Clinical Trial Note

A non-randomized confirmatory study regarding selection of fertility-sparing surgery for patients with epithelial ovarian cancer: Japan Clinical Oncology Group Study (JCOG1203)

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Received 11 November 2014; Accepted 17 February 2015

Abstract

Fertility-sparing treatment has been accepted as a standard treatment for epithelial ovarian cancer in stage IA non-clear cell histology grade 1/grade 2. In order to expand an indication of fertility-sparing treatment, we have started a non-randomized confirmatory trial for stage IA clear cell histology and stage IC unilateral non-clear cell histology grade 1/grade 2. The protocol-defined fertility-sparing surgery is optimal staging laparotomy including unilateral salpingo-oophorectomy, omentectomy, peritoneal cytology and pelvic and para-aortic lymph node dissection or biopsy. After fertility-sparing surgery, four to six cycles of adjuvant chemotherapy with paclitaxel and carboplatin are administered. We plan to enroll 250 patients with an indication of fertility-sparing surgery, and then the primary analysis is to be conducted for 63 operated patients with pathologically confirmed stage IA clear cell histology and stage IC unilateral non-clear cell histology grade 1/grade 2. The primary endpoint is 5-year overall survival. Secondary endpoints are other survival endpoints and factors related to reproduction. This trial has been registered at the UMIN Clinical Trials Registry as UMIN000013380.

Key words: gynecology, gynecol-surg, ovarian cancer, early stage, fertility-sparing surgery
Introduction

The purpose of this trial is to prospectively confirm whether fertility-sparing treatment (FST) should be recommended for epithelial ovarian cancer patients with stage IA clear cell histology (CCH) or with unilateral stage IC non-CCH grade 1/grade 2 (G1/G2) tumors who are ≤40 years old and wish to undergo the treatment.

In this study, staging is determined according to the International Federation of Gynecology and Obstetrics (FIGO) classification (2014). Stage IC patients are classified into three subgroups: (i) IC1, surgical spill; (ii) IC2, capsule ruptured before surgery or tumor on ovarian surface and (iii) IC3, malignant cells in the ascites or peritoneal washings (1).

Fertility-sparing surgery (FSS) is accepted as a standard treatment in ovarian cancer patients of reproductive age in stage IA non-CCH G1/G2 who wish to undergo FSS. There has been a consensus that FSS cannot be recommended, even if FSS is followed by adjuvant chemotherapy, to the other stage I patients with bilateral ovarian lesions, CCH or non-CCH grade 3 (G3) as well as patients beyond stage II (2,3).

Prior to 2010, it had been considered that FST should not be permitted in CCH regardless of disease stage. However, it was reported by Kajiyama et al. in 2008 (4) that recurrence was not observed in all four patients with stage IA CCH who underwent FST. Similarly, in a retrospective, multi-center (30 institutions) study conducted by the Gynecologic Cancer Study Group of Japan Clinical Oncology Group (JCOG) (“JCOG-FST study”), recurrence was not observed in all 15 patients with stage IA CCH, indicating that FST may be permitted in patients with stage IA CCH with the stipulation that surgery with optimal staging and postoperative adjuvant chemotherapy are performed (5). Therefore, we have included stage IA CCH in the eligibility criteria of this trial.

The JCOG-FST study also showed promising efficacy in the 67 patients with unilateral stage IC non-CCH G1/G2, for whom 5-year overall survival was 96.9%, and 5-year recurrence-free survival was 92.1%. Furthermore, the study demonstrated that the 5-year recurrence-free survival in stages IC1, IC2 and IC3 were similar at 92.9% (n = 43), 91.7% (n = 14) and 90.0% (n = 10), respectively, concluding that FST may be considered regardless of the IC sub-stage under the condition that postoperative adjuvant chemotherapy is performed (5). In addition, Fruscio et al. reported the recurrence rate in stage IC1 and IC2/3 non-CCH to be 6.7% (4/58 patients) and 12.8% (6/47 patients), respectively, showing that FST may be indicated for both stage IC1 and IC2/3 (6). However, Kajiyama et al. recently demonstrated from their observational study that recurrence-free survival in stage IC2/3 patients were worse than that in stage IC1 (P = 0.0471), and that FST cannot be recommended in patients with stage IC2/3 (7). Although stage IC2/3 may have higher risk of recurrence than stage IC1, we have included all IC sub-stage in this trial.

