A single-arm Phase II study evaluating combination chemotherapy utilizing oral etoposide and irinotecan for platinum-resistant and taxane-pretreated ovarian cancer has started. The aim of this study is to evaluate the efficacy and safety of this regimen as a test arm regimen in a subsequent Phase III trial. Patients with platinum-resistant and taxane-pretreated ovarian cancer are given etoposide at 50 mg/m² p.o. from days 1 to 21 and irinotecan 70 mg/m² i.v. at days 1 and 15, repeated every 28 days, up to six cycles. A total of 60 patients will be enrolled at 36 institutions. The primary endpoint is response rate. The secondary endpoints include adverse events and progression-free and overall survival.

Key words: Chemo-Gynecology – Gynecol-Med – clinical trials
Topoisomerase-I treatment induces an increase in the S-phase cell population with an increase in topoisomerase-II mRNA expression. Thus, topoisomerase-I can modulate topoisomerase-II levels to enhance the effect of topoisomerase-II inhibitors (13,14).

Eder et al. (15) reported the result of the in vivo study. They showed that a combination of irinotecan and etoposide showed more than an additive effect by both the tumor excision assay and tumor growth delay assay.

A Phase I study of topotecan and oral etoposide revealed severe myelosuppression but promising efficacy for ovarian cancer (16).

The dose-limiting toxicity of irinotecan is diarrhea, different from that of topotecan (myelosuppression). Then, utilizing etoposide with irinotecan may improve the risk–benefit balance of dual inhibition of topoisomerase. The result of the Phase I study was reported in ASCO 2002 (17).

The recommended dose for further study was oral etoposide: 50 mg/m²/days 1–21 and intravenous irinotecan: 60 mg/m²/days 1 and 15, repeated every 4 weeks.

In this Phase I study, four objective responses [two complete responses and two partial responses (PRs)] were achieved among 24 patients, including one PR in clear cell.

Nishio et al. (18) reported the result of a feasibility study run by selected hospitals in Tohoku and Kyushu districts in Japan. Response rate, time to progression and overall survival were 44%, 9 months and 17 months, respectively. This very promising result led us to conduct a nationwide Phase II study run by Japan Clinical Oncology Group (JCOG).

The protocol review committee of the JCOG approved this protocol in January 2009 and the study was initiated in April 2009. This trial was registered at UMIN-CTR as UMIN000001837 (http://www.umin.ac.jp/ctr/index.htm).

PROTOCOL DIGEST OF THE JCOG0503

OBJECTIVES

The aim of this study is to evaluate the safety and efficacy of oral etoposide and intravenous irinotecan for patients with platinum-resistant and taxane-pretreated ovarian, tubal and peritoneal cancer as the test arm regimen in a subsequent Phase III trial.

STUDY SETTING

The study is a multi-institutional open-label two-stage design Phase II trial.

RESOURCES

This study is supported by Grants-in-Aid for Cancer Research (20S-1 and 20S-6) and Health and Labor Sciences Research Grant for Clinical Cancer Research (18–6), from The Ministry of Health, Labor and Welfare of Japan.

ENDPOINTS

The primary endpoint is response rate in all eligible patients. For patients with measurable lesion, response is evaluated according to the RECIST criteria (19). For patients with non-measurable lesion, response is evaluated according to the GCIG CA-125 criteria (20). The secondary endpoints are progression-free survival, overall survival and adverse events. Overall survival is defined as days from registration to death from any cause, and it is censored at the last follow-up day when the patient is alive. Progression-free survival is defined as days from registration to disease progression (either of radiological, CA-125, symptomatic) or death from any cause, and it is censored at the latest day when the patient is alive without any evidence of progression.

