, was analyzed. The incidence of abnormal value was significantly lower in Group B than in Group A (Wilcoxon's rank sum test, 0 vs. 6 weeks).

sum test, but no significant difference was observed. However, regarding the change in the frequency of abnormal CPT ratio, the frequency was significantly lower in Group B than in Group A (Fig. 1).

Discussion

Paclitaxel, irinotecan hydrochloride and liposomal doxorubicin, among others, have specific non-hematological toxicities, inducing the deterioration of patient QOL. Therefore, it is important to decrease such toxicities. For neurotoxicity in particular, peripheral neuropathy is known as an adverse reaction to paclitaxel (7). Vasey *et al* (8) reported that the incidence of peripheral neuropathy in TC therapy was as high as 78% for sensory disorder and 16% for motor disorder. Recently, it was reported that Goshajinkigan, a traditional Japanese herbal medicine, is effective for chemotherapy-induced neurotoxicity. However, there are few reports on the electrophysiological evaluation of the severity of peripheral neuropathy.

In this study, we evaluated the peripheral neuropathy-alleviating effects of Goshajinkigan administered to patients with gynecological malignancy undergoing TC therapy in a parallel group randomized controlled trial. There were no significant differences between the presence and absence of Goshajinkigan treatment after 3 and 6 weeks of the study treatment in VAS evaluation for numbness, subjective neuropathy symptom questionnaire using FACT-Taxane and neuropathy grade according to CTCAE. Since an anticancer drug induces not only neuropathy, but also various complications, such as gastrointestinal symptoms, infections and mental symptoms, it is difficult to avoid biases in the cases of VAS and FACT-Taxane. This was considered to be the cause of the failure to obtain significant differences. However, in CTCAE for sensory neuropathy, an event of Grade 3 was noted in 2 patients (14.3%) of the Goshajinkigan non-treatment group, while no event of Grade 3 was noted in the Goshajinkigan treatment group. This suggests that the progression of neuropathy can be delayed by the use of Goshajinkigan.

It is generally difficult to evaluate the severity of peripheral neuropathy objectively. The CPT-measuring method has gradually prevailed since it was developed by Katims *et al* (9) in 1986, showing a high prevalence rate in the United States. It has been reported that this method can be used to make detailed neurological evaluations of diabetic peripheral neuropathy, carpal tunnel syndrome and alcoholic peripheral neuropathy (3-5).

No significant difference was noted in the changes in the CPT range between the groups with and without Goshajinkigan treatment, but the frequency of abnormal CPT ratio was significantly lower in the Goshajinkigan-treatment group. The progression of TC therapy-induced neurotoxicity over the 6-week observation period was not so marked so that it was not reflected in the CPT range, showing no significant difference. By contrast, the CPT ratio showed a significant difference as it may have reflected very mild sensory abnormalities, suggesting that Goshajinkigan inhibited the very early progression of neurotoxicity.

For the prevention and treatment of peripheral neuropathy induced by anticancer agents, various animal experiments and clinical studies were conducted using, in addition to NSAIDs and steroids, antihistaminic drugs, NGF (10,11), IGF (12), GDNF (13), amifostine (14,15), glutathione (16), α-lipoic acid (17), gabapentin (18) and carbamazepine (19), among others, but there are no established methods.

Goshajinkigan is a kampo drug prepared by adding Goshitsu (*Achyranthes root*, anti-allergic effect) and Shazenshi (*Plantago seed*, diuretic effect and interferon-inducing effect) to Hachimijiogan, which is composed of the following mixed crude drugs: *Rehmanma root*, *Cornus fruit*, *Dioscorea rhizome*, *Alisma rhizome*, *Poria sclerotium*, *Moutan bark*, *Cinnamon bark* and *processed Aconite root*, and was originally considered to be effective against 'numbness' due to diabetic peripheral neuropathy. Goshajinkigan is also effective for lumbar canal stenosis, lumbar spondylosis deformans and arteriosclerosis obliterans in the elderly. Similar to the pharmacological effect of Goshajinkigan, it is considered that the analgesic effect is exerted by the suppression of pain-transmitting substance release by κ-opioid receptor stimulation mediated by dynorphin, an endogenous opioid substance released by ShujiBushi (*processed Aconite root*) (20). It is also considered that the analgesic effect is exerted through the improvement of peripheral nocireceptor sensitivity, vasodilation and peripheral circulation by the promotion of NO production due to the effects of Takusha (*Alisma rhizome*) and Sanyaku (*Dioscorea rhizome*) mediated by bradykinin B2 receptor and muscarinic acetylcholine receptor (21).

It is expected that Goshajinkigan may become a first-line therapy against the neurotoxicity of anticancer drugs not only by alleviating the subjective symptoms of neuropathy, but also by repairing the nerves. It is essential to delay the progression of neuropathy in current cancer chemotherapy, which should be performed with maintenance of QOL.

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Phase II study of neoadjuvant chemotherapy with irinotecan hydrochloride and nedaplatin followed by radical hysterectomy for bulky stage Ib2 to IIb, cervical squamous cell carcinoma: Japanese Gynecologic Oncology Group study (JGOG 1065)

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Abstract. The efficacy and adverse events of neoadjuvant chemotherapy with irinotecan hydrochloride and nedaplatin were evaluated in patients with bulky stage Ib2 to IIb cervical squamous cell carcinoma. Eligibility included patients who received irinotecan (60 mg/m^2) on days 1 and 8 and nedaplatin (80 mg/m^2) on day 1 of a 21-day cycle. After 1-3 courses of chemotherapy, radical hysterectomy was performed. Sixty-eight patients were enrolled. Sixty-six were included in the full analysis set. Their median age was 47 years (range 22-71), the FIGO stage was Ib2 in 18 patients, IIa in 10, and IIb in 38. Radical hysterectomy was performed after NAC in 63 patients (95.5%). The number of administered courses of NAC was 1 in 13 patients, 2 in 43, and 3 in 10. The response rate, the primary endpoint of this study, was 75.8% (CR in 2 patients, PR in 48, SD in 12, PD in 0, and NE in 4). The mean number of treatment courses required for a response was 1.42 (1 course in 30 patients, 2 courses in 19, and 3 courses in 1). The incidences of grade 3 or 4 hematological toxicities were: neutropenia 72.2%, leukopenia 16.7%, anemia 13.6%, thrombocytopenia 7.6%, febrile neutropenia 1.5%, and elevations of alanine aminotransferase and aspartate aminotransferase 1.5%. Grade 3 or 4 non-hematologic toxicities were as follows: diarrhea 6.1%, nausea 3%, anorexia 1.5%, vomiting 1.5%, fever 1.5%, allergic reactions 1.5%, ileus 1.5% and vesicovaginal fistula 1.5%. Neoadjuvant chemotherapy with irinotecan and nedaplatin was an effective and well-tolerated treatment for patients with bulky stage Ib2 to IIb squamous cell carcinoma of the uterine cervix.