For these backgrounds, we have planned this trial to confirm whether FST can be recommended for patients with stage IA CCH and with stage IC non-CCH G1/G2 under the condition that FSS with optimal staging and postoperative adjuvant chemotherapy are performed.

The study protocol was approved by the JCOG Protocol Review Committee and institutional review board at each institution prior to starting patient accrual. Patient enrollment began in March 2014. This trial has been registered at the UMIN Clinical Trials Registry as UMIN000013380 [http://www.umin.ac.jp/ctr/index.htm].

Protocol digest of the JCOG1203

Purpose

The purpose of this trial is to confirm the effectiveness of FSS with optimal staging followed by adjuvant chemotherapy in epithelial ovarian cancer patients with stage IA CCH and with stage IC non-CCH G1/G2.

Study setting

A multi-institutional (40 centers), non-randomized, confirmatory study (phase III trial).

Study flow

Patients who are diagnosed or suspected as stage I epithelial ovarian cancer and have an indication of FSS are enrolled. All enrolled patients undergo FSS and pathological diagnosis is performed. Then, only patients who undergo complete FSS and are diagnosed both intraoperatively and pathologically as follows are included in the primary analysis group: (i) patients with stage IA CCH or (ii) patients with stage IC (unilateral) non-CCH G1/G2.

In terms of intention-to-treat principle, it can be controversial to determine a primary analysis group after surgery. However, there are several reasons why we have adopted this study design. First, for patients who wish to have children, we cannot conduct a randomized trial comparing FSS and non-FSS. Second, before surgery, we cannot identify patients with pathological stage IA CCH or stage IC unilateral non-CCH G1/G2, because preoperative tumor biopsy may spread ovarian cancer cells to intraperitoneal cavity. Third, we can switch an operative procedure from FSS to non-FSS even after obtaining pathological diagnosis, and we can choose our ‘intention’ regarding whether we would continue FSS or not even after surgery. Considering these viewpoints, we have determined the primary analysis group as patients who are diagnosed as pathologically confirmed stage IA CCH or stage IC unilateral non-CCH G1/G2.

Endpoints

The primary endpoint is 5-year overall survival of all patients in the primary analysis group. The 5-year overall survival of the non-primary analysis group is also to be analyzed as a secondary endpoint.

Other secondary survival endpoints are 10-year overall survival, 5- and 10-year recurrence-free survival and 5- and 10-year lethal recurrence-free survival. We defined lethal recurrence as recurrence showing lesions outside the remaining ovary in JCOG-FST study (5), as a considerable number of previous reports have suggested that patients with recurrence exclusively within the remaining ovary showed much better prognosis following salvage surgery compared with patients displaying other patterns of recurrence.

Endpoints related to reproduction are also to be evaluated, which include 5-year proportion of menstruation recovery, 5-year proportion of menstruation cycle recovery, 5- and 10-year proportion of pregnancy and 5- and 10-year proportion of giving birth. Other safety endpoints are surgical complications, adverse events of chemotherapy and serious adverse events.

Eligibility criteria for the first registration

Inclusion criteria

1. To fulfill either I or II.

(I) When tumor is detected in pelvic enhanced MRI and CT within 84 days before registration and it is presumed stage I epithelial ovarian cancer (neither surgery nor biopsy for ovarian tumor before registration), both of the followings are fulfilled:
   (i) Existence of ovarian tumor with solid part which is suspected as epithelial ovarian cancer.
   (ii) No lymph node or distant metastasis by imaging examination.

(II) When incomplete staging surgery is performed on a patient with ovarian tumor by laparotomy or laparoscopic surgery within 84 days before registration, and the tumor is diagnosed as epithelial ovarian cancer histologically, the following (i)–(iv) are fulfilled:
   (i) Diagnosed as either (a), (b) or (c) by some specimens of resected ovarian tumor or biopsy at surgery within 84 days before registration
      (a) Clear cell histology (CCH)
      (b) Non-clear cell histology epithelial cancer [serous, mucinous, endometrioid] (non-CCH) Grade 1
      (c) Non-clear cell histology epithelial cancer [serous, endometrioid] (non-CCH) Grade 2
   (ii) Possibility of one of the following stage (FIGO 2014) after FSS
      (a) Clear cell histology: stage IA
      (b) Non-clear cell histology: stage IC (unilateral)
      (iii) Needing to receive re-staging surgery
      (iv) The uterus and the ovary being left

2. The patient wishes to receive FSS by informed consent
3. Keeping an ability of childbirth
4. ECOG performance status (PS) of 0 or 1
5. Measurable disease or non-measurable disease
6. No prior treatment with irradiation or chemotherapy for any malignancy
7. Adequate organ functions
8. No abnormal finding to need treatment on 12-lead ECG
9. Written informed consent by the patient of 20 years or older.
   Written informed consent by both of the patient and the parent, if the patient is under 20 years old.

