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A Randomized Phase II/III Trial of 3 Weekly Intraperitoneal versus Intravenous Carboplatin in Combination with Intravenous Weekly Dose-dense Paclitaxel for Newly Diagnosed Ovarian, Fallopian Tube and Primary Peritoneal Cancer

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Retrospective studies and a Phase II trial demonstrated the promising efficacy and safety of intraperitoneal administration of carboplatin in ovarian, fallopian tube and primary peritoneal cancer. A Japanese Gynecologic Oncology Group 3016 randomized Phase III trial for these cancers showed dose-dense weekly administration of paclitaxel significant improvement of progression-free survival and overall survival over every 3-week administration. From June 2010, we have been conducting a randomized Phase II/III trial of intravenous versus intraperitoneal administration of carboplatin every 3 week in combination with dose-dense weekly administration of paclitaxel. The purpose of this trial is to prove the superiority of intraperitoneal administration of carboplatin over intravenous administration. Primary endpoint is progression-free survival and secondary endpoints include overall survival, quality of life assessment and cost–benefit. The first 120 patients will be evaluated for the feasibility of intraperitoneal arm and a total of 746 patients will be enrolled in a Phase III study.

Key words: ovarian cancer – intraperitoneal chemotherapy – carboplatin – paclitaxel – dose-dense chemotherapy

INTRODUCTION

In Japan, it is estimated that incidence of epithelial ovarian cancer is approximately 8000 per year and almost half of the patients died of this disease. There is no established screening method; therefore, 60–70% of the patients are at Stages III or IV when newly diagnosed. A standard treatment strategy for the advanced ovarian cancer is a maximum debulking surgery followed by chemotherapy. The standard chemotherapy regimen has been a combination of carboplatin at AUC of 5–6 and paclitaxel at 175 mg/m^2 given intravenously every 3 weeks (1). This regimen has been utilized as standard since 1999, yet the prognosis of advanced ovarian cancer is poor. Numerous efforts have been made to improve the survival, and two distinct innovations on the chemotherapy were achieved recently, which are intraperitoneal chemotherapy and weekly dose-dense administration of paclitaxel.

Three large randomized trials have been conducted in the USA and all of them showed improvement of overall survival (OS) and/or progression-free survival (PFS) (2–4). US National Cancer Institute and Gynecology Oncology Group (GOG) conducted a metanalysis and found that

intraperitoneal (IP) chemotherapy improved OS at the hazard ratio of 0.78 (5). In response to this result, US NCI has issued a clinical announcement in 2006 to recommend IP cisplatin-based chemotherapy for optimally debulked Stage III ovarian cancer patients. In spite of these efforts, IP chemotherapy has not been accepted in the gynecologic cancer community, mainly because of the toxicity. It is expected that replacement of cisplatin to carboplatin may reduce the toxicity without sacrificing the efficacy (6).

Another innovation was the application of dose-dense weekly paclitaxel. Japanese Gynecologic Oncology Group (JGOG) has conducted a large-scale randomized trial and demonstrated significant improvement in PFS and OS (7).

Therefore, it is of great expectation that the combination of dose-dense weekly administration of paclitaxel with IP administration of carboplatin will improve the prognosis further.

This protocol was designed by the Protocol Committee of Gynecologic Oncology Trial and Investigation Consortium (GOTIC) and Ovarian Committee member of JGOG. The protocol was approved by Clinical Trial Review Committee of GOTIC as GOTIC-001 on 9 September 2009, and that of JGOG as JGOG-3019 on 26 April 2010. The protocol was submitted for the Evaluation System of Investigational Medical Care of Ministry of Health, Labor and Welfare, Japan, and was approved to conduct under the Japanese governmental health insurance system on 16 April 2010. This trial was registered at the UMIN Clinical Trials Registry as UMIN000003670 (http://www.umin.ac.jp/ctr/index.htm).

PROTOCOL DIGEST OF GOTIC-001/JGOG-3019

Purpose

This study was designed to prove superiority of IP administration of carboplatin over IV administration in newly diagnosed carcinoma of the ovary, fallopian tube and primary peritoneum. The combination of paclitaxel is the dose-dense weekly fashion based on the JGOG-3016 trial result.

Study Setting

This is a multi-institutional randomized Phase II/III trial.

Resource

Grants-in Aid for Cancer Research (H21–014), from the Ministry of Health, Labor and Welfare, Japan. Gynecologic Oncology Trial and Investigation Consortium and JGOG support this trial.

Endpoints

The primary endpoint of this study is PFS. Secondary endpoints are OS, response rate in patients with measurable disease, quality of life assessment and cost–benefit.

Eligibility Criteria

(i) The patient must be planned to undergo laparotomy surgery for formal registration. Since this trial includes patents with both optimal and suboptimal residual disease, the patients with exploratory laparotomy are also eligible.
(ii) Patient who is preoperatively anticipated to be FIGO II to IV epithelial ovarian, fallopian tube or primary peritoneal cancer is eligible for pre-registration. And the patient must be clinically at Stages II–IV at the time of formal registration.
(iii) Patient who signed the consent for the placement of IP port system when she is assigned to the IP arm.
(iv) The patients who are planned to receive chemotherapy within 8 weeks after initial surgery.
(v) ECOG performance status must be 0–2.
(vi) Patient must have adequate organ functions.
(vii) Survival can be expected 3 month or more.
(viii) Age 20 or older.

Written informed consent must be obtained from the patient or legal guardian.

Exclusion Criteria

(i) Patients with borderline malignancies.
(ii) Patients who have received chemotherapy or radiation therapy for the current disease before enrolment.
(iii) Patients with any of the active concurrent malignancies or past history of malignancies of which the follow-up is within 5 years.
(iv) Patients with severe complications: patients with severe heart disease or cerebrovascular disease, or uncontrolled diabetes or hypertension, pulmonary fibrosis, interstitial pneumonitis, active bleeding, active gastrointestinal ulcer or sever neuropathy.
(v) Patients with history of hypersensitivity polyoxyethylene castor oil.
(vi) Patients with pleural effusion that need continuous drainage.
(vii) Patients with active infectious disease.
(viii) Patients with possibility of pregnancy or under breast-feeding.
(ix) Patients with symptomatic brain metastasis.
(x) Patients whose circumstances at the time of entry onto the study would not permit completion of study or required follow-up.

Study Flow

The patient who is anticipated to have Stage II, III or IV carcinoma of the ovary, fallopian tube or primary peritoneum will be pre-registered through Web Registration System of Kitasato University Clinical Trial Coordinating Center (CTCC), after written informed consent was obtained. At the time of surgery, the physician will call to the Kitasato CTCC

before closure of the abdominal wall. The coordinator will ask the stratification factors, clinical stages and the size of residual disease, then randomization result will be informed. This is considered as a formal registration. When the patient is randomized to IP arm, the Bard IP Port (#14 Fr) will be placed according to the surgical manual. For patient who randomized to the IV arm, IP port will not be placed. The protocol chemotherapy will be started within 8 weeks after confirmation of histology as epithelial cancer.

Control Arm Treatment

For patients randomized to IV arm will receive paclitaxel at 80 mg/m^2 as 1 h intravenous (IV) infusion followed by carboplatin at AUC 6 as a 30–120 min IV infusion on Day 1. IV administration of paclitaxel will be repeated at 80 mg/m^2 on days 8 and 15. This regimen is considered as one cycle.

Experimental Arm Treatment

For patients randomized to IP arm will receive paclitaxel at 80 mg/m^2 as 1 h IV infusion. During the paclitaxel infusion, 1000–1500 ml physiological saline or 5% glucose will be administered through IP port. This will allow the confirmation that IP port is not obstructed and dense adhesion does not occur surrounding the catheter. After completion of the hydroperitoneum, carboplatin at AUC 6 will be infused. To confirm that the hypersensitivity of carboplatin does not occur, 10 ml will be administered and after waiting for 10 min, the rest of the amount will be infused. These procedures will be done on day 1. IV administration of paclitaxel will be repeated at 80 mg/m^2 on days 8 and 15. This regimen is considered as one cycle.

