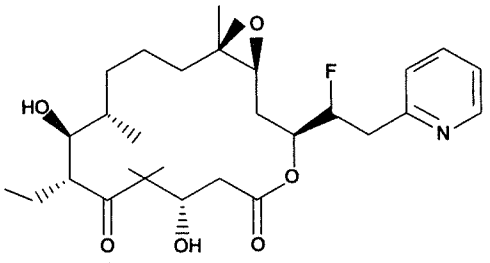
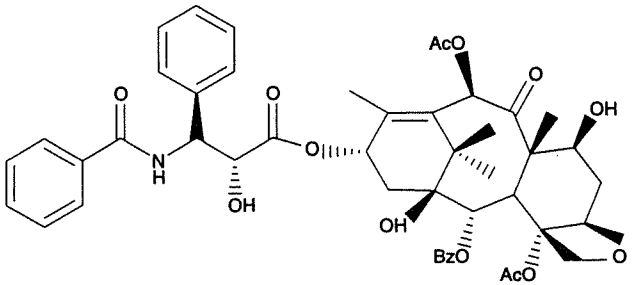
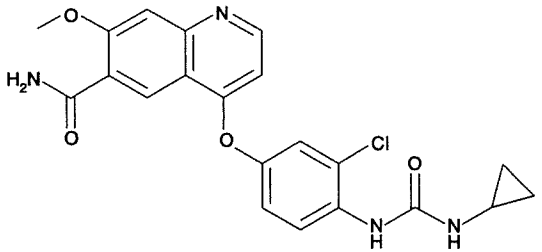
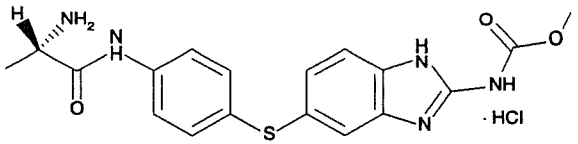
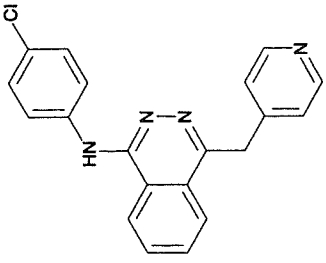
Table 3. Competitive environment (continued).

Compound	Company	Structure	Indication	Stage of development	Mechanism of action
Epothilon	Bayer AG		Ovarian	Phase III	Microtubule stabilization
Abraxane	American Biosciences, Inc.		Ovarian	Phase I	Microtubule stabilization
E 7080	Eisai Co. Ltd.		Ovarian	Phase I	Antiangiogenesis (VEGF)
MN-029	MediciNova, Inc.		Ovarian	Phase I	Vascular disruption

Information contained in this table was taken from Cima Science [59].

Table 3. Competitive environment (continued).

Compound	Company	Structure	Indication	Stage of development	Mechanism of action
Vatalanib	Bayer AG/Novartis Pharma		Ovarian	Phase II	Antiangiogenesis (VEGF)
Bevacizumab	Genentech, Inc.	$(C_{1034}H_{1591}N_{273}O_{338}S_6)$, $(C_{2235}H_{3413}N_{585}O_{678}S_{16})$	Ovarian	Phase III	Antiangiogenesis (VEGF)
MORAb-003	Morphotek, Inc.	–	Ovarian	Phase II	Folate receptor alpha inhibitor (FRA)
Aflibercept	Regeneron Pharmaceuticals, Inc.	–	Ovarian	Phase II	Antiangiogenesis (VEGF trap)

Information contained in this table was taken from Cima Science [59].

seventh position. SNS-595 has shown an antitumor effect in a wide range of human-derived tumors, such as lung, ovarian, colorectal, stomach, and breast cancers. In a Phase I study of patients with solid tumors, the following dose-limiting toxicities were reported: neutropenia, nausea, vomiting, and mucositis.

5.3 Microtubule

BMS-275183, a paclitaxel derivative that can be administered orally, has a high degree of oral bioavailability. Its activity is comparable to that of intravenously administered paclitaxel. The efficacy of BMS-275183 for treating lung, breast, ovarian, and colon cancers has been confirmed in animal models. In a Phase I study of 16 advanced solid tumor patients receiving 5 – 320 mg/m^2 continuously at weekly intervals, the recommended dose was determined to be 200 mg/m^2, a level that ensures safety. While hematologic toxicities were reported as adverse events, none of these were grade 3 or higher, and the frequency of toxicity was low.

E-7974, a synthetic derivative of hemiasterlin, a natural product derived from marine sponges, is an antitumor agent given intravenously. It has shown strong antitumor activity both *in vitro* and *in vivo*. It is also active in tumors that overexpress *P*-glycoprotein, a multi-drug resistant efflux pump. These activities indicate that E-7974 has more advantages than many other existing antitumor agents. The mechanism of action is inhibition of microtubule assembly; that is, it inhibits mitotic division by preventing tubulin polymerization and induces apoptosis by arresting cell cycle progression. While microtubule assembly inhibitors target beta-chains, E-7974 also binds to alpha-chains. E-7974 showed strong antitumor activity against paclitaxel-resistant ovarian cancer cells due to beta-tubulin mutation. In the Phase I study of patients with solid tumors, E-7974 was rapidly injected intravenously on days 1 and 15 of a 28-day cycle, and the recommended dose was determined to be 0.31 mg/m^2. The adverse drug reactions reported in the study could be controlled and were reversible.

Epothilone is a natural epothilone B analog produced by total synthesis (intravenous agent). Discovered from a substance produced by myxobacteria in soil, epothilone is an antitumor agent with a microtubule-stabilizing effect. Unlike paclitaxel, epothilone inhibits the proliferation of *P*-glycoprotein-overexpressing tumor cell lines at lower than nanomolar concentration. For this reason, epothilone is not recognized by the elimination mechanism. Other characteristics of epothilone include rapid intake into tumor cells and preferential accumulation within nuclei. In a Phase I study, 52 patients with solid tumors that were either refractory or had shown poor response to standard treatments were injected with epothilone intravenously for 30 min in a 3-week cycle. As a result, antitumor activity and partial remission were observed in two breast cancer patients. In 10 patients who had only one tumor, such as non-small-cell lung cancer or a malignant epithelial tumor, the symptoms

remained stable for 19 months. The reported adverse drug reactions were peripheral neuropathy and nausea, usually mild. Phase III studies (overseas) in patients with ovarian cancer, non-small-cell lung cancer, small cell lung cancer, breast cancer, prostate cancer, and other solid cancers are either underway or planned.

Abraxane is a novel paclitaxel preparation (injectable suspension). One vial contains 100 mg of paclitaxel and 900 mg of albumin. A recommended dose is the intravenous injection of 260 mg/m^2 for 30 min continuously once every 3 weeks. Since paclitaxel is not very soluble in water, polyoxyethylene castor oil (Cremophor) is needed as a solvent, and pretreatment with steroids or other drugs to prevent hypersensitivity reactions is also required. Abraxane, however, does not require any pre-treatment, and is therefore highly useful. In the United States, abraxane was approved and launched on 7 January 2005 for the treatment of 'breast cancer after the failure of combination chemotherapy for metastatic disease or relapse within six months of postoperative adjuvant chemotherapy'. Abraxane is still being developed in the United States to extend the approved indications to include breast cancer, lung cancer, ovarian cancer, head and neck cancer, and melanoma.