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Introduction

We previously reported a phase I study of combination chemotherapy with irinotecan hydrochloride (CPT-11) and nedaplatin (NED) for cervical squamous cell carcinoma (JGOG 1063) (1). We conducted a phase II clinical trial to evaluate the effectiveness and toxicity of neoadjuvant chemotherapy (NAC) with CPT-11 and NED in women with stage Ib2 or II cervical squamous cell carcinoma.

CPT-11 is a DNA topoisomerase I inhibitor developed in Japan. In a phase II study in patients with cervical carcinoma, it exhibited relatively high efficacy, with a response rate of 23% (2).

NED is a second-generation platinum compound developed in Japan. The response rate was 46% to patients with cervical cancer in phase II clinical trials. Its antitumor activity was suggested to be at least equivalent to that of cisplatin (CDDP). Since NED is less nephrotoxic than CDDP, its indication range was extended to patients with renal dysfunction. NED can be administered on an outpatient basis, without rehydration therapy. *In vitro* studies using gynecological cancer cell lines NDP exerted stronger antitumor activity than CDDP (3).

Patients with cervical cancer have been reported to have a high rate of response to CPT-11 plus CDDP (4-7). To further enhance efficacy and safety, CPT-11 has been combined with nedaplatin. Good outcomes have been reported (8-10). Clinically, Ohwada *et al* reported a high response rate of 81% in patients with primary cervical cancer (11). Combined therapy with CPT-11 and NED is thus expected to be useful for the management of advanced cervical cancer.

The purpose of NAC in this study was to increase the radicality of surgery by inducing tumor shrinkage, not to achieve a histological complete response. Therefore, patients could receive up to 3 courses of NAC, but if PR or CR was achieved during 1 or 2 courses, the physician could decide whether to proceed to surgery. NAC regimens need a high local response rate of the primary tumor and a prompt onset of effect.

Patients and methods

The study group comprised women in whom radical hysterectomy was indicated, but surgery was considered difficult. In clinical practice, this category includes patients with bulky tumors and those with high-grade parametrial invasion. Clinical stage Ib2 and IIa tumors were defined as measurable lesions >4 cm in diameter, and clinical stage IIb tumors were defined as measurable lesions >2 cm in diameter. Patients were enrolled from January 2007 through July 2007 at member hospitals of the Japanese Gynecologic Oncology Group (JGOG). The study protocol was approved by the institutional review board of each participating hospital. All patients provided informed consent before enrollment.

Eligibility criteria. Eligibility criteria were as follows: i) a histopathologically confirmed diagnosis of cervical cancer (squamous cell carcinoma); ii) any of the following clinical stages according to the Federation of Gynecology and Obstetrics (FIGO) staging system (1994 version): stage Ib2, stage IIa [measurable lesions >4 cm in greatest diameter on direct measurement or magnetic resonance imaging (MRI)], or stage IIb (measurable lesions >2 cm in greatest diameter on direct measurement or MRI); iii) the primary tumor can be directly measured or measured on MRI; iv) no previous treatment; v) an age of 20-75 years at enrollment; vi) a performance status (Eastern Cooperative Oncology Group) of 0 or 1; vii) extended hysterectomy is feasible; viii) preserved function of major organs (bone marrow, heart, liver, kidney, etc.) [neutrophil count ≥2000/μl, platelet count ≥100x10^3/μl, hemoglobin level ≥9.0 g/dl (values after blood transfusion are accepted), levels of aspartate aminotransferase and alanine aminotransferase ≤100 IU/l, total bilirubin level ≤1.5 mg/dl, serum creatinine level ≤1.2 mg/dl, creatinine clearance ≥60 ml/min, normal electrocardiogram or electrocardiographic changes not requiring treatment]; and ix) written informed consent for voluntary participation in this study.

Exclusion criteria. The exclusion criteria were as follows: i) distinct evidence of infectious disease; ii) serious concurrent disease (cardiac disease, uncontrolled diabetes mellitus, malignant hypertension, bleeding tendency, etc.); iii) active double cancer; iv) interstitial pneumonia or pulmonary fibrosis; v) body fluid retention requiring treatment; vi) unstable angina, a history of myocardial infarction within 6 months before enrollment, or serious arrhythmias requiring treatment; vii) contraindications for irinotecan or nedaplatin; viii) diarrhea (watery stool); ix) intestinal paralysis or ileus; x) pregnant women, breast-feeding women, or women who want to become pregnant; xi) a history of serious drug hypersensitivity or drug allergy; and xii) patients considered unsuitable as subjects by their attending physicians for study-related reasons.

Treatment. Patients received irinotecan (60 mg/m^2) on days 1 and 8 and nedaplatin (80 mg/m^2) on day 1 of a 21-day cycle. After 1-3 courses of chemotherapy, extended hysterectomy was performed. If a partial or better response was obtained after 1 or 2 courses, or if a response was considered unlikely, surgery could be performed.

Criteria for skipping treatment with irinotecan on day 8. Laboratory tests were always performed 1 day before or on the same day as treatment with irinotecan on day 8 to confirm the severity of adverse drug reactions and the patients' status. Treatment with irinotecan on day 8 was skipped if patients met any of the following criteria: neutrophil count <1500/μl, platelet count <100x10^3/μl, grade 1 or higher infection, a fever of 38°C or higher, or grade 1 or higher diarrhea.

Criteria for starting the next course. Before starting the second and subsequent course of chemotherapy, laboratory tests were always performed within 24 h before the time scheduled for treatment to adequately confirm the severity of adverse drug reactions and the patients' status. The next course of treatment was postponed if patients did not meet the following criteria: neutrophil count ≥1500/μl, platelet count ≥100x10^3/μl, serum creatinine level ≤1.5 mg/dl, grade 0 infection, grade 0 fever, and grade 0 diarrhea. However, the study treatment was discontinued if these criteria were not met up to a maximum of 5 weeks after the start of the previous course. Furthermore, if a granulocyte colony-stimulating factor (G-CSF) preparation was used to treat neutropenia, patients were observed for at least 3 days after the completion of treatment to confirm that the neutrophil count was ≥1500/μl.

The dose for the next course of treatment was reduced according to the severity of the adverse drug reactions that occurred during the previous course. If grade 4 non-hematologic toxicity developed, the protocol treatment was discontinued.

Criteria for reduction of irinotecan dose. The dose of irinotecan was decreased 10 mg/m^2 for the next course of treatment in patients who had any of the following conditions during the previous course: grade 3 or higher febrile neutropenia; grade 4

neutropenia persisting for ≥5 days; grade 3 or higher non-hematologic toxicity, excluding hair loss, nausea, vomiting, and fatigue; or if dose reduction was considered necessary by the patient's attending physician. Once the dose was reduced, treatment was continued at the lower dose (Table II).