Number of Cycles

The protocol treatment will be repeated for six cycles for patients with chemotherapy only after primary surgery. However, in patient, who will undergo interval debulking surgery after response to the suboptimal residual disease, they may receive up to eight cycles. Interval debulking surgery can be performed after three to five cycles of protocol chemotherapy, and then patient can receive three more cycles of chemotherapy.

Study Design and Statistical Considerations

This study was designed as a randomized Phase II/III trial.

Target sample sizes and event were as follows.

Phase A: 60 patients/arm
Phase B: 510 events (target sample size: 746 patients, including Phase A patients)

Planned patient accrual duration is 3 year and planned follow-up duration will be either 3 year or until the time when the 510 events are observed, whichever it comes first.

Sample sizes were determined based on the following considerations.

Phase II Part (Phase A)

In the previous JGOG-3016 study, treatment completion rate for dose-dense pacliaxel plus carboplatin (dd-TC) was 47.0%, and hematologic adverse event (more than or equal to grade 3) rate for dd-TC was the following, neutropenia: 91.7%, leukocytes: 80.4%, hemoglobin: 68.6%, platelets: 43.6%. Furthermore, the response rate for dd-TC was 55.8%. According to above evidence, we performed statistical simulations for these factors to find a sample size which would be necessary to obtain 95% confidence intervals of these estimates with 15% precisions in the IV arm, and we calculated that 46 patients is needed. We also assumed that treatment completion rate in the IP arm is expected to be lower than the IV arm and hematologic adverse event rates defined above are expected to be higher, thereby the required sample size in the IP arm would be larger than those of the IV arm. Furthermore, we also assumed that some patients would not have a measurable site. Thus, we plan the sample size of 120 patients (60 patients for each arm) to be targeted. Phase II patients will be included in the Phase III analysis.

Phase III Part (Phase A + Phase B)

The primary endpoint of this study is PFS. In the previous JGOG3016 study, the median PFS was approximately 28 months for dd-TC. Furthermore, in a meta-analysis conducted by the National Cancer Institute (NCI) and the Gynecologic Oncology Group, the hazard ratio for PFS in the IP as compared with the IV was 0.784, indicating the 21.6% hazard reduction in the IP treatment).

According to above evidence, we assumed that the median PFS was 28 months for the IV arm and the hazard ratio for PFS in the IP arm as compared with the IV arm was 0.78. The 22% hazard reduction would be acceptable as a new standard treatment regimen. With an accrual period of 3 years and a minimum follow-up period of 3 years, 746 patients (373 patients for each arm) and 510 events (239 in IP arm) are required in order to detect this hazard ratio using the log-rank test with an overall two-sided type I error of 0.05 and a power of 80%. The final analysis will be performed either after the required events will be observed or after the minimum follow-up period will be completed, whichever comes first. If the required events will not be observed after the minimum follow-up period will be completed, extension of the follow-up duration will be considered.

Randomization and Stratifications

Patients will be centrally randomized. A minimization technique will be used for random treatment allocation stratifying by the enrolling institutions, initial FIGO stage of disease (II, III or IV) and the size of residual disease (complete, less than 1 cm, between 1 and 2 cm and more than 2 cm).

Analysis Method

Phase III part: analysis set. Efficacy analyses will be performed on all randomly assigned patients based on the intent-to-treat principle. Patients receiving at least one partial infusion of the study drug will be qualified for safety analysis.

Primary efficacy analysis. The PFS curves will be estimated using Kaplan–Meier method. Non-parametric 95% confidence intervals will be calculated for the median PFS, and the curves will be compared in the two treatment groups based on the two-sided log-rank test with an overall significance level of 5%. Multiplicity adjustments in regard to interim analysis will be noted in the section of the interim analysis.

Secondary efficacy analysis. The OS curves will be also estimated using Kaplan–Meier technique and compared using log-rank test. The response rates in the case with measurable site, and the treatment completion rates will be estimated by arms. We define the treatment completion case as the patient who receives treatment to the sixth cycle. Exact 95% confidence intervals will be calculated for each response rate and treatment completion rate. The rates for the two treatment groups will be compared using Fisher's exact test and a normally approximated 95% confidence interval for the odds ratio.

Interim analysis. Under the proportional hazard assumption, alternative hypothesis and uniformly patients' enrollment, the half of the required events (255 events) would be observed when approximately 3.2 years go by from a starting point of this trial. One interim analysis will be carried out either when 3.5 years go by from a starting point of this trial or when the required events will be observed, whichever comes first. In order to maintain an overall significance level of 5%, the PFS curves would be compared with Type I error of 0.3% in the interim analysis and of 4.7% in the final analysis calculated by the O'Brien and Fleming-type alpha spending function.

Subgroup analysis. In order to support analyses of primary and secondary endpoints, all comparisons and estimates will be stratified by randomization factors and other demographic data.

Exploratory analysis. Statistical models (e.g. Cox's proportional hazard model and logistic regression model) will be used for further explorations.

Safety analysis. The number of patients for each adverse event will be summarized for each treatment group. The rates of adverse events will be estimated for each group and compared using an approximate 95% confidence interval for the odds ratio.

Quality of life and Cost-effectiveness analyses. Quality of life (QOL) and cost-effectiveness (CE) of IP arm and IV arm will be analyzed when 2 years go by from a starting point of this trial, assuming that 300 qualified patients would be observed at that time. CE data are also analyzed at the same time of QOL analysis. These endpoints will also be analyzed after the study completion (or study termination) with efficacy endpoints. Baseline QOL score will be analyzed using linear model adjusting for age and baseline ECOG performance status (PS). Other QOL scores will be analyzed using linear mixed model with age, PS and baseline QOL scores. Further details of QOL and CE analysis will be specified in the statistical analysis plan.

Analysis results of QOL evaluation will be published after 2 years go by from a starting point of this trial, assuming that 300 qualified patients would be observed at that time. For CE analysis, we define the analysis set of all patients who will be registered and agreed with informed consents of CE analysis. Analysis and report of cost-effectiveness with primary endpoints will be reviewed.

Feasibility Analysis. In the Phase II period, the feasibility of combination of IV dose-dense paclitaxel and IP carboplatin will be evaluated. The number of patients for treatment completion, hematologic and non-hematologic toxic effects will be summarized for each treatment group. The rates of toxic effects will be estimated for each group. Furthermore, the rates at the end of the treatment will be estimated for each treatment group. Exact 95% confidence intervals will be calculated for each rate. These rates for the two treatment groups will be compared using Fisher's exact test and an approximate 95% confidence interval for the odds ratio to aid the IDMC in reaching decisions about study continuation.

Study Monitoring

Study monitoring will be performed by the Kitasato University Clinical Trial Coordinating Center, to ensure data submission, patient eligibility, protocol compliance, safety and on-schedule study progress. On-site monitoring on the selective institution will be performed once a year. The monitoring reports will be submitted to the Independent Data and Safety Monitoring Committee every 6 months.

Participating Institutions

Leading institution as the study under the Evaluation System of Investigational Medical Care (ESIMeC) is Saitama Medical University International Medical Center. Other institutions waiting for the governmental approval for the ESIMeC as of 15 July 2010 are as follows. Iwate University, Jichi Medical University, Keio University, National Cancer Center Hospital, Tottori University, Tsukuba University, Gunma University and Saitama Medical University Medical Center. Other institutions are under the process of ESIMeC submission.

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Conflict of interest statement

None declared.