ELIGIBILITY CRITERIA

INCLUSION CRITERIA

For inclusion in the study, patients are required to fulfill all of the following criteria:

(i) cytologically or histologically proven ovarian, tubal or peritoneal cancer
(ii) platinum-resistant disease
(iii) taxane-pretreated disease
(iv) age: 20–75 years old
(v) PS (performance status): 0–2
(vi) one of the followings, or both of them:
   (a) patients have measurable lesion
   (b) patients have assessable lesion with elevated CA-125 (more than 70 U/ml)
(vii) no prior treatment with irinotecan, topotecan or etoposide
(viii) no prior radiation to abdomen
(ix) oral intake without parenteral nutrition
(x) both of the followings:
   (a) no drainage to effusion or ascites within 28 days
   (b) no effusion or ascites to be drained at registration
(xi) both of the followings:
   (a) no chemotherapy or surgery within 28 days
   (b) no hormonal or biologic therapy within 14 days
(xii) patients without severe organ dysfunction
(xiii) written informed consent

EXCLUSION CRITERIA

Patients are excluded if they meet any of the following criteria:

(i) synchronous or metachronous (within 5 years) malignance other than carcinoma in situ or intramucosal cancer
(ii) mental disease or mental symptoms that would affect the participant’s decision to participate
(iii) pregnant or lactating
(iv) continuous systemic steroid
(v) active bacterial or fungal infection with fever of 38.5°C or higher
(vi) uncontrollable hypertension
(vii) uncontrollable diabetes requires continuous insulin administration
(viii) history of myocardial infarction or heart failure within 6 months, or current unstable angina
(ix) bowel obstruction

TREATMENT METHODS
Etoposide is orally administered once a day at 50 mg/m² from days 1 to 21, and irinotecan is infused at 70 mg/m² on days 1 and 15, repeated every 28 days. Protocol treatment is continued up to six cycles unless disease progression, unacceptable toxicity or patient refusal.

FOLLOW-UP
Enhanced abdominal computed tomography (CT)/magnetic resonance imaging, chest CT/X-rays and tumor marker (CA-125) are evaluated at least every 8 weeks during the protocol treatment. Adverse events are evaluated at least every 2 weeks during the protocol treatment using CTCAE ver. 3.0.

STUDY DESIGN AND STATISTICAL ANALYSIS
This study is a Phase II trial with two-stage design by Southwest Oncology Group (21) to evaluate this regimen as the test arm for a subsequent Phase III trial.

The sample size was determined as follows by the SWOG design. We assumed that the expected value for the primary endpoint of 35% and the threshold value of 20%. In this endpoint, the sample size ensuring at least 80% power with one-sided α of 5% is 55. Considering the likelihood of some ineligible patients being enrolled, the total number of patients was set at 60.

INTERIM ANALYSIS AND MONITORING
We plan interim analysis for futility after 30 patients enrolled. In house monitoring will be performed every 6 months by the JCOG Data Center to evaluate the study progress and to improve the study quality.

PARTICIPATING INSTITUTIONS
The participating institutions (from north to south) are as follows: Hokkaido University Hospital, Sapporo Medical University, Iwate Medical University, Tohoku University Hospital, Institute of Clinical Medicine, Tsukuba University, National Defense Medical College, Saitama Cancer Center, Saitama Medical Center, Saitama Medical School, National Cancer Center Hospital, Jikei Kashiwa Hospital, Tokyo Metropolitan and Infectious diseases Center Komagome Hospital, The University of Tokyo Hospital, Jikei University Hospital, Cancer Institute University School of Medicine, Kitasato University School of Medicine, Niigata Cancer Center Hospital, Shinshu University School of Medicine, Aichi Cancer Center Hospital, Kyoto University Hospital, Osaka city University Hospital, Kinki University School of Medicine, Osaka Medical Center for Cancer and Cardiovascular Disease, Osaka City General Hospital, Sakai Hospital, Kinki University School of Medicine, Hyogo Cancer Center, Tottori University, Kure Medical Center Chugoku Cancer Center, Shikoku Cancer Center, Kyushu Cancer Center, Kurume University School of Medicine, Kyushu University Hospital, Faculty of Medicine Saga University, Kumamoto University Medical School, Kagoshima City Hospital and University of the Ryukyu.

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Conflict of interest statement
None declared.

References