Criteria for reduction of nedaplatin dose. The criteria for reducing the dose of nedaplatin were based on the platelet count. The dose of nedaplatin was reduced 10 mg/m^2 for the next course in patients who had any of the following conditions during the previous course: grade 4 thrombocytopenia (platelet count, <25x10^3/μl); a bleeding tendency caused by grade 3 thrombocytopenia (platelet count, ≥25x10^3/μl to <50x10^3/μl); platelet transfusion was received; or if dose reduction was considered necessary by the patient's attending physician. Once the dose was reduced, treatment was continued at the lower dose.

Evaluation of adverse events. Adverse events were evaluated according to the JCOG Japanese version of the Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0.

Surgery. Surgery was to be performed between 4 and 6 weeks after the completion of preoperative chemotherapy. In principle, radical hysterectomy was performed. However, if surgery was not considered feasible after NAC or if surgery was precluded by concurrent disease or other factors, non-surgical treatment such as radiotherapy could be administered at the discretion of the attending physician.

Postoperative treatment. In this clinical trial, postoperative therapy was not specified. Patients were followed up and given radiography or chemotherapy according to the criteria of each hospital.

Endpoints. The primary endpoint in this study was the response (PR+CR) rate. Response was evaluated at a single timepoint, referring to the World Health Organization Response Evaluation Criteria in Solid Tumors (RECIST guidelines). Time to treatment failure was not required. Secondary endpoints were: i) the number of courses required for response; ii) incidence of adverse events; iii) tumor marker levels (serum squamous cell carcinoma antigen); iv) completeness of surgery (presence or absence of residual tumor on intraoperative examination, rate of complete lymph node dissection, and negative resection margin rate); v) results of pathological examination of resected organs (histologic response, parametrial invasion, resection margin status, stromal invasion, vascular invasion, and lymphatic invasion); vi) relative ease or difficulty of surgery (bleeding volume and operation time); vii) proportion of patients with surgical complications; and viii) recurrence-free survival rate at 2 years.

Evaluation criteria for target lesion response. Tumor response was evaluated in accordance with RECIST guidelines. Before treatment and at the completion of each course, the longest diameter of target lesions was measured in a single direction on MRI or by direct measurement. We used MRI instead of computed tomography (CT) for two reasons. First, as compared with CT, MRI can more clearly depict tumor borders, facilitating the measurement of tumor diameter. Second, because cervical cancer invasion often extends vertically, MRI is more useful for measuring vertical extension on sagittal sections. Response was defined as: complete response (CR), disappearance of all target lesions including tumor-induced secondary changes; partial response (PR), a ≥30% decrease in the sum of the longest diameter of target lesions, as compared with the value before the start of treatment; stable disease (SD): no evidence of tumor shrinkage corresponding to PR or of tumor growth corresponding to progressive disease; progressive disease (PD), a ≥20% increase in the sum of the longest diameter of target lesions, as compared with the smallest previous value; not evaluable (NE), examination cannot be performed for some reason or response is not evaluated to be CR, PR, PD, or SD.

Table I. Patient characteristics.

Characteristics	Patients (n=66)
Age	
Median	47
Range	22-71
PS	
0	61
1	5
FIGO stage	
Ib2	18
IIa	10
IIb	38
Tumor size (cm)	
≤4	16
>4	50

Statistical analysis. Kaplan-Meier curves were generated for time to first recurrence and progression-free survival. We compared curves for the two groups with the log-rank test. All time estimates were done with the date of first chemotherapy as the baseline.

Results

A total of 68 patients were enrolled. Two patients did not meet the eligibility criteria and were excluded, and the remaining 66 were included in the full analysis set. As for their demographic characteristics, the median age was 47 years (range 22-71); the FIGO stage was Ib2 in 18 patients, IIa in 10, and IIb in 38; performance status was 0 in 61 patients and 1 in 5; and tumor diameter was ≤4 cm in 16 patients and >4 cm in 50 (Table I). Radical hysterectomy was performed after NAC, thereby completing the protocol treatment, in 63 patients (95.5%). Three patients discontinued protocol treatment: 1 directly refused treatment; 1 only received an exploratory laparotomy; and 1 did not undergo surgery because her attending physician preoperatively judged that operation was not feasible. The number of administered courses of NAC was 1 in 13 patients, 2 in 43, and 3 in 10. The mean interval from the date of staring course 1 of NAC to the date of starting the course 2 was 27.6 days (range 20-42). G-CSF was used in 10 of 53

Table II. Clinical response of neoadjuvant chemotherapy with CPT-11+NED.

Clinical response	Patients	Response rate	
CR	2	3.0%	75.8%
PR	48	72.7%	
SD	12	18.1%	
PD	0	0%	
Evaluation failure	4	6.1%	
No. of courses required until response		Average	
1 course	30		1.42 courses
2 courses	19		
3 courses	1		

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Table III. Hematological toxicities of chemothrapy with CPT-11+NED.

	Grade					
Toxicities	0	1	2	3	4	G3/4 (%)
Leukopenia	11	10	34	8	3	16.7
Neutropenia	7	4	8	37	10	71.2
Febrile neutoropenia	65	0	0	1	0	1.5
Anemia	15	15	27	8	1	13.6
Thrombocytropenia	34	20	7	2	3	7.6
AST/GOT evelation	53	12	1	0	0	0
ALT/GPT evelation	47	14	4	1	0	1.5
Creatinine	65	1	0	0	0	0
Bilirubine	60	4	2	0	0	0
Hypoalbuminemia	61	3	2	0	0	0

NCI-CTCAE ver.3.0.

patients. The reasons for postponing treatment were neutropenia in 35 patients, thrombocytopenia in 2, diarrhea in 1, and others in 5. The mean interval from the date of staring the course 2 of NAC to the date of starting course 3 was 27.1 days (range 21-34). G-CSF was used in 2 of 10 patients. The reasons for postponing treatment were neutropenia in 7 patients and thrombocytopenia in 1. Treatment with irinotecan was skipped on day 8 in 4 (6.1%) of 66 patients during course 1, 10 (18.9%) of 53 patients during course 2, and 3 (30.0%) of 10 patients during course 3. All of these patients skipped treatment because of neutropenia. The dose of irinotecan in the next course was decreased from 60-50 mg/m^2 in 4 (6.1%) of the 66 patients. The reason for this dose reduction was grade 4 neutropenia in 2 (50%) of the 4 patients. The dose of nedaplatin was reduced in 2 (3%) of the 66 patients. In 1 patient the dose was decreased from 80 to 70 mg/m^2, and in the other the dose was decreased to 60 mg/m^2. The reasons for dose reduction were grade 3 and 4 thrombocytopenia.

The response rate, the primary endpoint of this study, was 75.8% (CR in 2 patients, PR in 48, SD in 12, PD in 0, and NE in 4). The mean number of treatment courses required for a response was 1.42 (1 course in 30 patients, 2 courses in 19, and 3 courses in 1) (Table II). The combination of irinotecan and nedaplatin was considered an effective regimen for cervical cancer (squamous cell carcinoma).