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シンポジウム　卵巣がん予後向上へのチャレンジ

5. 進行卵巣癌に対する術前化学療法

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1. はじめに

進行卵巣癌の予後向上を目指した治療法の一つとして，術前化学療法（neoadjuvant chemotherapy：NAC)が注目されている．多くの retrospective study や non-randomized な prospective study での標準治療との比較では，NAC 療法により，良好な成績が得られている．日本臨床腫瘍研究グループ（Japan Clinical Oncology Group：JCOG）では，第 II 相 feasibility 試験により安全性，有効性を確認した後，現在第 III 相比較試験を行っている．世界的には他にも 3 試験が進行中であり，途中経過が国際学会で発表され，進行卵巣癌に対する NAC 療法の役割が明らかとなりつつある．進行卵巣癌に対する標準治療，NAC 療法および治療成績について解説し，今後の検討課題についても解説する．

2. 進行卵巣癌に対する標準治療

進行卵巣癌に対する標準治療では，まず初めに原発臓器，組織型の診断，進行期の診断と転移巣切除を兼ねた primary debulking surgery（PDS）と呼ばれる手術を行い，残存腫瘍が 1～2 cm 未満の optimal surgery が達成出来れば，化学療法を 6～8 コース行う．残存腫瘍 1～2cm 以上の suboptimal surgery の場合，化学療法の約半分が終わった中間期に interval debulking surgery（IDS）と呼ばれる手術を試みる場合もある．

進行卵巣癌に対する予後因子として，初回手術後の最大残存腫瘍径が重要であることが知られており，初回手術で optimal surgery が達成できた場合，suboptimal に終わった症例に比べて良好な予後が得られることが，多くの報告により示されている．このことが，卵巣癌治療において，optimal surgery を目指して初回に広汎で侵襲的な手術を行う根拠となっている．

現在の標準治療の問題点として，全身状態不良のため PDS を行うことが困難な症例が見られること，PDS において重篤な合併症が高率に見られること，optimal surgery が達成できるのは一部の症例に限られること，手術枠確保や他科との連携のため治療開始に時間を要すること，PDS で suboptimal の場合，再度腫瘍縮小手術（IDS）が必要となる可能性があること，などが挙げられる．

3. 進行卵巣癌に対する NAC 療法

一方，NAC 療法では，対象疾患の診断を確認，NAC を 2～6 コース行った後，IDS を施行，更に術後化学療法を 2～6 コース追加で行う．化学療法は最近では術前，術後とも 3～4 コースの場合が多い．従来，NAC 療法は，PDS で optimal とならなかった場合，全身状態不良で手術困難な場合，画像診断や腹腔鏡診断で，optimal 不能と診断された場合，などに標準治療が困難なための代替治療として行われてきた．

NAC 療法の利点としては，全身状態を改善し，より安全な状態で腫瘍縮小手術（IDS）を行いうること，合併切除の頻度が減少し，手術侵襲の軽減が期待できること，術式を拡大しなくても optimal surgery の可能性が高くなること，速やかな

表1 NAC療法と標準治療の比較（治療成績）

報告者（年） 治療法［症例数］	生存率の比較		腫瘍縮小手術	NAC群の選択
Jacob（1991）	MST		optimal（< 2cm）	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．
標準治療［n = 18］	18M		39%（7/18）	
NAC療法［n = 22］	16M		77%（17/22）	
	NS		p = 0.02	
Onnis（1996）	3 year	5 year	optimal（< 2cm）	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．
標準治療［n = 284］	31%	0.21	29%（83/284）	
NAC療法［n = 88］	27%	0.19	42%（37/88）	
	NS	NS	NA	
Schwartz（1999）	MST	5 year		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（< 0.001），PS不良（< 0.001）であった．
標準治療［n = 206］	2.18Y	20%	NA	
NAC療法［n = 59］	1.07Y	15%	NA	
	NS	NS		
Kayikçioğlu（2001）	5 year	MST	optimal（= 0）	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）．
標準治療［n = 158］	24%	38M	14%（22/158）	
NAC療法［n = 45］	30%	34M	49%（22/45）	
	NS	NS	p < 0.001	
Kuhn（2001）	MST		optimal（< 2cm）	対象は，多量の腹水（> 500ml）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．
標準治療［n = 32］	23M		63%（20/32）	
NAC療法［n = 31］	42M		84%（26/31）	
	p = 0.007		p = 0.04	

治療開始が可能であること，腫瘍摘出のための手術は1回のみですむこと，などが挙げられる．

ただし，NAC療法にも問題点はあり，化学療法の効果が得られなければ，手術の機会を逸してしまうこと，薬剤耐性出現の可能性が高まること，術式を縮小しすぎて根治性を損なう可能性があること，対象疾患の診断が不正確となる可能性があること，などである．

4. NAC療法と標準治療の比較

これまでにNAC療法と標準治療の比較成績は約20本程報告されている．大部分はretrospectiveであるが，non-randomizedのprospective studyも3〜4本報告されている．表1に治療成績を比較した報告の一部をまとめた[1)〜5)]．Jacob[1)]らは，生存率の改善は得られなかったものの，NAC群では高率にoptimalが達成できた，Onnisら[2)]，Schwartzら[3)]は，NAC群は条件が悪い対象でありながら，同等の治療成績が得られた，Kayikçioğluら[4)]は，NAC群は条件が悪い対象でありながら，高率にoptimalが達成できた，Kuhnら[5)]は，NAC群では，高率にoptimalが達成できて，予後の改善も見られた，と報告している．予後の改善が見られたとしているのは，Kuhnらの報告のみであり，全体としては，NAC群では，条件が悪い症例でも，同等の治療成績が得られるという結果である．表2に手術侵襲についてまとめた[3)4)6)〜8)]．多くの報告で，出血量の有意な減少，腸切，脾摘などの合併切除の有意な減少，重篤な合併症の有意な減少，ICU滞在期間や入院期間の有意な短縮が示されている．

5. JCOGの第II相，第III相臨床試験（JCOG 0206, JCOG0602）

良好な治療成績から，NAC療法は有用性が期待され，日本臨床腫瘍研究グループJCOGではNAC療法と標準治療との第III相比較試験を計画，まずその前段階として第II相feasibility試験を行った[9)10)]．対象は，CT/MRIなどの画像診断，穿刺細胞診により診断された卵巣癌，卵管癌，腹膜癌III/IV期症例で，登録された症例には，全例で腹腔鏡により診断を確認して，NAC療法を行っ

表2 NAC療法と標準治療の比較（手術侵襲）

報告者（年） 治療法［症例数］	手術侵襲の比較			NAC群の選択
Schwartz（1999）	出血量	ICU滞在	入院期間	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（< 0.001），PS不良（< 0.001）であった．
標準治療［n = 206］	1,000ml	1.26days	11days	
NAC療法［n = 59］	600ml	1.03days	7days	
	p = 0.001	p = 0.01	p < 0.001	
Kayikçioğlu（2001）	結腸切除	脾摘	虫垂浸潤	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）．
標準治療［n = 158］	16%	0.11	80%	
NAC療法［n = 45］	2%	0	22%	
	p = 0.01	p = 0.02	< 0.001	
Morice（2003）	腸切	脾摘	重篤な合併症	開腹あるいは腹腔鏡手術時に，通常の手技ではoptimal手術不可能と判断された，より進行した症例にNAC．
標準治療［n = 28］	0.61	7%	0.36	
NAC療法［n = 57］	0.19	5%	0.07	
	p = 0.01	NS	p = 0.01	
Hegazy（2005）	出血量	ICU滞在	入院期間	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）．
標準治療［n = 32］	735ml	4.4days	15.9days	
NAC療法［n = 27］	420ml	1.7days	10.5days	
	p = 0.02	p = 0.03	p < 0.05	
Lee（2006）	出血量	腸切	臓器切除	CT，MRIにより切除可能性を評価し，NAC群を決定．NACに同意しなかった人が，標準治療．背景因子に差はない．
標準治療［n = 22］	1,061ml	3例	2例	
NAC療法［n = 18］	620ml	1例	0例	
	p = 0.04	NA	NA	