5.4 Folate receptor inhibitor

MORAb-003 is a fully humanized monoclonal antibody against folate receptor alpha (FRA). In a Phase I study, favorable clinical activity and tolerability were demonstrated in platinum-resistant and -refractory advanced ovarian cancer patients. In a Phase II study of patients with platinum-sensitive ovarian cancer who were in the first relapse, those without symptoms received MORAb-003 alone, and those with symptoms received MORAb-003 combined with carboplatin plus taxane chemotherapy. An interim analysis conducted in 15 patients (seven with the single agent, eight with the combination therapy) showed no significant adverse drug reactions. The target number of subjects for the Phase II study is 60, and the primary end point is remission duration.

5.5 Vascular disruption

MN-029 is a second-generation benzimidazole carbamate vascular-disrupting agent. It is a vascular-targeting agent that induces necrosis of the central region of the solid tumor by binding to intracellular tubulins and eventually damaging tumor vasculature. The MN-029 molecule is designed so that it cannot easily pass through the blood–brain barrier, reducing adverse drug reactions that affect the central nervous system. Two types of antitumor agents specifically target tumor blood vessels: angiogenic inhibitors and vascular targeting agents. MN-029 is a vascular targeting agent. While angiogenic inhibitors suppress the formation of new blood vessels in growing tumors, MN-029 targets existing blood vessels in tumors to prevent blood vessels from supplying tumors with nutrients, thereby leading to necrosis of many tumor cells. With this activity, we can expect a better effect. In addition, we also consider that the concomitant use of MN-029 with an angiogenic inhibitor may have synergic effects. A Phase I study was completed in 2006, and a Phase II study in non-small-cell lung cancer and ovarian cancer is being prepared.

5.6 Antiangiogenesis

Vatalanib, a vascular endothelial growth factor receptor tyrosine kinase (VEGFR-TK) inhibitor, is an antitumor agent in tablet form with an amino-phthalazinone skeleton. Vatalanib inhibits angiogenesis by inhibiting the phosphorylation of VEGFR-TK, exerting antitumor effects. It inhibits all VEGFRs (VEGFRs 1 – 3), which will completely inhibit the signaling pathways of angiogenesis. Patient enrollment in a Phase III study of metastatic colorectal cancer was completed in 2004. In March 2005, a Phase III study of vatalanib as a second-line treatment for non-small-cell lung cancer was begun. In addition, a Phase I/II study to extend indications to include prostate, breast, pancreatic, and ovarian cancers is being conducted. In a Phase I study of patients with acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS) who received 500, 750, and 1000 mg orally twice daily, the tolerability of 500 and 750 mg twice daily was favorable. Reported adverse events, for which a causal relationship to vatalanib could not be excluded, were stupor, nausea, vomiting, and coma.

E-7080, a VEGF receptor (KDR/Flk-1) multikinase inhibitor, inhibits all VEGFs, including subtypes. The cell proliferation inhibitory concentration (IC_{50} value) for a small-cell lung cancer cell line H526 expressing c-Kit was 9.36 nM, and that of KRN633, an antiangiogenic and antitumor agent, was 301 nM. E-7080 inhibited the proliferation of cancers in xenograft models of human lung, pancreatic, and ovarian cancers. It also showed a tumor regression effect in some cancers. Phase I studies are underway in Japan, the United States, and the European Union.

Aflibercept, a fusion protein with a fragment of human immunoglobulin (Fc) coupled to the ligand-binding domain of soluble receptors of VEGF (VEGFRs-1 and -2), captures VEGF in the blood flow and neutralizes it, exerting antitumor effects. A Phase I study of solid tumor patients is underway. In August 2007, two Phase III studies of a combination of aflibercept and a standard chemotherapy was begun in patients with prostate and non-small-cell lung cancers. In the United States, a Phase II study is ongoing in patients with breast, kidney, ovarian, and non-small-cell lung cancers. In a Phase II double-blind study of patients with platinum-resistant ovarian cancer at 62 medical institutions in the European Union, the United States, and Canada, 162 patients were intravenously injected with 2 mg/kg or 4 mg/kg every 2 weeks. According to an interim analysis of 45 patients, five patients (11%) achieved partial response (PR).

Bevacizumab is a humanized monoclonal antibody against vascular endothelial growth factor (VEGF). In February 2004, it was approved in the United States for 'use in

combination with 5-fluorouracil (5-FU)-based chemotherapy for first-line treatment of metastatic colorectal cancer'. A Phase III study of bevacizumab monotherapy in renal cell cancer and combination therapy in non-small-cell, breast, and renal cell cancers is ongoing. In a Phase II study of platinum-resistant and refractory ovarian cancer patients, favorable results were reported: a response rate of 15.9%, mean response duration of 4.2 months, and time to progression of 4.3 months. An adverse event specific to the agent was gastrointestinal perforation. A global joint clinical study group headed by the United States Gynecologic Oncology Group (GOG) is currently performing a three-arm Phase III study of bevacizumab combined with paclitaxel plus carboplatin in epithelial ovarian cancer.

6. Potential development issues

A new tubulin inhibitor with less neurotoxicity and hypersensitivity should be developed. Moreover, novel topoisomerase I inhibitors and cytotoxic agents with a novel mechanism of action are needed to improve the efficacy and safety of second-line chemotherapy. Simultaneously, chemotherapy toxicity has to be minimized. However, efficacy and survival will be limited for patients with ovarian cancer using cytoxic agents unless biological agents are developed and introduced. Fewer patients have ovarian cancer than gastrointestinal and lung cancers, so development of biological agents for these cancers takes longer. We expect that more specific molecular targets for ovarian cancer will be identified. Further studies on chemoimmunotherapy and the combination of chemotherapy and gene therapy are needed.

7. Conclusion

Paclitaxel (175 mg/m^2/3 h) combined with carboplatin ACU 6 (TC regimen) is the current gold standard for treating ovarian cancer, and studies confirm that, thus far, a third cytotoxic agent added to this regimen does not improve survival. Improvements in efficacy seem to have limits when cytotoxic agents are used, but a promising biological agent is likely to emerge while Phase II studies of various biological agents continue. Of the molecular-target drugs, only bevacizumab is effective at present, warranting its use in monotherapy or combining it with an anticancer drug. No data show that maintenance and consolidation therapy improve survival in ovarian cancer. A meta-analysis of paclitaxel studies is needed to evaluate maintenance therapy. In the future, biological agents will play a leading role, and a variety of promising biological agents must be tested. Intraperitoneal chemotherapy (IP) reportedly prolongs survival period significantly compared with intravenous injection, and IP may be effective for patients with optimal disease, so an appropriate regimen and cycle number is urgently needed. Clear cell carcinoma and mucinous adenocarcinoma are less sensitive to a TC regimen than serous adenocarcinoma, and international clinical trials are needed for each of these refractory cancers. The goal of therapy for recurrent cancer is to delay progression, relieve symptoms, and improve QoL. Cytotoxic agents combined with carboplatin for chemosensitive disease, and cytotoxic as well as biological agents offering novel mechanisms of action against chemoresistant diseases, should be developed.