The incidences of grade 3 or 4 hematological toxicities were as follows (in descending order): neutropenia 72.2%, leukopenia 16.7%, anemia 13.6%, thrombocytopenia 7.6%, febrile neutropenia 1.5%, and elevations of alanine aminotransferase and aspartate aminotransferase 1.5% (Table III). The incidences of grade 3 or 4 non-hematologic toxicities were: diarrhea 6.1%, nausea 3%, anorexia 1.5%, vomiting 1.5%, fever 1.5%, allergic reactions 1.5%, ileus 1.5%, and vesicovaginal fistula 1.5% (Table IV). There were no deaths or other serious adverse events.

The serum level of squamous cell carcinoma antigen, a tumor marker, was abnormal (≥1.5 ng/ml) before treatment in 52 (78.8%) of 66 patients. After chemotherapy, the level fell to the normal range in 29 (55.8%) of these patients before surgery.

Table IV. Non-hematologic toxicities of chemothrapy with CPT-11+NED.

	Grade					
Toxicities	0	1	2	3	4	G3/4 (%)
Anorexia	14	38	13	1	0	1.5
Nausea	8	41	15	2	0	3.0
Vomiting	31	22	12	1	0	1.5
Diarrhea	26	24	12	4	0	6.1
Fever	46	14	5	1	0	1.5
Hemorrhage	61	5	0	0	0	0
Hair loss	11	37	18	0	0	0
Allergic reaction	62	3	0	1	0	1.5
Edema	60	4	2	0	0	0
Ileus	63	0	2	1	0	1.5
Constipation	54	10	2	0	0	0
Pyelonephritis	63	1	2	0	0	0
Fatigue	64	2	0	0	0	0
Weight loss	43	19	4	0	0	0
Fistula (GU-bladder vagina)	65	0	0	1	0	1.5

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Among the 50 patients who responded to NAC (CR+PR), the squamous cell carcinoma antigen level was abnormal in 41 (82.0%) before treatment. In 25 (61.0%) of these patients, the level decreased to normal after chemotherapy.

As for the radicality of surgery, 4 (6.4%) of 63 patients were judged by the operator to have residual tumor or to have undergone incomplete lymph node resection, and 7 (11.1%) had positive resection margins on histopathological examination of their resected specimens.

Table V. Pathological examination.

Pathological findings	Yes	No
Parametrial involvement	15	48
Histologic margin	7	56
Depth of stromal invasion	21 (<50%)	6
	36 (>50%)	
Vascular-lymphatic involvement	31	32
Lymph node metastasis	19	44

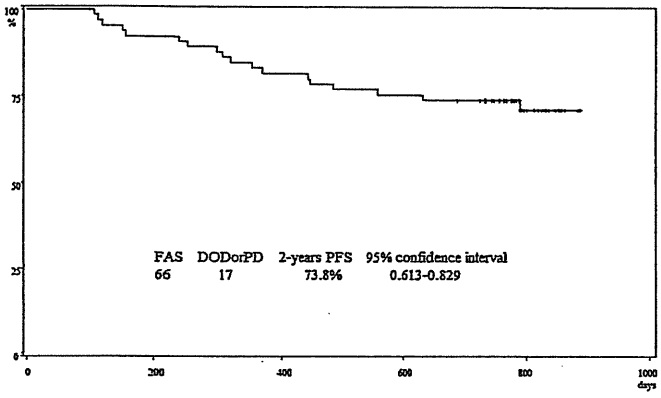

Figure 1. The two-year progression-free survival of all patients Kaplan-Meier method).

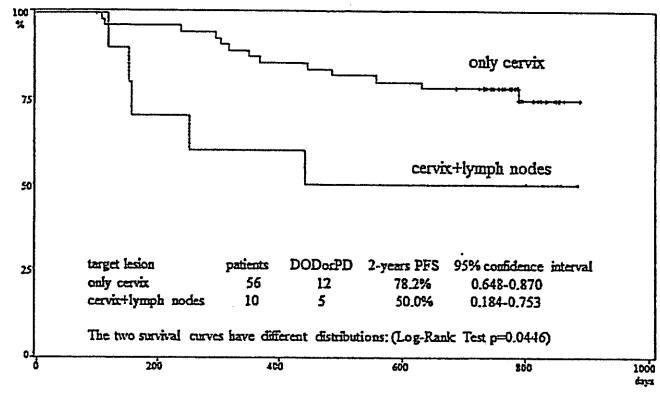

Figure 2. The two-year progression-free survival according to target lesion; only cervix vs. cervix+lymph nodes (Kaplan-Meier method).

Overall, 57 (90.5%) of 63 patients had a histologic response on histopathological evaluation of their resected specimens (grade 0 in 6 patients, grade 1a in 23, grade 1b in 8, grade 2 in 22, and grade 3 in 4). Among the 63 patients, parametrial invasion was present in 15 (23.8%), stromal invasion in 57 (90.5%; <50% in 21 and ≥50% in 36), vascular invasion in 31 (49.2%), and lymph node metastasis in 19 (30.2%) (Table V). Given that 38 (57.6%) of the 66 patients had stage IIb disease, the improvement in histopathological findings after NAC was regarded to be considerable.

The mean bleeding volume was 998 ml (range 158-3362), and the mean operation time was 294 min (range 136-566). As for surgical complications, grade 3 or 4 intraoperative bleeding occurred in 3.2% of the patients, which did not differ from the incidence associated with conventional extended hysterectomy. Dysuria was grade 0 in 33.9% of the patients, grade 1 in 25.8%, grade 2 in 19.4%, and grade 3 in 21.0%. The incidence of grade 1 or 2 lymphatic cyst was somewhat high (27.4%).

Two years after surgery, 17 patients had recurrence, including 9 who died of cancer. The progression-free survival rate at 2 years was 73.8% (95% confidence interval, 0.613-0.829) (Fig. 1). In this study, additional postoperative treatment was not specified and was left to the treatment policy of each hospital and the discretion of the attending physician. The breakdown of postoperative therapy was: no additional treatment in 30 patients (recurrence in 8), radiotherapy in 5 (recurrence in 1), concurrent chemoradiotherapy in 15 (recurrence in 7), and chemotherapy in 15 (recurrence in 1). In patients with target lesions only in the cervix and those with target lesions in both the cervix and lymph nodes, the progression-free survival rate at 2 years was 78.2 and 50.0%, respectively. This difference was significant (p=0.0446) (Fig. 2). The progression-free survival rate at 2 years according to disease stage was 94.1% for Ib2, 60.0% for IIa, and 68.4% for IIb. These differences were not significant.

