The History of the Gynecologic Cancer Study Group (GCSG) of the Japan Clinical Oncology Group (JCOG)

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The Gynecologic Cancer Study Group (GCSG) of the Japan Clinical Oncology Group (JCOG) was organized in 1994. The GCSG has developed under the leadership of three successive group representatives, five principal study investigators, the cooperation of group members and the support of several public research funds. At present, 38 institutions are participating as active members of the GCSG of the JCOG. In addition to gynecologic oncologists, medical oncologists, pathologists and radiotherapists are participating in our group. Our group manages female genital malignancies including uterine cervical, endometrial, ovarian, tubal and vulvar cancers. Because the incidences of uterine cervical (in younger women), endometrial and ovarian cancer have increased in Japan in recent years, we are developing new standard treatments especially for these malignancies. As of 31 May 2011, our group has conducted six JCOG clinical trials (three completed and three ongoing) and completed one JCOG accompanying study, which is now in preparation for publication. Our group has also conducted several retrospective studies, and Phase I and II trials independent of the JCOG Data Center. Our aim is to conduct unique and high-quality clinical trials which we can appeal to the world. In this review, we present the organization and achievements of our group, along with a list of participating institutions, as the history of the GCSG of the JCOG.

Key words: gynecologic cancer – treatment – clinical trial

ORGANIZATION OF THE GYNECOLOGIC CANCER STUDY GROUP OF THE JAPAN CLINICAL ONCOLOGY GROUP

The Gynecologic Cancer Study Group (GCSG) of the Japan Clinical Oncology Group (JCOG) was organized in 1994 with Dr Ryuichiro Tsunematsu as the first group representative. The original members of the GCSG were also members of a study group called ‘A Study for the efficacy of dose-intensive chemotherapy for advanced ovarian cancer’, which was organized by Dr Tsunematsu as the principal investigator with the support of Grants-in-Aid for Cancer Research from the Ministry of Health, Labour and Welfare (MHLW) during the 1994–97 fiscal years. This group was taken over by a study group organized by Dr Hiroyuki Yoshikawa entitled ‘A study for the development of new treatment methods for gynecologic malignancy’, which was supported by Grants-in-Aid for Cancer Research from the Ministry of Health, Labour and Welfare (MHLW) during the 1998–2001 fiscal years. In 1998, the group representative of the GCSG of JCOG was handed over to Dr Yoshikawa from Dr Tsunematsu. In 2001, a new study group called ‘A study for the multidisciplinary treatment aiming to improve the prognosis of advanced ovarian cancer’ was organized by Dr Yoshikawa with the support of Health Sciences Research Grants for Clinical Research from the MHLW during the 2001–03 fiscal years. After 2004, this study group headed by Dr Yoshikawa was renamed ‘A study for the multidisciplinary treatment for advanced ovarian cancer’ for the
ancer drugs have been developed; some of which are effective on gynecological malignancies. Therefore, at present, in addition to surgery and radiotherapy, chemotherapy has occupied an important position in treatment. Although the prognosis of those who have gynecologic malignancies has recently been substantially improved by combining these modalities, it is still not satisfactory for some diseases. Therefore, the GCSG has conducted clinical trials to develop more effective standard treatments. Our group covers female genital malignancies including uterine cervical, endometrial, ovarian, tubal and vulvar cancers. Because the incidences of uterine cervical (in younger women), endometrial and ovarian cancer have increased rapidly in Japan in recent years, we have continued developing new standard treatments especially for these malignancies.

ACHIEVEMENTS OF THE GCSG OF THE JCOG

As of 31 May 2011, the GCSG has conducted six JCOG clinical trials (three completed and three ongoing) and completed one JCOG accompanying study, which is now in preparation for publication. Our group also conducted several retrospective studies as well as Phase I and II trials independent of the JCOG Data Center. Here, we present the main findings of our studies.

OVARIAN CANCER

JCOG9412: PHASE II STUDY OF DOSE-INTENSIVE CYCLOPHOSPHAMIDE, DOXORUBICIN AND CISPLATIN WITH GRANULOCYTE COLONY-STIMULATING FACTOR IN PATIENTS WITH ADVANCED EPITHELIAL OVARIAN CANCER (1)

We conducted a Phase II study of dose-intensive cyclophosphamide, doxorubicin and cisplatin (CAP; 750 mg/m² cyclophosphamide, 55 mg/m² doxorubicin and 75 mg/m² cisplatin) for patients with Stage III–IV suboptimally debulked ovarian cancer. The aim of this study was to assess the safety and evaluate the antitumor activity (i.e. pathological complete response) of this regimen by using second-look laparotomy. After the primary surgery, patients with residual disease (≥1 cm) were treated with dose-intensive CAP every 3 weeks for six courses. Granulocyte colony-stimulating factor was administered from day 3 at 2 µg/kg. A pathological complete response (CR) rate at the time of planned interim analysis was observed in more than 4 (the lower cut-off point) of 28 patients. In December 1996, the projected accrual was closed in order to enroll 70 patients totally. Major toxicity was Grade 4 neutropenia (76.5%) accompanied by Grade 3 neutropenic fever (8.3%) at the latest monitoring. No treatment-related deaths occurred, and no Grade 3 or 4 neurological toxicity was observed. The toxicity of this treatment was considered to be tolerable.