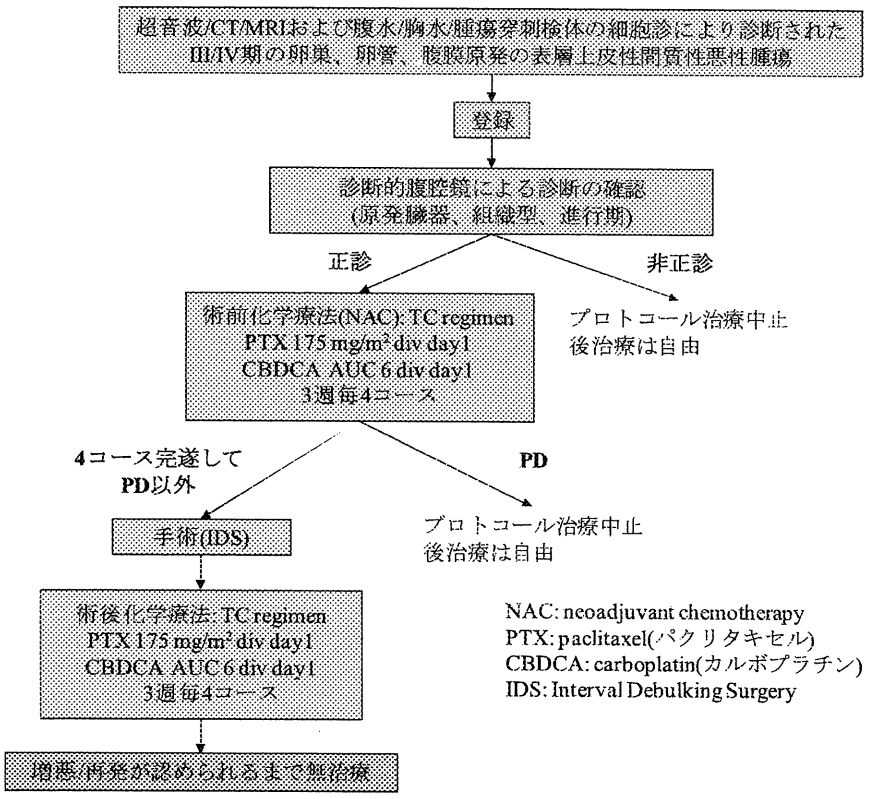

図1 JCOG0206試験シェーマ

た(図1参照)．適格規準としては，他疾患の混入を減らすための条件として，腫瘍マーカーの規準(CA125>200U/ml，CEA<20ng/ml)も設けられた．試験は，56例を目標に，2003年1月14日から約1年の予定で行われ，JCOG参加施設のべ27施設が参加，ほぼ予定通り登録を終了した．

Secondary endpointである，臨床診断による卵巣癌，卵管癌，腹膜癌III/IV期の診断の正診割合の検討では，56例中53例(95%)で正診であったことが腹腔鏡診断により確認され，臨床診断によりNACの対象疾患を十分に診断可能と判断された．また，primary endpointである有効性の検討では，NACが行われた53例の内，47例(89%)にIDSを施行，38例（72%）は残存1cm未満，29例（55%）は完全切除となった．最終的に22例(42%)で「画像診断にて病変を認めず，胸水を認めず，CA125<20U/ml」と，この試験において定義した完全腫瘍消失に至り，NAC療法は有効な治療と結論された．なお，NAC施行全53例の無増悪生存期間中央値は14M，3年無増悪生存割合は19%，生存期間中央値は45M，3年生存割合は60%であった（図2)．

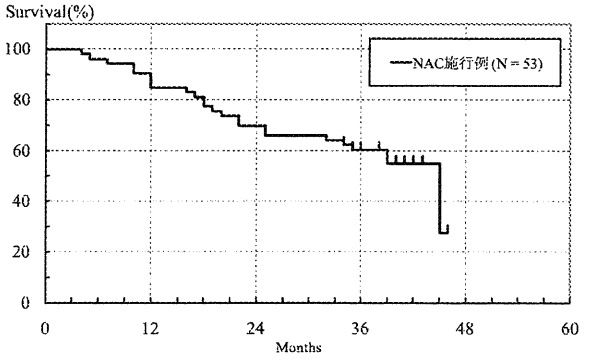

図2　JCOG0206登録症例のうちNAC施行例の生存期間

この試験では，NAC療法による特記すべき重篤な有害事象はなく，安全な治療法であることも示された．

JCOG0206の結果を受けて，JCOGでは同様の適格規準を満たす症例を対象に第III相比較試験を開始した[11]．腹腔鏡は行わず，臨床診断にて登

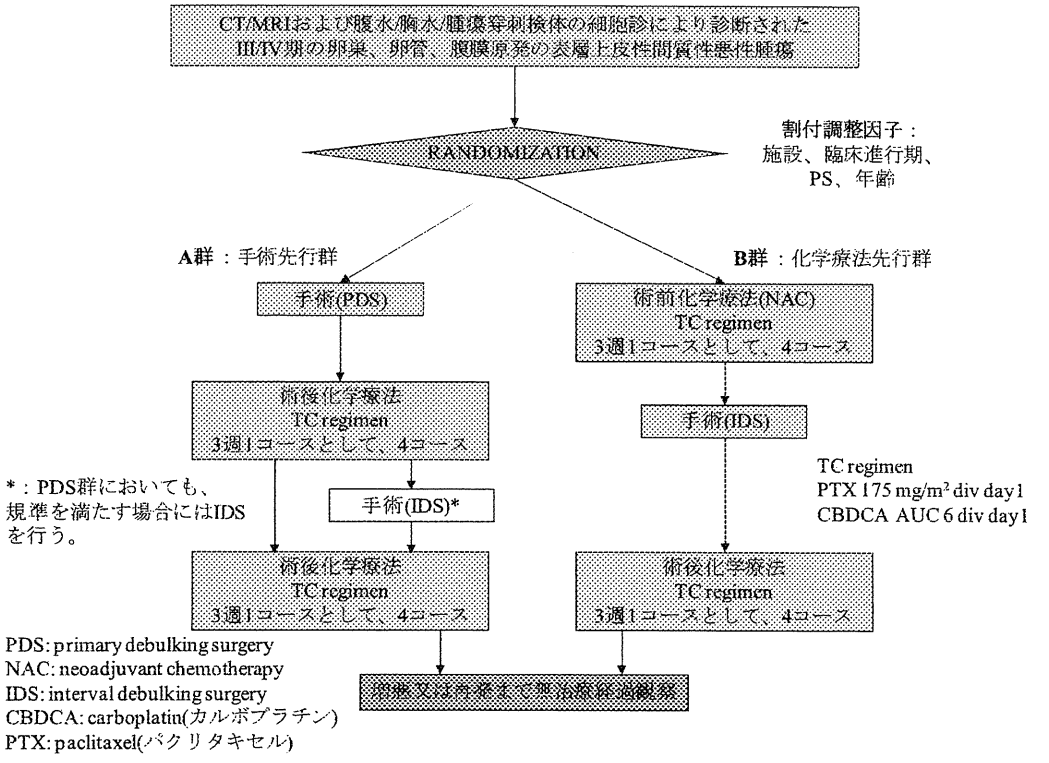

図3　JCOG0602試験シェーマ

表3 JCOG 試験参加施設

JCOG0206, JCOG0602 とも参加	北海道大学	新潟県立がんセンター新潟病院
	札幌医科大学	信州大学
	東北大学	愛知県がんセンター中央病院
	筑波大学	近畿大学
	群馬県立がんセンター（現在 inactive）	大阪府立成人病センター
	防衛医科大学校	呉医療センター・中国がんセンター
	埼玉県立がんセンター	四国がんセンター
	東京慈恵会医科大学附属柏病院	九州がんセンター
	国立がん研究センター中央病院	久留米大学
	東京慈恵会医科大学附属病院	九州大学
	東京大学	佐賀大学
	順天堂大学	鹿児島市立病院
	北里大学	
JCOG0206 のみ参加	長岡赤十字病院	名古屋医療センター
JCOG0602 から参加	岩手医科大学	大阪市立総合医療センター
	埼玉医科大学総合医療センター	近畿大学医学部堺病院
	がん・感染症センター都立駒込病院	兵庫県立がんセンター
	癌研究会有明病院	鳥取大学
	京都大学	琉球大学
	大阪市立大学	熊本大学（IRB 未承認）