8. Expert opinion

Although epithelial ovarian cancer is classified as chemosensitive, treatment with cytotoxic agents is not always completely effective. The TC regimen with an added third cytotoxic agent has not yet resulted in a better survival rate [12]. Similarly, patients treated with maintenance chemotherapy combined with cytotoxic agents [13-17] did not have a better survival rate. One strategy for ovarian cancer is to find a new prognostic factor and a biomarker that accurately reflects the disease status. New molecular-targeted therapies, including antiangiogenic agents (VEGF inhibitors) and signaling inhibitors (AKT/m-TOR signaling), and Src, Mek, c-Met, and Ret inhibitors and further immunotherapy using anti-CA125 antibody, are all investigational. So far, the one promising molecular-target drug to prolong survival [36-41] is bevacizumab, which is being compared in a GOG RCT with a placebo and is also being combined with TC (GOG218). Also, relapsed patients with chemosensitive disease are included in a current RCT of TC regimen combined with or without bevacizumab (GOG213). In addition, a GOG IP trial is assessing the combination of intravenous bevacizumab. It will take 4 – 5 years to evaluate the effect of bevacizumab.

Recent molecular studies support the hypothesis that clear cell carcinoma and mucinous adenocarcinoma are rare and refractory cancers that are biologically distinct from serous adenocarcinoma. Treatment of these cancers has not yet been adequately tested, so separate clinical trials are needed for each type. Clinical trials are usually conducted by histological subtype, although an international randomized trial for clear cell carcinoma is now underway [35]. Targeted therapy seems to be attractive for chemoresistant clear cell carcinoma, thus VEGFR inhibitor (sunitinib), PDGFR inhibitor (sorafenib), m-TOR inhibitor (temsirolimus), and monoclonal antibody (bevacizumab) are being evaluated. Mucinous adenocarcinoma often shows CK20- and CEA-positive patterns in immunohistochemistry, and furthermore, p53-negative and k-ras-positive in molecular markers, which suggests that mucinous adenocarcinoma resembles colorectal, stomach, and pancreas cancers more than serous ovarian adenocarcinoma. Because ovarian mucinous adenocarcinoma resembles gastrointestinal cancer, trials are needed to test the agents effective for gastrointestinal cancer. The GOG will start a randomized Phase II trial comparing TC regimen with capecitabine plus oxaliplatin (GOG241). We are planning a Phase II study of S-1 plus oxaliplatin in Japan.

For refractory cancers, molecular biology-based, cross-organ treatment with cytotoxic/cytostatic agents is needed.

Intraperitoneal chemotherapy may be effective for patients with optimal disease [13,18-22]. A combination of intravenous and intraperitoneal administration is expected to increase the effect of agents, therefore an optimal regimen and administration cycle is urgently needed. Improved formulation of drugs can also enhance intraperitoneal retention and lymphtropism, resulting in improved efficacy.

The main strategy for recurrent ovarian cancer is to find the gene related to drug resistance, then treat the cancer based on its molecular biology. Unless a specific molecular target is identified, it will be difficult to develop an efficacious treatment and prolong patient survival.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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Low response rate of second-line chemotherapy for recurrent or refractory clear cell carcinoma of the ovary: a retrospective Japan Clear Cell Carcinoma Study

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Abstract. Takano M, Sugiyama T, Yaegashi N, Sakuma M, Suzuki M, Saga Y, Kuzuya K, Kigawa J, Shimada M, Tsuda H, Moriya T, Yoshizaki A, Kita T, Kikuchi Y. Low response rate of second-line chemotherapy for recurrent or refractory clear cell carcinoma of the ovary: a retrospective Japan Clear Cell Carcinoma Study. *Int J Gynecol Cancer* 2008;**18**:937–942.

Clear cell carcinoma (CCC) of the ovary has been recognized to show resistance to anticancer agents in the first-line chemotherapy. Our aim was to evaluate the effect of second-line chemotherapy in a retrospective study. A total of 75 patients diagnosed with CCC and treated between 1992 and 2002 in collaborating hospitals were reviewed. Criteria for the patients' enrollment were 1) diagnosis of pure-type CCC at the initial operation, 2) treatment after one systemic postoperative chemotherapy, 3) measurable recurrent or refractory tumor, 4) at least two cycles of second-line chemotherapy and assessable for the response, and 5) adequate clinical information. Regimens of first-line chemotherapy were conventional platinum-based therapy in 33 cases, paclitaxel plus platinum in 24 cases, irinotecan plus platinum in 9 cases, and irinotecan plus mitomycin C in 7 cases. Treatment-free periods were more than 6 months in 24 cases (group A) and less than 6 months in 51 cases (group B). In group A, response was observed in two cases (8%): one with conventional platinum therapy and another with irinotecan plus platinum. In group B, three cases (6%) responded: two with platinum plus etoposide and one case with irinotecan plus platinum. Median overall survival was 16 months in group A and 7 months in group B ($P = 0.04$). These findings suggest recurrent or resistant CCC is extremely chemoresistant, and there is only small benefit of long treatment-free period in CCC patients. Another strategy including molecular-targeting therapy is warranted for the treatment of recurrent or refractory CCC.

KEYWORDS: ovarian clear cell carcinoma, recurrent, refractory, second-line chemotherapy.

Clear cell carcinoma (CCC) was initially termed as "mesonephroma ovarii" by Schiller in 1939[1], and the tumor has been strictly defined by World Health Organization as lesions characterized by clear cells growing in solid/tubular or glandular patterns as well as hobnail cells since 1973[2]. Since then, many publications have identified the distinctive behavior of the tumors. The CCC tumors showed resistance to conventional platinum-based chemotherapy[3,4], and the patients with CCC had poorer prognosis compared

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with those with serous tumors[5,6]. Recent studies confirmed the evidence in the analysis of measurable CCC patients: response was observed in 11–45% with conventional platinum-based regimen, whereas patients with serous subtype showed a significantly higher response rate of 73–81%[7,8]. Combination with paclitaxel and platinum, recognized as "Gold standard" regimen for ovarian cancer[9,10], is now used to treat the patients with all subtypes of ovarian neoplasms including CCC. However, the response rate was relatively low, ranging from 22% to 56%, in measurable CCC cases treated with paclitaxel and platinum[11–15].

In the second-line or salvage settings, the response rate for recurrent or refractory CCC was extremely lower than that for other histologic tumors: even in the patients with platinum-sensitive CCC disease, the response rate reported was lower than 10%[16]. Our aim of the present study was to evaluate the effects of second-line chemotherapy for recurrent or refractory CCC following one systematic chemotherapeutic regimen and whether the concept of platinum-sensitive or platinum-resistant tumors could be applicable to CCC.