This study is our first JCOG study, which was started in 1994. The results were presented at the 6th Biennial Meeting of the International Gynecologic Cancer Society held in Fukuoka, Japan, in 1997.

TREATMENT MODALITIES FOR GYNECOLOGICAL MALIGNANCIES AND TARGET DISEASES FOR CLINICAL TRIALS

In contrast to other malignancies, surgery and radiotherapy used to be the gold standards for the treatment of gynecological malignancies. However, since the late 1970s, many anticancer drugs have been developed; some of which are especially for these malignancies.
JCOG0206: Feasibility Study of Neoadjuvant Chemotherapy Followed by Interval Debulking Surgery for Stage III/IV Ovarian, Tubal and Peritoneal Cancers (2,3)

We performed this feasibility study to assess the safety and efficacy of neoadjuvant chemotherapy (NAC) followed by interval debulking surgery (IDS) for müllerian carcinomas such as ovarian, tubal and peritoneal cancers to determine whether we can omit diagnostic surgical procedures before the initiation of treatment. Eligible patients were presumed to have Stage III/IV müllerian carcinomas clinically diagnosed by imaging studies, cytology and tumor markers. All patients underwent diagnostic laparoscopy to confirm the clinical diagnosis. Four cycles of paclitaxel and carboplatin were administered as NAC followed by IDS and an additional four cycles of chemotherapy. The primary endpoint was the proportion of clinical complete remission (cCR) among Stage III/IV müllerian carcinomas. The major secondary endpoint was the positive predictive value (PPV) of clinical diagnosis. Fifty-six patients were enrolled into the study between January 2003 and February 2004. The PPV of overall clinical diagnosis for the tumor origin, histology and stage was 95% (53/56). Fifty-three patients received the protocol treatment and 22 (42%) achieved cCR. The median overall and progression-free survival (PFS) was 45 and 14 months, respectively. NAC without diagnostic laparoscopy for advanced müllerian carcinomas seemed to hold sufficient promise to be compared with upfront surgery in a Phase III trial. We proceeded to Phase III studies, which are presented later (JCOG0602).

JCOG0503: Phase II Trial of Oral Etoposide and Intravenous Irinotecan for Patients with Platinum-resistant and Taxane-pre-treated Ovarian Cancer (4)

We started this study because effective chemotherapy for patients with platinum-resistant ovarian cancer is currently an unmet medical need. Oral etoposide and intravenous irinotecan as monotherapies have demonstrated some efficacy for platinum-resistant ovarian cancer. Thus, combining these two topoisomerase inhibitors is an intriguing idea. After Phase I and feasibility studies, we began a nationwide Phase II study to evaluate the safety and efficacy of this regimen for patients with platinum-resistant and taxane-pre-treated ovarian, tubal and peritoneal cancers. Eligible patients were given etoposide at 50 mg/m² p.o. from days 1–21 and irinotecan 70 mg/m² i.v. at days 1 and 15; this was repeated every 28 days for up to six cycles. The primary endpoint was response rate; the secondary endpoints were adverse events, PFS and overall survival (OS). The expected and threshold values for the primary endpoint were set at 35 and 20%, respectively. Sixty patients are to be registered from April 2009 to March 2011 in the initial plan. The study period was extended, and 42 patients were registered as of 16 May 2011. This study is currently ongoing.

JCOG0602: Phase III Trial of Upfront Debulking Surgery Versus NAC for Stage III/IV Ovarian, Tubal and Peritoneal Cancers (5)

Based on the promising results of NAC in our previous study (JCOG0206), we have been performing a Phase III study of treatment starting with NAC versus standard treatment starting with primary debulking surgery (PDS) for Stage III/IV müllerian carcinomas since November 2006. The purposes of this study are to prove the non-inferiority of the efficacy of treatment starting with NAC and to demonstrate the decrease in adverse effects and reduced invasiveness. Three hundred patients will be randomized over 3 years according to the initial plan. NAC arm patients undergo four cycles of NAC with paclitaxel plus carboplatin followed by IDS and an additional four cycles of postsurgical chemotherapy. Standard arm patients undergo PDS and eight cycles of post-surgical chemotherapy with or without IDS. The primary endpoint is OS. The major secondary endpoints are the incidence of adverse events and parameters representing surgical invasiveness. The study period was extended, and 285 patients were registered as of 16 May 2011. The study is currently ongoing.