試験途中での新規参加施設以外は，IRB 承認をもって，試験参加とする．

表4 進行中，解析中の第 III 相試験

試験グループ	EORTC	RCOG/CTU-MRC	All India Institute of Medical Sciences	JCOG
試験名	EORTC55971	CHORUS	ID I473	JCOG0602
中心国	Belgium	United Kingdom	India	Japan
研究代表者	Vergote, I. B.	Kehoe, S.	Kumar, L.	Yoshikawa, H.
対象疾患	卵巣癌/卵管癌/腹膜癌	卵巣癌/卵管癌/腹膜癌	卵巣癌	卵巣癌/卵管癌/腹膜癌
進行期	IIIC/IV 期	III/IV 期	IIIC/胸水 IV 期	III/IV 期
試験のタイプ	第 III 相	第 II/III 相	第 III 相	第 III 相
悪性の確認方法	（登録前）腹腔鏡生検あるいは針生検	画像診断/腫瘍マーカー（登録後）腹腔鏡生検，針生検，穿刺細胞診	（登録前）細胞診，組織診	（登録前）穿刺細胞診
化学療法種類	Platinum + Taxane	CBDCA を含む regimen	TC regimen	TC regimen
NAC 群の化療回数	NAC3 + 3 コース	NAC3 + 3 コース	NAC3 + 3 コース	NAC4 + 4 コース
症例数	704	150（第 II 相）+ 400（第 III 相）	180	300
開始	1998.9.21	2004.3（第 III 相）	2001.11	2006.11.17
予定登録期間	4 年間	4 年間（第 III 相）	約 5 年間	3 年間
登録状況	2006.12.6 登録完了	登録中	登録中	登録中
試験デザイン	非劣性	（EORTC と合わせて 1,250 例で）非劣性	（恐らく）非劣性	非劣性
臨床試験登録番号	NCT00003636	NCT00075712	NCT00715286	UMIN000000523
臨床試験登録日	1999.11.1	2004.1.9	2008.7.14	2006.11.17

EORTC：European Organization for Research and Treatment of Cancer, JCOG：Japan Clinical Oncology Group
RCOG：Royal College of Obstetricians and Gynaecologists, CTU-MRC：Medical Research Council Clinical Trials Unit
CHORUS：Chemotherapy or Upfront Surgery

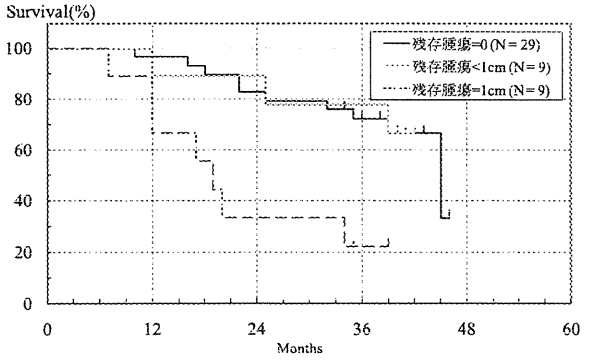

図4　JCOG0206登録症例のIDS後残存腫瘍径別生存期間

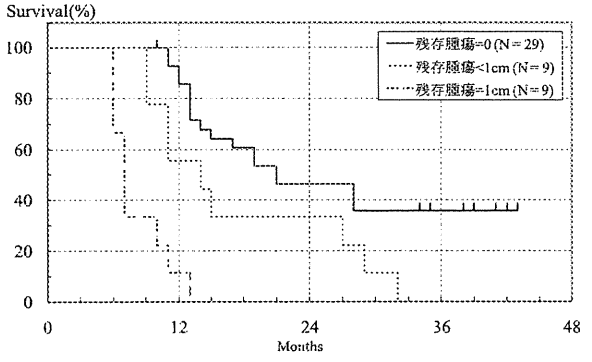

図5　JCOG0206登録症例のIDS後残存腫瘍径別無増悪生存期間

録後，症例は手術先行（標準治療群）と化学療法先行（NAC群）に割り振られる．標準治療群において，PDSで標準手術(子宮，附属器，大網切除)未完遂例ではIDS必須，標準手術完遂しsuboptimal症例ではIDS施行可としている(図3参照)．2006年11月17日から，300例を目標に3年の予定で開始したが，期間を1.5年延長して現在登録を継続している．これまでにのべ36施設が参加している．JCOG試験参加施設の一覧を示す(表3)．

6. 進行中，解析中の第III相比較試験

臨床試験のデータベースである，ClinicalTrial.gov [http://clinicaltrial.gov/] などの情報によれば，ヨーロッパの臨床試験グループであるEORTC（European Organization for Research and Treatment of Cancer）では，いち早く第III相試験を開始した．対象疾患の診断に生検が必須であること，化学療法は術前，術後合わせて6コースであること，プラチナ，タキサンの組み合わせ自由であること，などの違いがある．イギリスのRCOG (Royal College of Obstetricians and Gynaecologists)と，CTU-MRC(Medical Research Council Clinical Trials Unit)のグループでは，CHORUS (Chemotherapy or Upfront Surgery) 試験を行っている．化学療法はCBDCAを含むregimen，登録は画像診断と腫瘍マーカーのみで，登録後悪性を確認する．最終解析はEORTC症例と合わせて行う予定としている．インドのグループではIIIC期と胸水IV期のみの卵巣癌を対象に試験を行っている．開始されたのは，2001年と早いが，2008年にNCIの臨床試験データベースに登録された．これらの試験は，いずれもNAC療法が標準治療に劣らないことを示す非劣性試験である（表4)．

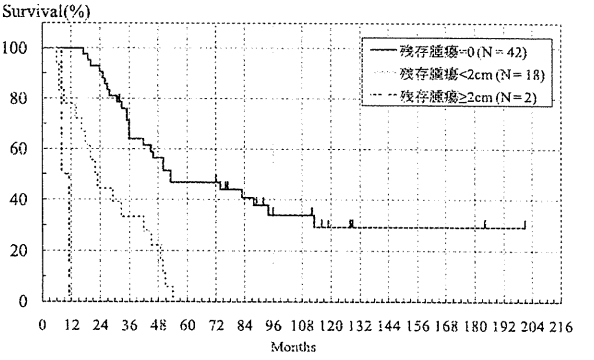

図6　東京大学における進行卵巣癌治療症例の中間期手術後残存腫瘍系別生存期間

インドのグループは2006年，2007年にASCO (American Society of Clinical Oncology)で中間の解析を，EORTCは登録終了後の初期解析を2008年のIGCS（International Gynecologic Cancer Society)で発表している．NAC群では，optimal surgeryが高率に達成出来て，手術による出血や合併症などの頻度が少なく，生存期間，無増悪生存期間はほぼ同等という結果であった．

7. 卵巣癌に対するNAC療法の治療成績のまとめ

これまでのNAC療法の治療成績をまとめると，NAC療法では手術に関する侵襲が少なく，手術先行治療と遜色のないあるいは同等の成績が得

られている．第III相試験の結果が出揃い，非劣性が確認されれば進行卵巣癌の標準治療となることが期待される．

8. NAC療法の今後の課題

NAC療法を行う場合，特に標準治療として行っていく場合に，解決しなければならない課題がある．NAC療法対象疾患の診断方法，(手術を先行しない場合の）臨床進行期の定義，化学療法抵抗性の明細胞腺癌，粘液性腺癌の取り扱い，至適なNACのregimen，術前，術後化学療法投与回数，投与方法，IDSの適応，およびその判定方法，IDSにおけるoptimal surgeryの定義などが挙げられる．なかでも，IDSにおける手術目標であるoptimal surgeryの定義について，以下に検討する．

9. IDSにおけるoptimal surgeryの定義の検討

標準治療では，残存1cm未満を目指してPDSを行ない，化学療法を6〜8コース行うが，NAC療法は，化学療法3〜4コースの後に，IDSを行い，更に3〜4コース化学療法を追加する治療である．これまでの，NACの報告では，PDSのoptimalと全く同じ定義をIDSにも適応しているが，両者の残存腫瘍は，化学療法を既に受けているか否か，今後予定される回数，とも異なっており，同じ目標でいいとは考えにくい．NAC療法でのIDS時の残存腫瘍と予後について検討した．

JCOG0206登録症例の予後を，全生存期間で見ると残存腫瘍0と残存腫瘍1cm未満は同様の70%台の3年生存であるが(図4)，無増悪生存期間で見ると，残存腫瘍1cm未満では全例が3年以内に再発しており，3年無増悪生存36%の残存0と差が見られる（図5)．症例数が少なく，追跡期間も短いため，結論は出せないが，長期予後を期待できるのは残存腫瘍0のみと考えられる．

これとは別に，1986年から2000年に東京大学で治療を行った進行卵巣癌症例の中間期手術後の残存腫瘍と予後の関連を検討した[12]．東京大学では，PDSで完全切除となった症例以外は，原則として化学療法2〜4コース後の中間期に，効果判定あるいは腫瘍縮小目的に再手術を行う方針であった．結果的に，残存腫瘍を有する91例中66例に，2〜6コース後に中間期手術が行われており，そのうち3〜6コース後に中間期手術を行った62症例の手術後の残存腫瘍と予後の関連を検討した．手術先行の標準治療であるが，中間期手術後の残存腫瘍は，NAC療法のIDSにおける残存腫瘍と，化学療法を受けた回数，残された治療などほぼ同等と考えられ，予後に与える影響が検討できると考えられる．