Materials and methods

Cases with pure-type CCC of the ovary, who were treated between 1992 and 2002, were identified by scanning the medical records of the collaborating institutions and central pathologic review. Patients received initial treatment and follow-up at six institutions belonging to Japan Clear Cell Carcinoma Study Group; National Defense Medical College Hospital, Tohoku University Hospital, Aichi Cancer Center Hospital, Jichi Medical College Hospital, Tottori University Hospital, and Iwate Medical University Hospital. Of all the patients treated in these hospitals, the following patients were selected: 1) patients whose tumor specimens were confirmed as pure-type CCC of the ovary by two pathologists in central pathologic review; 2) patients who received one regimen of systemic therapy as postoperative chemotherapy; 3) patients who had measurable recurrent or refractory tumor by computed tomography or magnetic resonance imaging at the beginning of second-line chemotherapy; 4) patients who received at least two cycles of second-line chemotherapy and the response of the second-line chemotherapy was assessable; and 5) patients whose clinical information was assessable.

Response for measurable disease was evaluated with computed tomography or magnetic resonance images. A complete response was defined as the complete disappearance of all detectable disease for at least 4 weeks. A partial response (PR) was defined as a greater than 50% decrease in tumor size for at least 4 weeks. Stable disease (SD) was defined as the absence of any significant change in measurable lesions for at least 4 weeks. Progressive disease (PD) was defined as the appearance of a new lesion or a greater than 25% increase in tumor size. Serum levels of tumor markers including CA125 were not used for response evaluation of chemotherapy in the present study.

The time to progression was defined as the interval from the first day of second-line chemotherapy until the date of tumor progression. Survival duration was determined as the time from the first day of second-line chemotherapy until death or the date of last follow-up contact. Kaplan–Meier method was used for calculation of patient survival distribution. The significance of the survival distribution in each group was tested by a generalized Wilcoxon test and the log-rank test. The Chi-square test and Student's t test for unpaired data were used for statistical analysis. A P value of less than 0.05 was considered statistically significant. Analysis of the data was carried out using the Stat View software ver. 5.0 (SAS Institution Inc., Cary, NC).

Results

Seventy-five patients who met the criteria were identified and analyzed in the present study. Characteristics of the patients are summarized in Table 1. Median age of the patients was 52 years, ranging from 27 to 76 years. Median follow-up period was 9 months (range: 2–72 months) in these patients. Regimens of first-line chemotherapy were conventional platinum-based therapy in 33 cases, paclitaxel plus platinum in 24 cases, irinotecan plus platinum in 9 cases, and irinotecan plus mitomycin C in 7 cases. Treatment-free period was more than 6 months in 24 cases (group A) and less than 6 months in 51 cases (group B). Second-line chemotherapy used in the present study was conventional platinum-based therapy in 9 cases, platinum plus etoposide in 13 cases, paclitaxel plus platinum in 23 cases, docetaxel plus platinum in 4 cases, irinotecan plus platinum in 15 cases, irinotecan plus mitomycin C in 6 cases, and others in 5 cases, respectively. Median cycle of the second-line chemotherapy was three cycles (range: 2–9 cycles), and a total of 212 cycles were administered.

Table 2 presents the response of each regimen used in group A and group B. In group A, the response was observed in two cases (8%): one treated with cyclophosphamide, adriamycin, and cisplatin therapy and another with irinotecan hydrochloride plus platinum. SD was observed in five cases (21%): two cases treated

Table 1. Characteristics of the patients who received second-line chemotherapy

Characteristics	$n = 75$ (%)
Age (years)	
Median: 52	
Range: 27–76	
FIGO stage	
I/II	31 (41)
III/IV	44 (59)
Residual tumor (primary surgery)	
None	36 (48)
≤1 cm	7 (9)
>1 cm	32 (43)
Primary chemotherapy regimen	
CAP, CP	33 (44)
Paclitaxel and platinum	24 (32)
CPT-11 and platinum	9 (12)
CPT-11 and mitomycin C	7 (9)
Others	2 (3)
Treatment-free period (months)	
Group A	
>13	12 (16)
6–12	12 (16)
Group B	
<6	51 (68)
Second-line chemotherapy regimen	
CAP, CP	9 (12)
Platinum and etoposide	13 (17)
Paclitaxel and platinum	23 (31)
Docetaxel and platinum	4 (5)
CPT-11 and platinum	15 (20)
CPT-11 and mitomycin C	6 (8)
Others	5 (7)

CAP, cyclophosphamide, adriamycin, and cisplatin; CP, cyclophosphamide and cisplatin; CPT-11, irinotecan hydrochloride; MEP, mitomycin C, etoposide, and cisplatin.

with paclitaxel plus platinum and three cases with irinotecan hydrochloride plus platinum. Non-PD rates in group A were 25% in cyclophosphamide, adriamycin, and cisplatin therapy, 33% in paclitaxel plus platinum, and 57% in irinotecan plus platinum, respectively.

In group B, three cases (6%) responded: two with platinum plus etosposide and one case with irinotecan hydrochloride plus platinum. SD was observed in six cases (12%) of 51 patients. Non-PD rates in group B were 18% in platinum plus etoposide, 12% in paclitaxel plus platinum, and 38% in irinotecan plus platinum, respectively. Overall non-PD rate was 29% in group A and 18% in group B. The details of the patients who showed PR and SD response are presented in Table 3; seven cases in group A and nine cases in group B.

Median overall survival of all cases was 11 months (95% confidence interval, 9.5–13.4 months); 17 months in PR cases, 14 months in SD cases, and 7 months in PD tumors. Survival of non-PD tumors was slightly better than that of PD tumors, but the difference was not statistically significant ($P = 0.07$; Fig. 1). Overall survival of group A was significantly better than that of group B ($P = 0.04$; Fig. 2). Median survival was 16 months in group A and 7 months in group B, respectively. Multiple-regression analysis for overall survival after the initiation of second-line chemotherapy was carried out using these variables: age (<52 vs >53 years), physical status (0 vs 1, 2), FIGO stage (I, II vs III, IV), residual tumor at the primary surgery (absent vs present), first-line chemotherapy, treatment-free period (<6 vs >6 months), and second-line chemotherapy. Survival analysis for all the CCC patients revealed that long treatment-free period was the only independent better prognostic factor ($P < 0.001$; relative risk, 0.14; 95% CI, 0.01–0.06). Regimens of first-line or second-line chemotherapy were not selected as independent prognostic factors.