Discussion

The response rate, the primary endpoint, was 75.8% (CR in 2 patients, PR in 48, SD in 12, PD in 0, and NE in 4). The tumor shrinkage rate was <30% in 11 of the 12 patients with SD. The response rate was non-inferior to those previously reported for NAC in patients with cervical cancer. It is noteworthy that only 1.42 courses of NAC on average were required to produce a response (1 course in 30 patients, 2 courses in 19, and 3 courses in 1). Fifty-six of 66 patients (84.8%) received 1 or 2 courses of NAC. Moreover, no patient had PD. CPT-11 and NED had a high response rate against primary lesions, as well as a prompt onset of effect, making it an optimal regimen for NAC.

Although a number of studies of NAC using a variety chemotherapeutic agents have been evaluated in patients with locally advanced cervical cancer and high response rates ranging from 76 to 95% have been demonstrated (12-17).

The rate of progression-free survival at 2 years was 73.8% (95% confidence interval, 0.613-0.829) in initially treated patients with stage Ib2 to IIb cervical squamous cell carcinoma who received NAC with irinotecan plus nedaplatin followed by radical hysterectomy. Because 57.6% of the study group had stage IIb disease and 75.8% had tumors exceeding 4 cm in diameter, we consider our results to be satisfactory. In addition, the study protocol did not specify additional treatment after surgery, and such treatment was left to the treatment policies of each hospital and the discretion of the attending physician. Postoperative treatment was performed as follows: no additional treatment in 30 patients (recurrence in 8), radiotherapy in 5 (recurrence in 1), concurrent chemoradiotherapy in 15 (recurrence in 7), and chemotherapy in 15 (recurrence in 1). Because chemotherapy was associated with good outcomes, future studies should assess whether multidisciplinary treatment combining surgery with preoperative and postoperative chemotherapy can improve outcomes (7,18). Patients with lymph nodes as target lesions had significantly poorer outcomes. More

aggressive, individualized treatment strategies may be necessary in this subgroup of patients.

In Japan, stage Ib2 to IIb cervical cancer is generally treated by radical hysterectomy. In the United States, the National Comprehensive Cancer Network (NCCN) and National Cancer Institute (NCI) guidelines recommend concurrent chemoradiotherapy for patients with stage Ib2 to IIb disease, and surgery is not included as a treatment option (19,20). Since the 1980s, however, many attempts have been made to improve survival by performing surgery after preoperative chemotherapy in patients with stage Ib2 to IIb cervical cancer (21-28). Preoperative chemotherapy may eliminate micrometastases, facilitate complete tumor resection, and enable resection of previously unresectable tumors.

Some studies have shown that NAC is therapeutically useful, whereas others have not. The Meta-analysis Group in the UK conducted a meta-analysis of 6 randomized controlled trials comparing NAC plus surgery with surgery alone. NAC was found to significantly improve progression-free survival (hazard ratio, 0.76; 95% confidence interval 0.62-0.94; p=0.01), but not overall survival (hazard ratio, 0.85; 95% confidence interval 0.67-1.07; p=0.17). In the NAC group, histopathological findings such as lymph node metastasis and parametrial invasion improved significantly. The NAC group also showed slight trends toward better outcomes in terms of local recurrence, distant recurrence, and resection rate. However, the meta-analysis concluded that it was unclear whether NAC improves long-term outcomes (29).

In 2003, the results of a meta-analysis of 5 clinical studies comparing NAC plus surgery with surgery alone in 872 patients with stage I or II (some with stage III) cervical cancer were reported. As compared with surgery alone, NAC plus surgery was found to significantly improve overall survival (hazard ratio, 0.65) and disease-free survival (hazard ratio, 0.68) at 5 years (30). However, this meta-analysis had several limitations, such as the inclusion of patients with various stages of cervical cancer and the lack of a comparison with chemoradiotherapy. Preoperative chemotherapy has thus not been accepted as standard treatment.

Since 2002, the European Organization for Research and Treatment of Cancer (EORTC) has been conducting a randomized controlled trial (EORTC 55994) comparing concurrent chemoradiotherapy, currently standard treatment, with preoperative chemotherapy followed by surgery in patients with stage Ib2-IIb cervical cancer. This study is ongoing and conclusions have yet to be reached (30). At present, evidence demonstrating that NAC plus surgery is superior to surgery alone or concurrent chemoradiotherapy is still not available (31).

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REVIEW Open Access

Clear cell carcinoma of the ovary: Is there a role of histology-specific treatment?

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Abstract

Several clinical trials to establish standard treatment modality for ovarian cancers included a high abundance of patients with serous histologic tumors, which were quite sensitive to platinum-based chemotherapy. On the other hand, ovarian tumor with rare histologic subtypes such as clear cell or mucinous tumors have been recognized to show chemo-resistant phenotype, leading to poorer prognosis. Especially, clear cell carcinoma of the ovary (CCC) is a distinctive tumor, deriving from endometriosis or clear cell adenofibroma, and response rate to platinum-based therapy is extremely low. It was implied that complete surgical staging enabled us to distinguish a high risk group of recurrence in CCC patients whose disease was confined to the ovary (pT1M0); however, complete surgical staging procedures could not lead to improved survival. Moreover, the status of peritoneal cytology was recognized as an independent prognostic factor in early-staged CCC patients, even after complete surgical staging. In advanced cases with CCC, the patients with no residual tumor had significantly better survival than those with the tumor less than 1 cm or those with tumor diameter more than 1 cm. Therefore, the importance of achieving no macroscopic residual disease at primary surgery is so important compared with other histologic subtypes. On the other hand, many studies have shown that conventional platinum-based chemotherapy regimens yielded a poorer prognosis in patients with CCC than in patients with serous subtypes. The response rate by paclitaxel plus carboplatin (TC) was slightly higher, ranging from 22% to 56%, which was not satisfactory enough. Another regimen for CCC tumors is now being explored: irinotecan plus cisplatin, and molecular targeting agents. In this review article, we discuss the surgical issues for early-staged and advanced CCC including possibility of fertility-sparing surgery, and the chemotherapy for CCC disease.

Keywords: Review, Ovarian cancer, Clear cell carcinoma, Surgical staging, Fertility-sparing, Chemotherapy, Molecular targeting agents

Background

Clear cell adenocarcinoma (CCC) is a distinct entity from other epithelial ovarian carcinomas (EOC). CCC is thought to arise from endometriosis or clear cell adenofibroma, however, the origin of serous cyst adenocarcinoma (SCA) is thought to be Mullerian epithelium derived from either ovarian surface epithelium or fallopian tube (endosalpingiosis). CCC has specific biological and clinical behavior, compared with other histological types. However, in the studies used as evidence for recommended treatment as standard treatment of EOC, most of the enrolled patients were not clear cell histology, and these study results do not provide a scientific rationale for CCC. In this review, we summarize the treatment of CCC.