生存期間を見てみると，2cm未満の残存腫瘍であっても，残存腫瘍を有する場合には長期予後を得るのは困難であり5年生存0%であったが，残存腫瘍0の症例では47%の5年生存が得られていた(図6)．IDSの時点で残存腫瘍を有する場合，残された化学療法で制御するのは困難であり，長期予後を目指すためには，完全切除が必要と考えられる．今後NAC症例の集積により，さらに明らかにしていく必要があると考えられる．

10. ま と め

現在進行中の第III相試験の結果により，進行卵巣癌に対するNAC療法の役割が明らになると期待される．今後，IDSの目標などいくつかの課題についてさらなる検討が必要と考えられる．

なお，本論文の要旨は第48回日本婦人科腫瘍学会シンポジウムにおいて発表した．学会開催よりも後に，EORTCの第III相試験の最終報告がなされたが，本論文では学会発表時の内容のままとした．

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Phase II Clinical Study of the Combination Chemotherapy Regimen of Irinotecan Plus Oral Etoposide for the Treatment of Recurrent Ovarian Cancer (Tohoku Gynecologic Cancer Unit 101 Group Study)

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Objective: To evaluate the efficacy and safety of the combination chemotherapy regimen of irinotecan plus oral etoposide for the treatment of patients with recurrent ovarian cancer after previous treatment with platinum and taxane agents.

Patients and Methods: A total of 42 patients with recurrent ovarian cancer who had an evaluable lesion and provided informed consent for participation in the present study were analyzed. Irinotecan was administered intravenously at a dose of 60 mg/m^2 on days 1 and 15. Etoposide was administered orally at a daily dose of 50 mg/body weight from days 1 to 21. A 28-day period comprised one cycle. The tumor response, adverse events, progression-free survival, and overall survival were examined. Tumor response was evaluated based on the Response Evaluation Criteria in Solid Tumors and the serum CA125 levels (Gynecologic Cancer Intergroup criteria). Adverse events were assessed according to the NCI-CTCAE (version 3.0).

Results: Partial response was observed in 21 patients, stable disease in 14 patients, and progressive disease in 7 patients. The response rate was 50.0%, and the clinical benefit (partial response + stable disease) rate was 83.3%. Hematological toxicities of at least grade 3 severity included leukopenia in 21 patients (50.0%), neutropenia in 22 patients (52.4%), thrombocytopenia in 1 patient (2.4%), anemia in 9 patients (21.4%), and febrile neutropenia in 3 patients (7.1%). Nonhematological toxicities of at least grade 3 severity included queasy feeling in 5 patients (11.9%), vomiting in 3 patients (7.1%), and diarrhea in 2 patients (4.8%). Acute myeloid leukemia occurred in one patient (2.4%).

Conclusions: It is suggested that combination chemotherapy with irinotecan plus oral etoposide offers significant clinical benefit to patients with recurrent ovarian cancer previously treated with platinum and taxane agents.

Key Words: Recurrent ovarian cancer, Irinotecan, Oral etoposide, Chemotherapy

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Patients with ovarian cancer who develop recurrence within 6 months of first-line chemotherapy with platinum and taxane agents are considered to be resistant to these agents and to have a poor prognosis.[1–3] Randomized controlled studies using a single agent have been conducted in these patients.[4–6] While selecting treatment for patients with recurrent cancer, it is of fundamental importance to select agents that do not show cross-resistance to the agents used as first-line therapy. Combination chemotherapy is reported to yield higher response rates than single-agent treatment, but this does not always translate into prolonged overall survival because these regimens also exert potent toxicity. Based on the aforementioned viewpoints, combination chemotherapy for patients with platinum and taxane drug resistance requires a regimen with a reduced toxicity and increased efficacy. In a study conducted by Matsumoto et al,[7] in which irinotecan (100 mg/m^2), a topoisomerase-I inhibitor, was administered alone on days 1, 8, and 15 every 4 weeks to patients with platinum- and taxane-resistant ovarian cancer, the response rate was 29%. In Europe and the United States, studies have been conducted using etoposide, a topoisomerase-II inhibitor. In a study conducted by Rose et al,[8] in which 41 patients with recurrent ovarian cancer were given oral etoposide alone (50 mg/kg of body weight) from days 1 to 21 every 4 weeks, the response rate was 34.6% in the platinum-sensitive patients and 26.8% in the platinum-resistant patients. Because basic research on the combination chemotherapy regimen of irinotecan plus etoposide confirmed that the 2 agents exert synergistic antitumor activity,[9] combination therapy with these 2 agents is expected to be effective in patients with recurrent/advanced ovarian cancer resistant to platinum and/or taxane agents. Yamanaka et al[10] conducted a phase I clinical study of combined irinotecan plus etoposide therapy as second-line therapy; according to that study, the dose-limiting toxicities were neutropenia and gastrointestinal toxicity, and the recommended doses of the drugs in this combined regimen were 70 mg/m^2 for irinotecan (days 1 and 15) and 50 mg/d (days 1 to 21) for oral etoposide.

Nishio et al[11] reported a response rate of 44.4% in a pilot study of the combination regimen of irinotecan plus oral etoposide. To corroborate the results from the study by Nishio et al, we evaluated the efficacy and safety of combined irinotecan plus oral etoposide therapy in patients with recurrent ovarian cancer in a multicenter phase II clinical study under the sponsorship of the Tohoku Gynecologic Cancer Unit.

SUBJECTS AND METHODS

Sample Size

With the expected efficacy rate set at 40% and the threshold efficacy rate at 20% for the study treatment under the conditions of $\alpha = 0.05$ and $\beta = 0.20$, the required number of subjects was 36. We targeted enrollment of 40 subjects, anticipating 4 cases of dropout.

Subjects

The subjects were 42 patients with recurrent ovarian cancer who had been treated previously with platinum and taxane agents, and they provided informed consent for participation in the present study between June 2002 and March 2008. Each institution obtained institutional review board approval of the protocol before study initiation.

Eligible Criteria

The eligibility criteria were as follows: patients (1) with histologically or cytologically confirmed diagnosis of ovarian cancer; (2) with recurrent ovarian cancer who had been treated previously with platinum and taxane agents; (3) with a measurable or evaluable lesion (including serum levels of CA125); (4) with an Eastern Cooperative Oncology Group performance status of 0, 1, or 2; (5) between 20 and 75 years of age; (6) who fulfilled the following criteria for hematological and biochemical parameters (white blood cell count, ≥3000/mm^3; absolute neutrophil count, ≥1500/mm^3; platelet count, ≥100,000/mm^3; hemoglobin, ≥9.0 g/dL; aspartate aminotransferase and alanine aminotransferase levels, ≤2 times the upper limit of the institutional normal range; serum total bilirubin, ≤1.5 mg/dL; serum creatinine, ≤1.5 mg/dL; creatinine clearance, ≥50 mL/min; (7) with an estimated life expectancy of at least 2 months; and (8) who had voluntarily provided written consent for participation in this study.

Exclusion Criteria

The exclusion criteria were as follows: patients (1) with a definite infectious disease; (2) with serious underlying diseases (including heart disease, poorly controlled diabetes, malignant hypertension, and bleeding tendency); (3) with active multiple primary cancers; (4) with interstitial pneumonia or lung fibrosis; (5) with body fluid retention requiring treatment; (6) with brain metastasis that was considered to require prompt treatment; (7) with unstable angina or myocardial infarction occurring within 6 months before recruitment, or severe arrhythmia requiring treatment; (8) with diarrhea (watery stool); (9) with intestinal ileus or intestinal obstruction; (10) who were pregnant or nursing newborns, or who wished to conceive; (11) with a history of severe drug hypersensitivity or drug allergy; and (12) who were judged by the attending physician as being unsuitable candidates for the safe implementation of the study.

Administration Methods and Schedules

Administration

Irinotecan mixed with 500 mL or more of physiological saline or glucose was administered by intravenous

drip infusion over 90 minutes. Etoposide was administered orally.