Discussion

In a large series of platinum-sensitive relapsed ovarian tumors including all histologic subtypes, overall response was 54% of the patients treated with the conventional platinum-based chemotherapy and 66% of the patients treated with paclitaxel plus platinum chemotherapy[17]. In the platinum-resistant tumors, however, response rate using anticancer agents usually range from 25% to 30%[18]. In the present study, overall response rate of the second-line chemotherapy was 6.7% in all the patients of group A and group B (Table 2); 8% in platinum-sensitive tumors and 6% in platinum-resistant tumors. Although response rates of two groups were similar, long treatment-free period was identified as the only better prognostic factor in relapsed or refractory CCC. As shown in Figure 1, non-PD cases had a slightly better prognosis. Thereby, a higher abundance of non-PD cases might have improved the survival of group A. On the other hand, tumor biological behavior of each group was completely different; median survival of PD cases was 12 months in group A and 6.5 months in group B, respectively. These tumor characteristics as well as non-PD ratio might have determined the prognostic profiles. But the extremely low response rate of second-line chemotherapy, as presented in the present study, seemed to confirm the chemoresistance of CCC and to imply the potential and subsequent reason for the poor prognosis of this tumor.

In the first-line treatment for CCC, response rate was 11–45% with conventional platinum-based regimen[7,8] and 22–56% in combination with paclitaxel and platinum[11–15]. Overall response was quite lower

Table 2. Response to second-line chemotherapy in the patients with treatment-free period 6 months or more (group A) and with treatment-free period less than 6 months (group B)

Regimen	PR	SD	PD	Response rate[a] (%)	Non-PD rate (%)
Group A					
CAP, CP	1	0	3	25	25
Platinum + etoposide	0	0	2	0	0
Paclitaxel + platinum	0	2	4	0	33
Docetaxel + platinum	0	0	1	0	0
CPT-11 + platinum	1	3	3	14	57
CPT-11 + mitomycin C	0	0	3	0	0
Docetaxel	0	0	1	0	0
Subtotal	2 (8%)	5 (21%)	17 (71%)	8	29
Group B					
CAP, CP	0	0	5	0	0
Platinum + etoposide	2	0	9	18	18
Paclitaxel + platinum	0	2	15	0	12
Docetaxel + platinum	0	0	3	0	0
Weekly paclitaxel	0	0	2	0	0
CPT-11 + platinum	1	2	5	13	38
CPT-11 + mitomycin C	0	1	2	0	33
CPT-11 + docetaxel	0	0	1	0	0
MEP	0	1	0	0	100
Subtotal	3 (6%)	6 (12%)	42 (82%)	6	18
Total	5 (7%)	11 (15%)	59 (79%)	6.7	21

CAP, cyclophosphamide, adriamycin, and cisplatin; CP, cyclophosphamide and cisplatin; CPT-11, irinotecan hydrochloride; MEP, mitomycin C, etoposide, and cisplatin.
[a]No patient experienced a complete response.

in CCC tumors in comparison with all ovarian tumors with non-CCC. Another candidate regimen for the first-line treatment of CCC could be combination therapy with irinotecan plus cisplatin, as the response rate of the regimen was reported to be 30–42%[19,20]. Additionally, progression-free survival was similar between combination with paclitaxel plus carboplatin and irinotecan plus cisplatin[21]. As was presented

Table 3. Profiles of 16 patients who obtained PR or SD by the second-line chemotherapy for persistent or recurrent clear cell carcinoma of the ovary

Patient number	Age (years)	First-line therapy	Treatment-free period (months)	Second-line therapy	Response duration (months)
Group A (n = 24)					
1	41	TC	15	CP	PR × 4
2	53	CAP	80	CPT-P	PR × 3
3	57	TC	10	CPT-P	SD × 4
4	54	CPT-P	13	CPT-P	SD × 4
5	53	CPT-P	20	CPT-P	SD × 3
6	52	CPT-P	20	TC	SD × 3
7	42	CPT-M	15	TC	SD × 3
Group B (n = 51)					
1	54	CAP	None	EP	PR × 4
2	36	CAP	None	EP	PR × 3
3	50	CAP	None	CPT-P	PR × 3
4	56	TC	None	CPT-P	SD × 4
5	62	TC	None	CPT-P	SD × 3
6	63	TC	None	CPT-M	SD × 3
7	55	CPT-M	None	TC	SD × 2
8	59	CAP	None	TC	SD × 2
9	42	CAP	None	MEP	SD × 3

CAP, cyclophosphamide + adriamycin + cisplatin; EP, etoposide + cisplatin; TC, paclitaxel + carboplatin; CPT-P, irinotecan hydrochloride + cisplatin; CPT-M, irinotecan hydrochloride + mitomycin C.

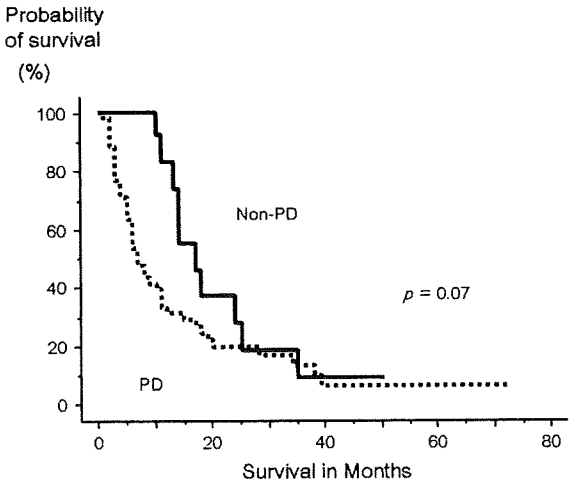

Figure 1. Kaplan–Meier curve comparing overall survival of the patients with non-PD cases and those with PD cases after second-line chemotherapy. Although probability of overall survival was slightly better in non-PD tumors compared with PD tumors, the difference was not statistically significant ($P = 0.07$).

in this study, low response of second-line chemotherapy for CCC reflects the lower response of the first-line chemotherapy.

There are few reports involving the response of second-line chemotherapy of CCC. A systemic review from a single institution documented a low response rate of anticancer drugs in recurrent CCC; 9% in the platinum-sensitive tumors and 1% in platinum-resistant disease[22]. Their report, which included third-line of greater therapy, suggested that combination with paclitaxel plus carboplatin could be a candidate in the platinum-sensitive tumors and that single-agent gemcitabine might be effective in the platinum-resistant tumors. Utsunomiya *et al.*[13] reported on the effects of combination with paclitaxel and platinum for 13 cases with recurrent or refractory CCC tumors. Response was observed in 20% (1/5) of late recurrent CCC (>12 months) and in 25% (1/8) of early recurrent (<12 months) or refractory CCC. In the present study, objective response was not observed in combination therapy with paclitaxel and platinum. However, dormancy rate of the regimen was 33% in platinum-sensitive tumors, and the therapy could be a candidate for the treatment of recurrent CCC. Another candidate for recurrent or refractory CCC might be a combination therapy with irinotecan and platinum because dormancy rate of the regimen was 57% in platinum-sensitive tumors and 38% in platinum-resistant group. Sugiyama *et al.* reported on a series of recurrent of refractory ovarian cancer patients treated with irinotecan and cisplatin. A total of 40% of the responders included one case of platinum-resistant CCC; partial response of the patient lasted for 2 months[23]. Another case report documented a complete remission of platinum-sensitive CCC tumor after two cycles of irinotecan and nedaplatin[24]. Previous reports, together with our results, suggest that the most recommendable regimens for recurrent CCC are combination therapy with paclitaxel plus platinum or irinotecan plus platinum.