Surgical treatment

The standard surgical treatment of patients with EOC is based on hysterectomy, bilateral salpingo-oophorectomy and partial omentectomy with peritoneal sampling and lymphadenectomy, and cytoreductive surgery is added especially for advanced cases. The surgical treatment of CCC is usually determined based on the guideline of EOC. In this section, we summarize the surgical treatment of CCC patients.

Surgical staging

It has been reported that the incidence of lymph node metastasis in stage I (pT1) EOC was approximately 5-

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residual tumor after primary surgery [21]. We previously reported that there is no significant prognostic difference between the patients with the tumor diameter less than 1 cm and those with the tumor diameter more than 1 cm, and complete surgery is only the independent prognostic factor [9]. Kennedy et al. reported that among patients with advanced stage cancers (FIGO stages III and IV), CCC patients were more often optimally debulked than non-CCC patients (60% vs. 37%, $p = 0.033$) [22]. From these findings, the goal of primary surgical treatment for CCC may be complete resection.

Fertility-sparing surgery

Fertility-sparing surgery (FSS) for reproductive-age patients with EOC has been adopted for stage IA and non-clear cell histology grade 1 (G1)/grade2 (G2) according to the 2007 guidelines of the American College of Obstetrics and Gynecology (ACOG) and unilateral stage I tumor without dense adhesions showing favorable histology (ie, non-clear cell histology G1/G2) according to the 2008 guidelines of the European Society for Medical Oncology (ESMO). In Japan, stage IA tumor or unilateral stage IC tumor on the basis of intraoperative capsule rupture and favorable histology are candidate for FSS according to the 2010 guidelines of the Japan Society of Gynecologic Oncology (JSGO). These 3 guidelines commonly eliminate CCC for the candidate of FSS. In contrast, in the 2010 guidelines of the National Comprehensive Cancer Network (NCCN), a stage I patient with CCC is an acceptable candidate for FSS. For the patients to receive FSS, randomized study cannot be performed because of ethical aspect. In this review, we summarize the FSS for CCC based on the retrospective studies.

Schilder et al. demonstrated that no recurrence was observed among 5 patients with stage IC CCC who received FFS; however, the detail of stage or postoperative chemotherapy was not recorded [23]. Kajiyama et al. reported the clinical outcome of 10 patients with stage I CCC treated with FSS (IA:4, IC(intraoperative capsule rupture): 5, IC(positive for malignant ascites):1) and demonstrated as follow [24]: (1) Among 10 patients, 9 patients received chemotherapy after surgery, (2) one patient with IC(positive for malignant ascites) who received postoperative chemotherapy recurred. Sato et al. reported 30 patients with stage I CCC who received FFS and reported as follow [25]: (1) Among 15 IA cases, 9 cases received chemotherapy after surgery and no one recurred, (2)Among 15 IC patients, 11 patients received chemotherapy after surgery, and 2 patients (IC(intraoperative capsule rupture):2) recurred among 11 patients who received chemotherapy and 3 patients (IC(intraoperative capsule rupture):2, IC(positive for malignant ascites or surface capsule involvement):1) recurred among 4 patients who did not received chemotherapy. (3) Recurrent sites are residual ovary (n = 3), lymph node (n = 2), peritoneum (n = 2) and liver (n = 1). (4) The 5-year survival rate is 93.3%. These data are shown in Table 2.

We summarized Kajiyama's and Sato's reports in detail: (1) Among 19 patients, 12 patients received postoperative chemotherapy and no one recurred. (2) Among 21 IC patients, 17 patients received postoperative chemotherapy, and recurrent rate of IC(intraoperative capsule rupture) and IC(positive for malignant ascites or surface capsule involvement) are 25%(4/16) and 40%(2/5). (3) Among 17 IC patients who received postoperative chemotherapy, 3 (18%) patients recurred and among 4 IC patients who did not received chemotherapy, 3 (75%) patients recurred.

Recently, Kajiyama et al. also analyzed the OS of 16 patients with stage I CCC who underwent FSS and compared survival with 204 patients receiving radical surgery, or 64 patients with non-CCC undergoing FSS and demonstrated that patients with CCC who underwent FSS did not show a poorer survival than non-CCC patients who underwent FSS, or those at the corresponding stage with no CCC [26].

From these findings, CCC IA patient may be candidate for FFS and postoperative chemotherapy may be useful for CCC IC patient who received FFS.

Chemotherapeutic treatment

Clear cell carcinoma (CCC) is a quite unique ovarian tumor showing resistance to platinum-based chemotherapy. The effect of the gold standard therapy for ovarian carcinomas, combination with paclitaxel and carboplatin (TC), is not satisfactory for CCC. Irinotecan hydrochloride, a topoisomerase I inhibitor, is a candidate for the treatment for CCC. Irinotecan combined with cisplatin (CPT-P) has been recognized to have an activity no less than TC for CCC. A world-wide prospective clinical study to compare CPT-P and TC as the first-line chemotherapy for CCC, GCIG/JCOG (Gynecologic Cancer Intergroup/Japanese Gynecologic Oncology Group)

Table 2 Relapse rates of clear cell carcinoma patients who received FSS

stage	author	year	number of patients	relapse
Stage IA	Kajiyama [23]	2008	4	0% (0/4)
	Satoh [24]	2010	15	0% (0/15)
	total		19	0% (0/19)
Stage IC	Schilder [22]	2001	5	0% (0/5)
	Kajiyama [23]	2008	6	17% (1/6)
	Satoh [24]	2010	15	33% (5/15)
	total		26	23% (6/26)

Table 4 Response rates of salvage chemotherapy for recurrent or refractory clear cell carcinoma

regimen	author	year	response/ number of patients, response rate
Megestrol acetate	Walailak [45]	2001	2/10, 20%
Cyclopshosphamide+ cisplatin	Takano [46]	2008	1/9, 11%
Irinotecan+Platinum	Sugiyama [29]	1998	1/3, 33%
	Takano [46]	2008	2/15, 13%
Etoposide+Platinum	Takano [46]	2008	2/13, 15%
Paclitaxel+Carboplatin	Utsunomiya [32]	2006	3/13, 23%
	Crotzer [43]	2007	2/7, 29%
Gemcitbine	Crotzer [43]	2007	1/9, 11%
	Yoshino [47]	2012	1/5, 20%
Docetaxel+Irinotecan	Yoshino [47]	2012	1/11, 9%
Temsirolimus	Takano [46]	2011	1/5, 20%

these reports, the longest progression-period of 14 months was obtained by Temsirolimus [47]. The observed response duration was surprisingly longer than those obtained by any cytotoxic agents so far with no serious toxicities. The report encouraged us to investigate another chemotherapeutic strategy for CCC.

From the reported cases, however, it could be concluded that CCC is a potentially extremely chemo-resistant tumor against cytotoxic agents, especially in recurrent or refractory settings. Another strategy including molecular targeting agents might be needed for the treatment of these tumors.