Administration Schedules

Irinotecan (60 mg/m^2) was administered on days 1 and 15, and etoposide (50 mg/body) was administered from days 1 to 21. A 28-day period comprised one cycle, and 4 or more treatment cycles were repeated. The following patients were withdrawn from the study: patients with (1) progressive disease (PD) detected before the completion of 4 treatment cycles; (2) severe adverse reactions, who were considered unsuitable candidates for treatment continuation; (3) a decreased neutrophil count (<1500/mm^3), decreased platelet count (<75,000/mm^3), or diarrhea not recovering within 2 weeks after a scheduled treatment day.

Criteria for Modification of the Dosage and Administration

Skipping of Irinotecan Treatment

Clinical laboratory testing was necessarily performed within 24 hours before irinotecan administration on day 15, and the severity of adverse reactions and the patients' condition were well evaluated. Irinotecan was skipped for the day in patients with at least one of the following conditions: (1) neutrophil count, less than 1500/mm^3; (2) platelet count, less than 75,000/mm^3; (3) diarrhea, not less than grade 2 in severity.

Start of the Next Cycle

If the hematological values and the patients' condition did not meet the following criteria within 2 days before the start of the next cycle, the start of the next cycle was delayed by up to 2 weeks: (1) neutrophil count, 1500/mm^3 or greater; (2) platelet count, 75,000/mm^3 or greater; (3) resolution of diarrhea.

Dose Reduction

In patients who experienced at least one of the following conditions during the previous cycle, the doses of irinotecan and etoposide were decreased to 50 mg/m^2 and 25 mg/kg of body weight per day, respectively: (1) grade 4 neutropenia lasting for at least 7 days; (2) febrile neutropenia lasting for at least 4 days; (3) grade 4 thrombocytopenia; and (4) grade 3 thrombocytopenia with bleeding. The dose of irinotecan was reduced to 50 mg/m^2 in patients with grade 2 or higher diarrhea.

Supportive Therapy

Granulocyte colony-stimulating factor (G-CSF) was therapeutically administered to patients developing grade 4 neutropenia during the first cycle. Prophylactic treatment with G-CSF after the start of the second cycle was permitted in patients with grade 4 neutropenia during the first cycle and those with grade 3 neutropenia. Antiemetic drugs were administeredprophylactically.

Continuation of Treatment and Subsequent Therapy

Treatment cycles were repeated 4 times or more until treatable patients without PD showed disease progression (except those who discontinued the study treatment or those who were withdrawn from the study). The study treatment was discontinued in patients with adverse reactions that did not recover by 2 weeks. The subsequent therapy was not specified for these patients.

Assessments

The primary outcome was the tumor response, and the secondary outcomes were adverse events, progression-free survival, and overall survival. The patients who were definitively diagnosed as having developed recurrence within 6 months of the last administration day of the previous treatment course were determined to be platinum/taxane resistant, and those who received a similar diagnosis 6 months or longer after that day were defined to be platinum/taxane sensitive. The tumor response, progression-free survival, and overall survival were compared between the 2 groups.

(1) Assessment of the tumor response: The tumor response, evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria, was assessed by means of computed tomography or magnetic resonance imaging in patients with measurable lesions. As another method of evaluation, increase in the serum CA125 levels as a marker of recurrence was assessed according to the Gynecologic Cancer Intergroup criteria by Rustin et al[12] in patients without measurable lesions.
(2) Assessment of adverse events: Adverse events were assessed according to the National Cancer Institute Common Toxicity Criteria (NCI-CTCAE), version 3.0.
(3) Overall survival and progression-free survival were analyzed by constructing Kaplan-Meier curves, and the median values in the platinum-taxane–resistant and platinum-taxane–sensitive patients were calculated and analyzed by the log-rank test.

RESULTS

Patients' Characteristics

The median age of the 42 patients enrolled in this study was 51 years (range, 34–75 years). The performance status score was 0 in 27 patients (64.3%), 1 in 11 (26.2%) patients, and 2 in 4 (9.5%) patients. Thirty-one patients (73.8%) were included in the platinum-taxane–resistant group and 11 (26.2%) in the sensitive group. The histological diagnoses included serous adenocarcinoma (n = 33 [73.8%]), mucous adenocarcinoma (n = 3 [7.1%]), clear cell adenocarcinoma (n = 4 [9.5%]), and endometrioid adenocarcinoma (n = 2 [4.8%]). The number of prior chemotherapy regimens was 1 in 23 patients (54.8%), 2 in 13 patients (31.0%), and 3 or more in 6 patients (14.3%). Platinum and taxane agents had been used as the agents for the previous first-line therapy for all the patients. Recurrence was diagnosed according to the

TABLE 1. Patients' characteristics

	R (n = 31)	S (n = 11)
Age, median, range, yrs	56 (34–74)	59 (38–69)
ECOG Performance Status, n (%)		
0	19 (61.3)	8 (72.7)
1	9 (29.0)	2 (18.2)
2	3 (9.7)	1 (9.1)
Previous Regimens, n (%)		
1	17 (54.8)	6 (54.5)
2	9 (29.0)	4 (36.4)
≥3	5 (16.1)	1 (9.1)
Cell Type, n (%)		
Serous	24 (77.4)	9 (81.8)
Mucinous	2 (6.5)	1 (9.1)
Clear cell	3 (9.7)	1 (9.1)
Endometrioid	2 (6.5)	0 (0)
Response Method, n (%)		
RECIST	14 (45.2)	5 (45.5)
CA125 criteria	17 (54.8)	6 (54.5)

ECOG, Eastern Cooperative Oncology Group; R, Platinum/Taxane resistant; S, Platinum/Taxane sensitive.

RECIST criteria in 18 patients (42.9%) and according to the CA125 levels defined by the Gynecologic Cancer Intergroup criteria in 24 patients (57.1%) (Table 1).

Treatment Results

A total of 343 treatment cycles were administered to the 42 patients. Thirty-one patients in the platinum-taxane–resistant group and 11 in the platinum-taxane–sensitive group received 240 and 103 treatment cycles, respectively. The mean number of treatment cycles was 7.4 in the platinum-taxane–resistant group and 9.4 in the platinum-taxane–sensitive group.

Tumor Response

Among the 42 patients, partial response (PR) was observed in 21 patients (50.0%), stable disease (SD) in 14 patients (33.3%), and PD in 7 patients (16.7%). The response rate was 50.0%, and the clinical benefit (PR + SD) rate was 83.3% (Table 2).

Platinum-Taxane–Resistant Group

Of the 31 patients, 13 (41.9%) showed PR, 11 (35.5%) showed SD, and 7 (22.6%) showed PD. The response rate was 41.9%, and the clinical benefit rate was 77.4%. In the 13 patients showing PR, the median treatment period elapsed before PR was confirmed was 3 months (range, 1–7 months); the median response duration was 9 months (range, 3–33 months). The median progression-free survival was 13 months (range, 2–32 months) in the 11 patients showing SD.

Platinum-Taxane–Sensitive Group

Of the 11 patients, 8 (72.7%) showed PR and 3 (27.3%) showed SD. The response rate was 72.7%, and the clinical benefit rate was 100%. In the 8 patients showing PR, the median treatment period elapsed before PR was confirmed was 3 months (range, 1–7 months). The median response duration was 10.5 months (range, 7–18 months). The median progression-free survival was 14 months (range, 6–28 months) in the 3 patients showing SD.

Adverse Events

Hematological toxicities that were at least grade 3 in severity included leukopenia in 21 patients (50.0%), neutropenia in 22 patients (52.4%), thrombocytopenia in 1 patient (2.4%), and anemia in 9 patients (21.4%). Febrile neutropenia occurred in 3 patients (7.1%). Nonhematological toxicities that were at least grade 3 in severity included a queasy feeling in 5 patients (11.9%), vomiting in 3 patients (7.1%), and diarrhea in 2 patients (4.8%). Acute myeloid leukemia developed as a secondary cancer in 1 patient (2.4%) during the treatment (Table 3).