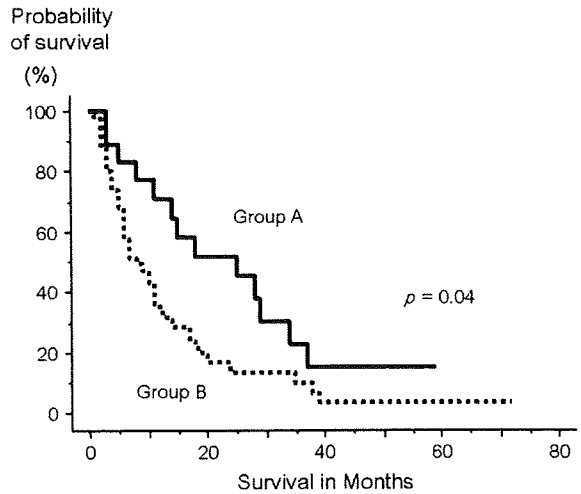

Figure 2. Kaplan–Meier curve comparing overall survival of the patients with treatment-free period more than 6 months (group A) and those with treatment-free period less than 6 months (group B). Probability of overall survival after second-line chemotherapy was significantly better in group A compared with group B ($P = 0.04$).

As the present study was a retrospective multi-institutional investigation, inclusion of some selection bias or referral bias could not be omitted. To our knowledge, our study included the largest series of recurrent CCC patients treated as second-line chemotherapy. From the results, however, it could be said that CCC is a potentially resistant tumor against anticancer drugs, especially in recurrent or refractory settings. Another strategy including molecular targeting agents might be needed for the treatment of these tumors. These observations need to be confirmed in a prospective trial of CCC-specific research, such as GCIG/JGOG3017 (Gynecologic Cancer Intergroup/Japanese Gynecologic Oncology Group).

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特集 婦人科がん治療の臨床試験—新たなエビデンスを求めて—

進行卵巣癌に対するNAC化学療法
—NAC vs. 術後—

恩田貴志*

進行卵巣癌の予後改善を目指した治療法の一つとして，近年，術前化学療法（NAC）が注目されている。Retrospective studyでは，PS不良あるいは初回手術で切除不能と判断された症例に対するNAC療法の治療成績は，標準治療である手術先行に比して遜色ないことが示されている。現在，ヨーロッパと日本の臨床試験グループにおいて，切除可能と考えられる症例も含めて，進行した卵巣癌，卵管癌，腹膜癌を対象に第Ⅲ相比較試験が行われている。これらのprospective studyにより，進行卵巣癌に対するNAC療法の役割が明らかとなることが期待される。

はじめに

進行卵巣癌の治療は，主として手術療法と化学療法の組み合わせで行われる。現在の標準治療は，卵巣癌であることの診断，正確な進行期の診断，子宮，付属器，大網のほか転移病巣の可及的摘出を目的とした初回腫瘍縮小手術（primary debulking surgery；PDS）と呼ばれる開腹手術を最初に行い，その後に化学療法を追加する治療である。化学療法は，タキサン系薬剤とプラチナ製剤との併用が標準であり，主としてpaclitaxel（PTX）とcarboplatin（CBDCA）の併用療法（TC療法）が6～8コース行われる。

標準治療において，PDSでoptimal surgery（残存腫瘍径1cm未満という定義が多く用いられる）が達成できれば良好な予後が期待できるが，進行卵巣癌の場合，一般には40～60%程度の症例にしか達成できず，予後は不良である。進行卵巣癌の予後改善を目指した治療法の一つとして，近年，術前化学療法（neoadjuvant chemotherapy；NAC）が注目されている。卵巣癌に対するNAC療法は，最初に化学療法を3～4コース行った後，腫瘍縮小手術（interval debulking surgery；IDS）を行い，さらに残りの3～4コースの化学療法を追加する治療である。ここでは，卵巣癌に対するNAC療法について解説する。

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I. 卵巣癌に対するNAC療法の利点と問題点

進行卵巣癌に対するNAC療法の利点として，

(1) 手術枠の確保や他科との連携を要する手術先行に比べて，速やかに治療を開始することが可能である。

(2) 腫瘍や胸水，腹水によるPSの低下をNACにより改善し，また治療開始時にしばし

ばみられる血栓症の改善も期待でき，より安全に侵襲の大きな手術を行いうる。

(3) NACによる腫瘍量，範囲の減少により他臓器合併切除の頻度が減少し，また，(術式を拡大しなくても) optimal surgeryの達成が期待でき，それにより重篤な合併症の減少も期待できる。

などがあり，進行卵巣癌においては，NAC療法によって治療成績および患者のQOL (quality of life) の改善が期待される。一方，NAC療法にも種々の問題点が挙げられる。

(1) 最初に診断を兼ねたPDSを行わないため，対象疾患，進行期の診断が不正確となる可能性がある。

(2) 化学療法の効果が得られなければ，腫瘍縮小手術の機会を逸する，optimal surgeryの達成を逸する，などの可能性がある。

(3) 腫瘍量の多い状態で化学療法を行うため，薬剤耐性細胞の出現数が多くなり，また血流不十分な細胞の存在により，薬剤耐性の出現の可能性も高くなる。

(4) 腫瘍縮小手術に際して，肉眼的な腫瘍および範囲の縮小により，術式を縮小しすぎて根治性を損なってしまう可能性がある。

以上のように，NAC療法には標準療法に比べて，利点も問題点もあり，現時点ではNAC療法が標準治療に優るか否か結論は出ていない。

II. 卵巣癌に対するNAC療法の治療成績

NAC療法に関する報告のうち，標準治療との比較を行った報告につき紹介する。従来，全身状態や合併症などのため，侵襲の大きな初回手術が困難な症例，PDSが試験開腹に終わった症例，画像診断あるいは腹腔鏡診断により切除不能と判断される症例に対して，標準治療の代替の治療としてNAC療法が行われていた。表1に示すように，ほとんどの報告で，NAC療法は全身状態不良や初回手術不能の症例に行われたものである。現在までの報告のうち，Kuhnら[1]の報告以外は，いずれもretrospective studyである。

1. 腫瘍縮小手術におけるoptimal surgery達成率，治療成績の比較（表2）

Jacobら[2]は，PDSにて生検のみの試験開腹に終わり他院より紹介された患者に対するNAC療法と標準治療を比較した。生存期間中央値 (median survival time；MST) で有意差は認められなかったが，NAC群で77%，標準治療群で39%とNAC群で有意 ($p=0.02$) に高率にoptimal surgeryが達成できた。

Onnisら[3]，Kayikçioğluら[4]，Loizziら[5]，Inciuraら[6]，Everettら[7]，Leeら[8]，Houら[9]は，CTなどの画像診断や，全身状態によりNAC群を決定，標準治療を行った症例と比較した。NAC群では標準治療群と同程度あるいは有意に高率にoptimal surgeryが達成され，NAC群で標準治療群に劣らない生存率を得ることができた。