Incorporation of molecular targeting agents for the treatment of CCC

In the aspects of molecular characteristics as well as clinical behavior, it is hypothesized that CCC belongs to a different entity from other histological subtypes of ovarian carcinoma. First of all, the incidences of p53 mutation and p53 overexpression were much less frequent in CCC than in other histologic types of epithelial ovarian cancer [49,50]. On the other hand, mutation of p53 gene was quite frequent in serous subtype of ovarian cancers, and most of the alterations were missense mutations [51]. In addition to p53 status, CCC has a quite unique expression pattern of several molecules. Glutathione peroxidase 3 (GPX3) was found at levels 30-fold higher on average in CCC compared with the other ovarian cancer subtypes through studies with cDNA arrays and serial analysis of gene expression [52]. Elevated expression of GPX3 might contribute to chemoresistance phenotype, which is often observed in the patients with CCC. Another investigation using oligonucleotide microarrays reported that glutaredoxin (GLRX) and superoxide dismutase 2 (SOD2), in addition to GPX3, were highly expressed in clear cell type ovarian cancer, suggesting that high levels of these proteins relating with antioxidant function render CCC to be more resistant to chemotherapy [53,54].

Further, a report using oligonucleotide probe arrays showed that a transcription factor, hepatocyte nuclear factor-1 (HNF-1) was upregulated in CCC cell lines [55]. Overexpression of HNF-1 was confirmed by immunohistological staining of clinical samples. Further, overexpression of HNF-1 was observed in the specimens of borderline clear cell tumor and benign clear cell tumor [56]. The expression of HNF-1 was detected in not only atypical endometrial tissue, but also in endometriosis with degenerative and regenerative changes, suggesting that early differentiation into the clear cell lineage takes place in the endometriotic epithelium, and HNF-1 contributes to carcinogenesis of CCC.

Recently, immunohistochemical analysis showed that hypoxia-inducible factor 1 alpha (HIF-1alpha) expression levels were significantly higher in CCC than in other histological types of ovarian cancers [57]. Upstream target of HIF-1alpha, mammalian target of rapamycin (mTOR), was also reported to be up regulated in CCC [58,59], which was selected for molecular target of CCC.

There are two international collaborating studies led by Gynecologic Oncology Group (GOG) to evaluate efficacy of molecular targeting agents for CCC of the ovary [60,61]. It is true that there existed super-responders against molecular targeting agents in the patients with CCC. Consequently, further studies to evaluate these new drugs should include biomarker analysis to predict response or adverse effect for clinical application.

Conclusions

CCC has unique characteristics among ovarian cancers. We have to deal with the tumor using completely different techniques of treatment modality in terms with surgery and chemotherapy. Especially, we have to focus on histology-specific features of molecular pattern. We hope the day will come when CCC tumors would be easily handled by the selection of effective surgery and chemotherapy including molecular targeting agents.

Abbreviations

CCC: Clear cell adenocarcinoma; SAC: Serous cyst adenocarcinoma; EOC: Epithelial ovarian carcinomas; PFS: Progression free survival; OS: Overall survival; FSS: Fertility-sparing surgery; ACOG: American college of obstetrics and gynecology; ESMO: European society for medical oncology; JSGO: Japan society of gynecologic oncology; NCCN: National comprehensive cancer network; GCIG: Gynecologic cancer intergroup; JCOG: Japanese gynecologic oncology group; CPT-P: Irinotecan hydrochloride + cisplatin; TC: Paclitaxel + carboplatin; GPX3: Glutathione peroxidase 3; GLRX: Glutaredoxin; SOD2: Superoxide dismutase 2; HNF-1: Hepatocyte nuclear factor-1; HIF-1: Hypoxia-inducible factor 1; mTOR: Mammalian target of rapamycin; GOG: Gynecologic oncology group.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions
Dr Takano and Dr Tsuda wrote the manuscript. Dr Takano, Dr Tsuda, and Dr Sugiyama approved it. All authors read and approved the final manuscript.

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3017, is now ongoing. Additionally, molecular-targeting agents are evaluated for advanced or recurrent CCC. We would discuss the chemotherapeutic regimens as primary or second-line therapy for CCC in this review.

Primary chemotherapy using cytotoxic agents

It has been implied that CCC of the ovary showed resistance to conventional platinum-based chemotherapy [27-29]. Recent studies have confirmed the evidence in the analysis of patients with measurable CCC. Objective response was observed in 11-27% with conventional platinum-based regimen, whereas patients with serous adenocarcinoma (SAC) subtype showed a significantly higher response rate of 73-81% [30-32]. A report showed survival benefit of conventional chemotherapy with paclitaxel and platinum after complete surgery in CCC patients [33]. However, the result from large series of CCC patients treated with paclitaxel and platinum showed no survival benefit compared with conventional platinum-based chemotherapy in both early and advanced cases [9]. The results suggested that TC therapy, which is commonly used for ovarian carcinoma, is not effective enough for CCC patients. Reported response rates of primary therapy for CCC are summarized in Table 3 [9,29-33].

Irinotecan hydrochloride, a semisynthetic derivative of camptothecin, has additive and synergic effects in combination with cisplatin *in vitro* [34,35]. The combination therapy with irinotecan hydrochloride and cisplatin (CPT-P) was reported to be effective for patients with various solid tumors. Especially, a large clinical trial revealed that CPT-P had significant activity for extensive small-cell lung cancer [36]. Additionally, CPT-P had been reported to be effective in first-line and second-line chemotherapy for the treatment of CCC of ovary [37,38]. A large retrospective analysis indicated that CPT-P had a potential therapeutic effect at least no less than TC therapy [39]. A phase II study (JGOG3014) to compare CPT-P and TC for first-line treatment for CCC was conducted. The study revealed that completion rate of six cycles and five-year progression-free survival was similar in both arms [40]. Interesting to note, in the patients with residual tumor less than 2 cm, overall survival was marginally improved in CPT-P group in comparison with TC group ($p = 0.056$). Subsequently, a phase III randomized study to compare CPT-P and TC as adjuvant chemotherapy for CCC is on-going (GCIG/JGOG3017) [41]. The winner regimen will be the first regimen for histologically individualized therapy for ovarian cancers.

Table 3 Response rates of primary chemotherapy for clear cell carcinoma

regimen	author	year	response/ Number of patients, response rate
Conventional Platinum-based	Goff [28]	1996	1/6, 17%
	Sugiyama [29]	2000	3/27, 11%
	Ho [30]	2004	4/15, 27%
	Takano [9]	2006	5/30, 17%
Taxane-Platinum	Enomoto [31]	2003	2/9, 22%
	Ho [30]	2004	9/16, 56%
	Utsunomiya [37]	2006	8/15, 53%
	Takano [9]	2006	9/28, 32%
Irinotecan-cisplatin	Takano [9]	2006	3/10, 30%

Another issue concerning chemotherapy for CCC is adjuvant therapy for patients with stage I disease. CCC is regarded as grade 3 tumor, and clinical guidelines recommend adjuvant chemotherapy for all patients with CCC, even at stage Ia. A large retrospective analysis of stage I CCC revealed that there were no statistical differences of progression-free survival (PFS) and overall survival (OS) between patients with chemotherapy and without chemotherapy [16]. Also, multivariate analysis showed that peritoneal cytology status ($p = 0.02$) and pT status ($p = 0.04$) were independent prognostic factors for PFS, however, adjuvant chemotherapy was not a prognostic factor ($p = 0.80$). The results suggested adjuvant chemotherapy had little impact upon survival of stage I CCC patients. Further strategy, such as a molecular targeting agent, is needed to improve survival of CCC, especially cases with positive peritoneal washing.