Reduced doses of irinotecan and etoposide were administered in the subsequent cycle to 13 patients (31.0%) who developed hematological toxicities, but there was no case of diarrhea that necessitated dose reduction in the subsequent cycle. Of the 13 patients, the hematological toxicities were grade 3 thrombocytopenia in 1 patient, febrile neutropenia in 3 patients, grade 4 neutropenia lasting for at least 7 days in 7 patients, grade 3 queasy feeling in 1 patient, and grade 3 vomiting in 1 patient. The latter 2 patients received reduced doses according to the judgment of the physicians.

Twelve of the 301 cycles (4.0%) were delayed because the patients did not meet the criteria for the start of the next cycle. Eleven cycles (3.7%) were delayed because of decrease of the neutrophil count to less than 1500/mm^3 and

TABLE 2. Response

	CR	PR	SD	PD	Overall Response	CR/PR + SD
R	0 (0)	13 (41.9)	11 (35.5)	7 (22.6)	13 (41.9)	24 (77.4)
S	0 (0)	8 (72.7)	3 (27.3)	0 (0)	8 (72.7)	11 (100)
Total	0 (0)	21 (50.0)	14 (33.3)	7 (16.7)	21 (50.0)	35 (83.3)

CR, complete response.

TABLE 3. Toxicity (N = 42)

	Grade				
	1	2	3	4	≥3 (%)
Leukopenia	6	12	17	4	21 (50.0)
Neutropenia	6	13	12	10	22 (52.4)
Thrombocytopenia	4	2	1	0	1 (2.4)
Anemia	4	24	8	1	9 (21.4)
Nausea	25	7	5	0	5 (11.9)
Vomiting	15	6	3	0	3 (7.1)
Diarrhea	4	0	2	0	2 (4.8)
Neurotoxicity	0	0	0	0	0
Renal toxicity	0	0	0	0	0
Febrile neutropenia	—	—	3	0	3 (7.1)
Secondary malignancy	—	—	0	1	1 (2.4)*

*Acute myeloid leukemia.

1 (0.3%) because of a decrease of the platelet count to less than 75,000/mm^3. However, the following cycle was started within 7 days in all of these patients. The irinotecan dose on day 15 was skipped in 7 of the 301 cycles (2.3%) because of a neutrophil count of less than 1000/mm^3.

The total number of G-CSF treatment days during the 343 cycles was 172, and the mean number of treatment days was 0.5 per cycle. One patient (2.4%) who developed acute myeloid leukemia was withdrawn from the study.

Progression-Free Survival

The median progression-free survival was 7 months (range, 1–33 months) in the 31 platinum-taxane–resistant patients and 11 months (range, 7–36 months) in the 11 platinum-taxane–sensitive patients. Analysis using the log-rank test revealed no statistically significant difference in the median progression-free survival between the 2 groups of patients ($P = 0.45$; Table 4).

Overall Survival

The median overall survival was 19 months (range, 4–73 months) in the 31 platinum-taxane–resistant patients and 21 months (range, 11–46 months) in the 11 platinum-taxane–sensitive patients. The difference between the 2 groups was not statistically significant ($P = 0.98$; Table 4).

DISCUSSION

Combination of a topoisomerase-I inhibitor and a topoisomerase-II inhibitor is theoretically expected to result in a synergistic effect between the 2 drugs. Data from in vitro studies have demonstrated synergistic or additive effects of the component drugs in the combination regimens of irinotecan (SN-38) plus etoposide, and topotecan plus etoposide.[13–17] In a phase II study of combined irinotecan plus etoposide therapy conducted in patients with small cell and non–small cell lung cancer, the antitumor efficacy was not as high as expected. Etoposide was administered intravenously in that study, whereas in general, oral administration of etoposide is recommended for ovarian cancer. The combination regimen of irinotecan and oral etoposide is expected to exhibit a higher efficacy against ovarian cancer. A phase I/II clinical study of combined topotecan and oral etoposide was conducted in Germany, but the trial had to be discontinued prematurely because of the occurrence of severe bone marrow suppression. However, a high response rate was noted at a low dose of etoposide.[18] We considered that the use of irinotecan, considered to exert relatively milder hematological toxicity than topotecan, may resolve the toxicity issue described earlier. Occurrence of diarrhea is a concern during the administration of irinotecan. Divided-dose administration on days 1 and 15 may prevent the occurrence of serious diarrhea compared with single-dose administration. The recommended dose of irinotecan was determined to be 70 mg/m^2 in a phase I study. Considering that gastrointestinal toxicity was the dose-limiting toxicity and also the report by Nishio et al, irinotecan was administered at a dose of 60 mg/m^2 in this study.

The subjects of the present study included 11 platinum-taxane–sensitive patients. Of the 11 patients, 6, 4, and 1 previously received 1, 2, and 3 regimens of the TC therapy, respectively. They experienced serious adverse events during the prior therapy, including grade 3 peripheral nerve disorder, grade 4 neutropenia, and grade 3/4 thrombocytopenia. Although TC therapy is usually performed again in patients with a treatment-free interval of 6 months or longer, all the 11 patients rejected the therapy and requested the study therapy. It was also intended to determine whether the antitumor effect, progression-free survival, and overall survival of the study therapy were different between platinum-taxane–resistant and sensitive cases.

About the tumor response, the response rate was 41.9% and 72.7% in the platinum-taxane–resistant and platinum-taxane–sensitive groups, respectively. The overall response rate in the 42 patients was 50.0%, almost equivalent to that

TABLE 4. Treatment and survival

	R (n = 31)	S (n = 11)
No. Cycles		
Median	6	7
Mean	7.4	9.4
Range	2–27	3–27
PFS, mos		
Median	7	11
Range	1–33	7–36
OS, mos		
Median	19	21
Range	4–73	11–46

PFS, Progression-free survival; OS, overall survival.

in the feasibility study conducted by Nishio et al[11] using the same treatment regimens.

Neutropenia of at least grade 3 severity occurred in 22 patients (52.3%), and febrile neutropenia occurred in 3 patients (7.1%). Because these patients were treatable with G-CSF and there were no deaths related to the study treatment, the toxicities were considered to be acceptable. However, an upper limit for the number of cycles was not defined, and acute myeloid leukemia developed in one patient. The patient was treated by chemotherapy for leukemia but did not achieve remission and died of acute respiratory failure 4 months after the start of the treatment for leukemia. In general, a total dose of etoposide of more than 6 g may be associated with an increased risk of development of leukemia. Ratain et al[19] reported that the mean total dose of etoposide was 6795 mg/m^2 in patients with non–small cell lung cancer who developed secondary leukemia, which was significantly higher than the total dose of 3025 mg/m^2 in those who did not develop leukemia. Sugita et al[20] reported that administration of etoposide 2 times or more per week may be associated with an increased risk of occurrence of secondary leukemia. The patient who developed leukemia in our study received oral etoposide at the total dose of 14.2 g/kg of body weight. Even in patients in whom SD is maintained, treatment should not be continued aimlessly, and an upper limit for the number of treatment cycles should be defined beforehand.

The mean progression-free survival was 11 months in the platinum-taxane–sensitive group, which was a little longer than the 7 months achieved in the platinum-taxane–resistant group. There was no statistically significant difference between the groups, perhaps because patients in the platinum-taxane–sensitive group received an average of 2 cycles more than those in the platinum-taxane–resistant group. Moreover, there was no statistically significant difference in the mean overall survival between the platinum-taxane–sensitive and platinum-taxane–resistant groups. This study included patients with serological recurrence. The findings in this study seemed to be similar to those reported by Rustin et al,[21] who demonstrated that early treatment of relapse detected based on the marker levels did not yield a better prognosis.

In Japan, pegylated liposomal doxorubicin (Doxil) has been approved for the treatment of recurrent ovarian cancer, whereas gemcitabine and topotecan are still not approved. Therefore, as a second-line chemotherapy for ovarian cancer, the administration of irinotecan and etoposide is plausible because they show no cross-resistance to paclitaxel or carboplatin. Combination chemotherapy with irinotecan and oral etoposide offered significant clinical benefit in patients with recurrent ovarian cancer. Thus, this combination regimen is useful from the viewpoint of maintenance of the quality of life because the divided-dose schedule of irinotecan produced a low incidence of diarrhea, a specific toxicity of irinotecan, and the incidence of hematological toxicities was not greatly increased.

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