Exclusion criteria
1. Simultaneous or metachronous (within 5 years) double cancers except carcinoma in situ or intramucosal tumor
2. Active systemic infections to be treated
3. Body temperature of 38°C or more
4. Women during pregnancy, possible pregnancy or breast-feeding
5. Psychiatric disease
6. Continuous systemic steroid treatment
7. Uncontrolled diabetes mellitus or routine administration of insulin
8. Uncontrolled hypertension
9. Unstable angina or prior myocardial infarction within 6 months
10. HBs antigen positive, HCV antibody positive, HIV antibody positive
11. Interstitial pneumonia, pulmonary fibrosis, severe pulmonary emphysema
12. Hypersensitivity to polyoxyethylated castor oil
13. Hypersensitivity to alcohol

Treatment methods
Surgery
If a patient has not undergone surgery to treat ovarian tumor by the time of enrollment, FSS is performed within 28 days of enrollment as the initial surgery. The standard operative procedures with optimal staging include salpingo-oophorectomy of the affected side, infracolic omentectomy, peritoneal cytology, pelvic and para-aortic lymph nodes dissection or biopsies, contralateral ovary biopsy and biopsy of various sites in the peritoneum. Biopsies of the contralateral ovary and various sites of the peritoneum are performed only when metastasis is suspected. As a general rule, one-stage surgery is recommended. However, when it is not confirmed that the patient has ovarian cancer at initial surgery, the surgery can be kept to FSS with non-optimal staging (for example, salpingo-oophorectomy of the affected side alone) and a two-stage restaging laparotomy with optimal staging can be conducted after a definitive histologic diagnosis of ovarian cancer. Restaging surgery should be performed within 56 days of the initial surgery.

When surgery with non-optimal staging was previously performed at the enrollment institution or other institution, the standard operative procedures with optimal staging will be added as restaging surgery within 28 days of enrollment.

Postoperative adjuvant chemotherapy
Patients are included in the primary analysis group when they are confirmed to have epithelial ovarian cancer with stage IA CCH or stage IC non-CCH G1/G2 after FSS with optimal staging and histological examination. Those patients receive postoperative adjuvant chemotherapy. A larger number of courses may be desirable from a prognostic viewpoint, while a smaller number of courses may be desirable from a reproductive viewpoint. Therefore, we decided, as the community consensus of JCOG Gynecologic Cancer Study Group, that four cycles of a combination therapy with paclitaxel (175 mg/m², day 1) and carboplatin (AUC = 6, day 1) are administered every 3 weeks to patients diagnosed with stage IA CCH or with stage IC1 non-CCH G1/G2 having relatively good prognosis and six cycles of the same combination therapy are administered to patients with stage IC2/3 non-CCH G1/G2 having relatively poor prognosis.

In the non-primary analysis group, postoperative therapy is not specified in the protocol. Figure 1 shows schema of this study.

Study design and statistical methods
The study is designed as a non-randomized, confirmatory (phase III) trial. The planned accrual period is 5 years, and the follow-up period is set as 10 years after completion of accrual. Patients are enrolled in this study when they wish to undergo FST. Because randomization of standard treatment including total hysterectomy, bilateral salpingo-oophorectomy and optimal staging (non-FST) vs. study treatment (FST) cannot be ethically conducted in patients who wish to undergo fertility preservation, this study is designed and conducted as a non-randomized, single-arm confirmatory study. Based on historical data, the 5-year overall survival is assumed to be 90% when standard treatment (non-FST) is performed (8,9), and the expected 5-year overall survival of the study treatment was considered to be 95%. The threshold 5-year overall survival is set at 85%. This is because the study treatment can be accepted even if it is worse than the standard treatment within 5%, considering its advantage of fertility
preservation. Using the above parameters, the required sample size for analysis (number of patients with stage IA CCH and with stage IC unilateral non-CCH G1/G2 tumor for the primary analysis) is determined to be 60 women with a one-sided significance level of 5% and power of 80%. Accounting for some patients lost to follow-up, the planned enrollment for the primary analysis is determined to be 63 women.