Second-line chemotherapy for CCC

In a large series of platinum-sensitive relapsed ovarian tumors including all histological subtypes, overall response was 54% of the patients treated with the conventional platinum-based chemotherapy, and 66% of the cases treated with paclitaxel plus platinum chemotherapy [42]. In the platinum-resistant tumors, however, response rate using anti-cancer agents usually range from 25 to 30% [43]. In the second-line or salvage settings, the response rate for recurrent or refractory CCC was extremely lower than that for other histological tumors: even in the patients with platinum-sensitive CCC disease, the response rate reported was lower than 10% [44,45]. So, we have summarized reported cases that achieved objective response (Table 4) [30,33,44-48].

Recently, single agent gemcitabine could be a candidate for salvage therapy for CCC, as the authors suggested [44,48]. Other regimens that showed objective response included irinotecan/platinum, etoposide/platinum, and paclitaxel/carboplatin; however, the efficacy was limited with progression-free interval approximately 6 months. Despite importance of response, it would be more important to monitor if adverse effects of chemotherapy worsen quality of life of the patients. Among

Table 1 Rates of lymph node metastasis in early-staged clear cell carcinoma and serous adenocarcinoma

author	year	number of patients	pT stage	metastatic rate
clear cell carcinoma				
Di Re[2]	1989	11	pT1	9% (1/11)
Petru[3]	1994	2	pT1	0% (0/2)
Onda[4]	1996	16	pT1/2	31% (5/16)
Baiocchi[5]	1998	21	pT1	5% (1/21)
Suzuki[6]	2000	9	pT1	11% (1/9)
Sakuragi[7]	2000	23	pT1/2	17% (4/23)
Negishi[8]	2004	46	pT1	12% (5/42)
			pT2	75% (3/4)
Takano[9]	2006	173	pT1a	9% (3/36)
			pT1c	7% (7/99)
			pT2	13%(5/38)
Harter[10]	2007	7	pT1	0% (0/7)
Desteli[11]	2010	4	pT1	0% (0/4)
Nomura[12]	2010	36	pT1/2	6% (2/36)
Subtotal		**348**		**11%(37/348)**
Serous cystadenocarcinoma				
Di Re[2]	1989	40	pT1	28% (11/40)
Petru[3]	1994	21	pT1	38% (8/21)
Onda[4]	1996	21	pT1/2	33% (7/21)
Baiocchi[5]	1998	106	pT1	26% (27/106)
Suzuki[6]	2000	13	pT1	31% (4/13)
Sakuragi[7]	2000	25	pT1/2	8% (2/25)
Morice[13]	2003	26	pT1	31% (8/26)
Negishi[8]	2004	35	pT1	4% (1/24)
			pT2	36% (4/11)
Harter[10]	2007	13	pT1	15% (2/13)
Desteli[11]	2010	7	pT1	14% (1/7)
Nomura[12]	2010	12	pT1/2	50% (6/12)
Subtotal		**319**		**25%(81/319)**

20% [1-6]. Reported rates of lymph node metastasis in CCC and serous cystadenocarcinoma (SAC) were summarized in Table 1 [2-14]. From the results investigating a large number of CCC cases, retroperitoneal lymph node metastasis was observed in 9% in pTIa tumors, 7% in pTIc tumors, and 13% in pT2 tumors in CCC, which suggested that incidence of lymph node metastasis in CCC was lower than that of SAC [9]. Based on the subtotal of reported cases with pT1 and pT2 tumors, approximately one half incidence of lymph node metastasis in CCC in comparison with SAC was confirmed: 11% in CCC, and 25% in SAC.

Lymphadenectomy is so important to detect metastatic lymph nodes, as the patients with positive lymph nodes had poorer prognosis. However, the role of lymphadenectomy remains unclear based on the therapeutic aspect. Several authors reported that lymph node metastasis is independent prognostic factor for CCC [7,8,15]. Magazzino et al. analyzed 240 CCC retrospectively and reported as followed [15]: (1) Of 240 cases, 47.9% had lymphadenectomy and most of cases received platinum based chemotherapy after primary surgery. (2) The cases who received lymphadenectomy had longer progression-free survival (PFS) than the cases who had no lymphadenectomy in stage I/II, III/IV and all stage ($p = 0.0258$, $p = 0.00337$, $p = 0.0001$). (3) In advanced cases, lymphadenectomy prolonged the overall survival (OS). (4) In CCC, lymphadenectomy and clinical stage are independent prognostic factors by multivariate analysis. However, we reported that pN status showed only a marginal significance upon PFS and no significance upon OS based on the analysis of 199 CCC [16]. Other reports failed to show the usefulness of lymphadenectomy as prognostic factor [17,18]. Further examination will be required to confirm the role of lymphadenectomy for CCC.

In our studies, multivariate analysis revealed that peritoneal cytology status was independent prognostic factor for PFS ($p = 0.04$), but not for OS, and in addition, completion of surgical staging procedures was not a prognostic factor [16]. Higashi et al. analyzed 224 CCC patients with stage I and reported as followed [19]: (1) there was no significant difference in both OS and PFS of CCC between stage IA and IC (intraoperative capsule rupture), and the 5-year OS rate of stage IC(intraoperative capsule rupture) CCC patients was comparable to those with the non-CCC. (2) Stage IC CCC patients except for IC (intraoperative capsule rupture), such as positive ascites/washing and capsule surface involvement, had a poorer OS and PFS than those with IC (intraoperative capsule rupture). The results suggested stage I CCC cases other than intraoperative capsule rupture were at a considerable risk for recurrence and mortality.

Finally, the role of complete surgical staging still remains unclear for CCC. Several reports demonstrated that adjuvant chemotherapy had little impact on the survival of stage I CCC patients [16,20]. From these findings, complete surgical staging procedures are required at least to detect high-risk patients of recurrence; however, the extent of the surgery could not improve overall survival of CCC.

Cytoreductive surgery

Optimally cytoreduced patients of EOC were reported to show a significant survival benefit over those patients who are suboptimally debulked, and there is a significant survival advantage in patients who are able to be debulked to less than 1 cm of residual disease. Hoskins et al. reported that patients with clear cell and mucinous histology had poor outcome even when they had small