Kuhnら[1]は，多量の腹水貯留を認める進行卵巣癌症例を対象にNAC療法と標準治療のnon-randomizedの第II相比較試験を行った。NAC群で84%，標準療法群で63%と，NAC群で有意に ($p=0.04$) 高率にoptimal surgeryが達成でき，MSTにおいてNAC群42 M，標準治療群23 Mと有意な予後改善を認めた。

Vergoteら[10]は，PDSによる切除可能性を試験開腹または腹腔鏡により判断し，切除可能例には標準治療，不能例にはNAC療法の方針で治療を行った1989～1997年の治療成績を，NAC療法導入以前，全例に標準治療を行った1980～1988年の治療成績と比較した。3年生存率において，NAC療法導入後42%，導入以前26%，とNAC療法導入後有意に ($p=0.0001$) 予後が改善された。

2. 腫瘍縮小手術における手術侵襲の比較（表3）

Schwartzら[11]は，NAC療法群と標準治療の腫瘍縮小手術の侵襲につき比較した。NAC療法群で出血量，ICU滞在日数，入院日数などが標準治療群に比して有意に少なかった。

表1　NAC治療成績報告におけるNAC療法選択の規準

報告者（年）	NAC群の選択	NAC群の特徴
Jacob（1991）	NAC群，標準群とも他院で生検のみ施行。標準治療群は，進行期，組織型，分化度，年齢をmatchさせたcontrol。	
Onnis（1996）	胸水，肝転移の有無，試験開腹による切除可能性の評価によりNAC療法群を決定。	NAC療法群は，より進行した症例が多い。
Vergote（1998）	試験開腹，腹腔鏡による切除可能性の評価によりNAC療法例を決定。	NAC例は切除不能と診断された症例。
Schwartz（1999）	全身状態，合併症による手術可否の評価，CTによる切除可能性の評価によりNAC療法群を決定。	NAC療法群は，有意に高齢（$p<0.001$），PS不良（$p<0.001$）。
Kayikçioğlu（2001）	胸水，肝転移，切除不能な多発転移の有無，全身状態によりNAC療法群を決定。	NAC療法群は有意に高齢（$p=0.01$），PS不良（$p<0.001$）で，Ⅳ期症例が多い（$p=0.03$）。
Kuhn（2001）	対象は，多量の腹水（＞500 m*l*）を有する卵巣癌Ⅲc期に限定。臨床試験に同意が得られなかった症例に標準治療。	標準治療群とNAC療法群の背景に有意差なし。
Morice（2003）	試験開腹，腹腔鏡による切除可能性の評価によりNAC療法群を決定。	NAC群は切除不能と診断された症例。
Hegazy（2005）	試験開腹，腹腔鏡による切除可能性の評価によりNAC療法群を決定。	NAC群は有意に高齢（$p=0.04$）。
Loizzy（2005）	多量の胸水，腹水，全身状態，CTによる切除可能性の評価によりNAC療法群を決定。標準治療群は，組織型，進行期をmatchさせたcontrol。	NAC群は有意に高齢（$p=0.03$），有意にPS不良（$p=0.02$）。
Lee（2006）	CT，MRIにより切除可能性を評価し，NAC群を決定。	NAC群は切除不能と診断された症例。
Everett（2006）	肝転移，大きな上腹部転移，広範なリンパ節転移，重篤な合併症などによりNAC群を決定。	NAC群は有意にⅣ期（$p=0.042$），低分化（$p=0.025$）症例が多い。
Inciura（2006）	多量の腹水，大きな骨盤内or腹部腫瘍の存在により，NAC療法群を決定。	NAC群は切除困難と診断された症例。
Hou（2007）	重篤な合併症，および画像診断で腹部を越えた進展，広範な腹腔内進展，によりNAC群を決定。	NAC群で有意にⅣ期症例が多い（$p<0.05$），NAC群でより高齢，より低分化腫瘍であったが有意差はなし。

Kayikçioğluら[4]は，結腸切除，脾摘を要した割合は，標準治療群でそれぞれ16%，11%，NAC療法群で2%，0%と，他臓器合併切除割合が，NAC療法群で有意に（$p=0.01$，$p=0.02$）低率であったと報告している。

Vergoteら[10]の報告では，時代により手術手技や周術期管理の違いはあると考えられるが，NAC療法導入後，手術関連死亡率の減少を認めた。

Moriceら[12]，Hegazyら[13]，Leeら[8]，Houら[9]の報告においても同様にNAC群において，腸切割合，重篤な合併症割合の減少，手術時間の短縮，出血量，輸血量の減少，ICU滞在日数，入院日数の短縮を認めた。

3. メタアナライシスによるNAC療法の治療成績の解析

Bristowら[14]は，卵巣癌Ⅲ/Ⅳ期に対する，22編，835症例のNAC療法の成績をmeta-analysisにより解析を行った。MSTは24.5 M，optimal surgery達成率は65%で，optimal症例

表2　NAC 療法と，標準治療の比較（腫瘍縮小手術における optimal surgery と治療成績）

報告者（年） 治療法［症例数］	生存期間の比較		生存割合の比較		腫瘍縮小手術
Jacob（1991）	MST				optimal（<2 cm）
標準治療［n＝18］	18 M				39%（7/18）
NAC 療法［n＝22］	16 M				77%（17/22）
	NS				p＝0.02
Onnis（1996）			3 year	5 year	optimal（<2 cm）
標準治療［n＝284］			31%	21%	29%（83/284）
NAC 療法［n＝88］			27%	19%	42%（37/88）
			NS	NS	NA
Vergote（1998）			3 year		
NAC 導入前［n＝112］			26%		
NAC 導入後［n＝173］			42%		
			p＝0.0001		
Kayikçioğlu（2001）	MST			5 year	optimal（＝0）
標準治療［n＝158］	38 M			24%	14%（22/158）
NAC 療法［n＝45］	34 M			30%	49%（22/45）
	NS			NS	p<0.001
Kuhn（2001）	MST				optimal（<2 cm）
標準治療［n＝32］	23 M				63%（20/32）
NAC 療法［n＝31］	42 M				84%（26/31）
	p＝0.007				p＝0.04
Loizzy（2005）	MST	DFI			optimal（<1 cm）
標準治療［n＝30］	40 M	16 M			60%（18/30）
NAC 療法［n＝30］	32 M	21 M			63%（19/30）
	NS	NS			NS
Lee（2006）	MST	DFI			optimal（<2 cm）
標準治療［n＝22］	55 M	17 M			46%（10/22）
NAC 療法［n＝18］	53 M	15 M			78%（14/18）
	NS	NS			p＝0.04
Everett（2006）	MST				optimal（<1 cm）
標準治療［n＝102］	42 M				54%（55/102）
NAC 療法［n＝98］	33 M				86%（84/98）
	NS				p<0.001
Inciura（2006）	MST	DFI			optimal（<2 cm）
標準治療［n＝361］	25 M	15 M			67%（242/361）
NAC 療法［n＝213］	24 M	13 M			63%（134/213）
	NS	NS			NS
Hou（2007）	MST	DFI			optimal（<1 cm）
標準治療［n＝109］	47 M	14 M			71（77/109）
NAC 療法［n＝63］	46 M	16 M			95（60/63）
	NS	NS			<0.001