Based on experience in clinical practice, the ratio of the primary analysis group to the non-primary analysis group to be enrolled in this trial is expected to be ∼1:3, and the total planned enrollment is set to include 250 patients. When the enrollment of 63 or more patients for the primary analysis is attained before reaching the total planned enrollment of 250 patients, subject enrollment to this trial is to be terminated at that point. In contrast, when 63 patients for the primary analysis cannot be obtained with the enrollment of 250 patients, or when such a situation is predicted, the protocol will be revised, and total planned enrollment will be upward adjusted.

The purposes of this trial’s primary analysis are to determine whether FST can be introduced as a new standard treatment in routine medical care. FST is to be regarded as a standard treatment when (i) FST significantly exceeds the pre-determined threshold (85%) of 5-year overall survival in patients with the primary analysis group, i.e. stage IA CCH and with stage IC non-CCH G1/G2, and (ii) point estimate of lethal recurrence-free survival, a key secondary endpoint, exceeds 85%.

Overall survival, recurrence-free survival and lethal recurrence-free survival are estimated by the Kaplan–Meier method and confidence intervals are derived with the Greenwood’s formula. The
primary endpoint is evaluated with a point estimate at 5 years and its 90% confidence interval corresponding to one-sided 5% significance level.

Study monitoring
This study is a single-arm trial and its primary endpoint is 5-year overall survival. The expected number of events in this study is supposed to be small because the 5-year overall survival is expected to exceed 90%. Therefore, the interim analysis during accrual period does not seem to be effective as the safeguard and is not planned in this study. However, when the efficacy of the protocol treatment is unexpectedly low, it is necessary to terminate patient enrollment and to publish the study results early. In other words, although the primary endpoint of this study is 5-year overall survival, the study treatment should be considered problematic if many recurrences are observed unexpectedly. Therefore, when lethal recurrence is observed in 10% (≥26 patients) of the planned enrollment of 63 patients for the primary analysis with semi-annual periodic monitoring reports during the accrual period, patient enrollment is suspended, and it is to be judged by the Data and Safety Monitoring Committee whether early termination of the study is necessary. However, even in the case of early termination of accrual, 5-year follow-up after early termination of enrollment and the primary analysis is to be conducted as planned.

Participating institutions (from north to south)
Sapporo Medical University, Hokkaido University Hospital, Iwate Medical University, Tohoku University Hospital, Niigata Cancer Center Hospital, University of Tsukuba, National Cancer Center Hospital, The Jikei University School of Medicine, The University of Tokyo Hospital, Juntendo University Hospital, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Cancer Institute Hospital of Japanese Foundation for Cancer Research, NTT Medical Center Tokyo, Kitasato University School of Medicine, Keio University Hospital, The Jikei University Kashihwa Hospital, Saitama Medical University International Medical Center, National Defense Medical College, Saitama Cancer Center, Shinshu University, Shizuoka Cancer Center, Aichi Cancer Center Hospital, Nagoya University School of Medicine, Osaka City General Hospital, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka City University Hospital, Kinki University Faculty of Medicine, Sakai Hospital Kinki University Faculty of Medicine, Kyoto University Hospital, Tottori University, Hyogo Cancer Center, National Hospital Organization Kure Medical Center Chugoku Cancer Center, National Hospital Organization Shikoku Cancer Center, Kyushu University Hospital, National Hospital Organization Kyushu Cancer Center, Kurume University School of Medicine, Saga University, Kumamoto University Medical Scholl, Kagoshima City Hospital and University of the Ryukyus Hospital.

Acknowledgements
We thank JCOG Data Center and Operations Office members (A Kimura, H Kaba, H Fukuda, et al.), protocol reviewers and the Gynecologic Cancer Study Group of JCOG members who gave us great supports on drafting this protocol.

Funding
This study was supported in part by the National Cancer Center Research and Development Fund (23-A-16, 23-A-17 and 26-A-4) and the Health and Labour Sciences Research Expenses for Commission from the Ministry of Health, Labour, and Welfare of Japan (H26-Applied Research for Innovative Treatment of Cancer-General-054).

Conflict of interest statement
None declared.

References