NA：not available，MST：median survival time，DFI：disease free interval

表3　NAC 療法と，標準治療の比較（手術合併症などの比較）

報告者（年） 治療法［症例数］	手術合併症などの比較						
Vergote（1998）				手術関連死亡率			
NAC 導入前［n＝112］				6%			
NAC 導入後［n＝173］				0%			
				NA			
Schwartz（1999）	出血量					ICU 滞在	入院期間
標準治療［n＝206］	1,000 m*l*					1.26 days	11 days
NAC 療法［n＝59］	600 m*l*					1.03 days	7 days
	p＝0.001					p＝0.01	p＜0.001
Kayikçioğglu（2001）			結腸切除	脾摘			
標準治療［n＝158］			16%	11%			
NAC 療法［n＝45］			2%	0%			
			p＝0.01	p＝0.02			
Morice（2003）		輸血割合	腸切	脾摘	重篤な合併症		
標準治療［n＝28］		39%	61%	7%	36%		
NAC 療法［n＝57］		21%	19%	5%	7%		
		NS	p＝0.01	NS	p＝0.01		
Hegazy（2005）	出血量					ICU 滞在	入院期間
標準治療［n＝32］	735 m*l*					4.4 days	15.9 days
NAC 療法［n＝27］	420 m*l*					1.7 days	10.5 days
	p＝0.02					p＝0.03	p＜0.05
Lee（2006）	出血量						
標準治療［n＝22］	1,061 m*l*						
NAC 療法［n＝18］	620 m*l*						
	p＝0.04						
Hou（2007）	出血量	輸血量			手術時間		入院期間
標準治療［n＝109］	1,033 m*l*	2.4 U			276 min		8.5 days
NAC 療法［n＝63］	546 m*l*	1.2 U			211 min		5.7 days
	p＜0.0001	p＝0.03			p＜0.0001		p＜0.0001

NA：Not available

の割合が10%増えるごとに，1.9 M の予後の改善が認められた。また，NAC のコース数が1コース増えるごとに，4.1 M の生存期間の短縮が認められた。GOG（Gynecologic Oncology Group）による臨床試験で，PDS で suboptimal となった症例の MST は 24 M であることと比較して，NAC 療法の治療成績（MST 24.5 M）は，せいぜい，これら suboptimal 症例と同等であるとしている。

しかしながら，解析に含まれる報告の多くは，前述のように全身状態不良や初回手術不能の症例など，もともと optimal surgery が期待できない症例に対する治療成績であり，NAC 療法により，少なくとも治療成績が損なわれることはないことを示しているとも解釈できる。

III. 卵巣癌に対する NAC 療法の臨床試験

現在進行中あるいはあるいは解析中の NAC 療法に関する prospective な試験を解説する。

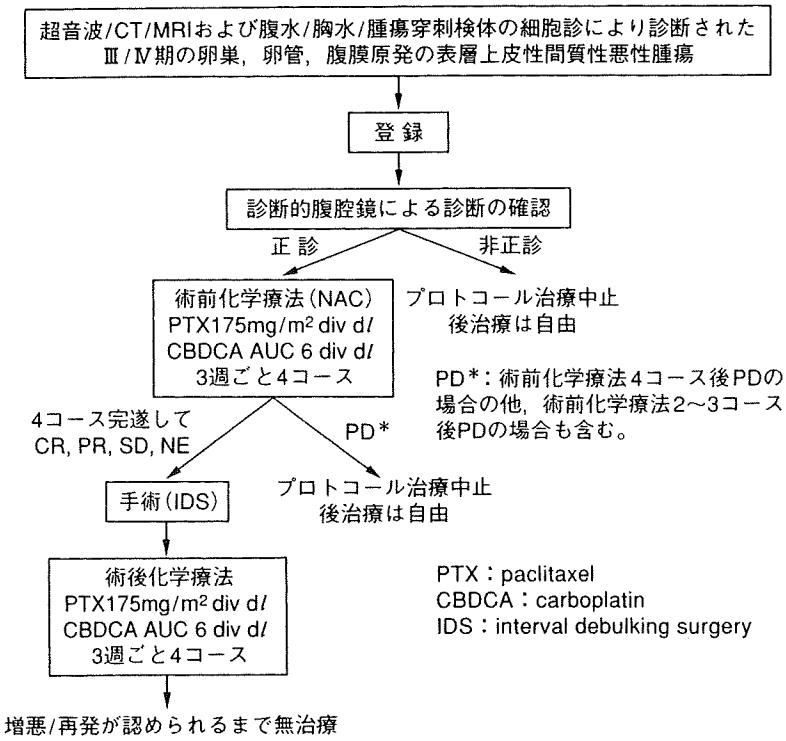

図1　JCOG0206シェーマ

1. EORTC（European Organization for Research and Treatment of Cancer）による無作為比較試験

EORTCのVergoteらは，retrospective studyの結果を踏まえて，第Ⅲ相無作為比較試験としてEORTC 55971[15]を行った。卵巣癌，卵管癌，腹膜癌のⅢc/Ⅳ期を対象に，診断的腹腔鏡，試験開腹，穿刺組織診のいずれかの方法で原発診断，組織診断，進行期診断を確認した後，NAC療法群と手術先行の標準治療群に割り付けした。卵管癌，腹膜癌は，組織学的所見，化学療法感受性，予後が卵巣癌とほぼ同一であり，卵巣，卵管の摘出なしでは鑑別診断困難であることから対象に含めている。プロトコール治療は，NAC療法群では，3コースの化学療法の後，IDSを行い，術後3コースの化学療法追加，標準治療群ではPDSを行い，optimal症例では，6コースの化学療法，suboptimal症例では，3コースの化学療法の後，IDSおよび3コースの化学療法追加である。化学療法としては，プラチナ製剤（cisplatin：CDDP，CBDCA）＋タキサン系薬剤（PTX，docetaxel：DTX）のいずれの組み合わせでも可としている。この試験は，NAC療法が標準治療に対して，効果の点で劣らないことを検証する非劣性試験である。704例の登録を予定して開始され，2006年12月で登録終了となり現在データ集積中である。

2. JCOG（Japan Clinical Oncology Group）の臨床試験

1）NAC療法のFeasibility study

JCOGの婦人科腫瘍グループでも，初回手術可能な症例も含めたⅢ/Ⅳ期卵巣癌に対してNAC療法と標準治療の第Ⅲ相比較試験を計画した。しかしながら，計画のあった2002年当時，初回手術可能な症例に対するNAC療法の経験が十分ではないと考えられたため，第Ⅲ相比較試験に先立って，2003年1月から「Ⅲ/Ⅳ期卵巣癌，卵管癌，腹膜癌に対する術前化学療法のfeasibility study」（JCOG0206）[16]を行った。試験の目的は，NAC療法の有効性と安全性を確認することに加えて，診断確認のための手術（開腹あるいは腹腔鏡など）を行わなくても，