Multicenter Retrospective Study for Prognostic Factors of Stage IV Epithelial Ovarian Cancer (6)

We conducted a multicenter retrospective analysis to elucidate the prognostic factors of Stage IV epithelial ovarian cancer (EOC). The data for all patients with Stage IV EOC that was surgically confirmed and initially treated in each institution between January 1990 and December 1997 were collected from 24 member institutions of the GCSG in November 1999. In total, 275 patients with Stage IV ovarian cancer were identified. The most common site of the extra-peritoneal disease was malignant pleural effusion (39.6%). Of the 225 patients who underwent an attempt at surgical debulking, 70 (31.1%) were optimally cytoreduced. Most patients received platinum-based combination chemotherapy for primary chemotherapy. In multivariate analysis, performance status, histology and residual disease after cytoreductive surgery were independent prognostic predictors of outcomes. The overall median survival for optimally debulked patients was 32 months compared with 16 months for suboptimally debulked patients (P < 0.0001; hazard ratio, 0.415). Optimal surgical debulking, performance status and histology appeared to be important prognostic factors of survival in patients with Stage IV EOC.

Multicenter Phase I Study of Chemotherapy Consisting of Cisplatin, Paclitaxel and Escalating Doses of Doxorubicin in Advanced Ovarian Cancer (7)

We designed a Phase I/II study in patients with advanced ovarian cancer (AOC) for first-line chemotherapy using a combination of a fixed dose of cisplatin and paclitaxel, which was the standard regimen at that time, with escalating doses of
doxorubicin, which has been shown to have favorable effects on AOC according to a meta-analysis, given at every 3 weeks. Eligible patients had Stage III or IV ovarian cancer. Dose-limiting toxicity (DLT) was defined as prolonged Grade 4 neutropenia, febrile neutropenia or non-hematologic toxicity ≥ Grade 3. Four different dose levels were planned. The dose of doxorubicin was escalated from 20 to 50 mg/m² in sequential cohorts, and fixed doses of 75 mg/m² cisplatin and 110 mg/m² paclitaxel in a 24 h infusion were tested. Between December 1998 and December 2000, 28 patients entered the study. The patients received a mean of 5.4 courses. Non-hematologic toxicity was generally mild, except for Grade 3 vomiting. No Grade 3 neurotoxicity was observed. Hematologic toxicities were Grade 3–4 neutropenia in all patients and Grade 3 anemia in 44% patients. At Level IV, two of six patients developed DLT that manifested as febrile neutropenia in two and diarrhea in one. Clinical response was observed in 17 of evaluable patients (89%). The recommended dose was at Level IV with 50 mg/m² doxorubicin. Further studies including anthracyclines for first-line chemotherapy of ovarian cancer are warranted because of its favorable antitumor activity.

Multicenter Retrospective Study for Fertility-Sparing Surgery for Stage I EOC (8)

The objective of this study was to assess the clinical outcomes and fertility in patients treated conservatively for unilateral Stage I invasive EOC. A multi-institutional retrospective investigation was undertaken to identify patients with unilateral Stage I EOC treated with fertility-sparing surgery. Favorable histology was defined as Grade 1 or 2 adenocarcinoma excluding clear cell histology. A total of 211 patients treated between 1985 and 2004 were identified from 30 institutions. The median follow-up duration was 78 months. Five-year OS and recurrence-free survival were 10 and 97.8%, respectively, for Stage IA and favorable histology (n = 108); 100 and 100%, respectively, for Stage IA and clear cell histology (n = 15); 100 and 33.3%, respectively, for Stage IA and Grade 3 (n = 3); 96.9 and 92.1%, respectively, for Stage IC and favorable histology (n = 67); 93.3 and 66.0%, respectively, for Stage IC and clear cell histology (n = 15); and 66.7 and 66.7%, respectively, for Stage IC and Grade 3 (n = 3). Forty-five (53.6%) of 84 patients who were nulliparous at surgery and married at the time of investigation gave birth to 56 healthy children. Our data confirm that fertility-sparing surgery is a safe treatment for Stage IA patients with favorable histology and suggest that Stage IA patients with clear cell histology and Stage IC patients with favorable histology could be candidates for fertility-sparing surgery followed by adjuvant chemotherapy.

Cervical Cancer

JCOG0102: Phase III Randomized Trial of NAC Followed by Radical Hysterectomy Versus Radical Hysterectomy for Bulky Stage I/II Cervical Cancer (9,10)

We compared NAC followed by radical hysterectomy (RH) with RH for bulky Stage I/II cervical cancer. Patients with Stage IB2, IIA (≥4 cm), or IIB squamous cell carcinoma of the uterine cervix were randomly assigned to receive either BOMP (7 mg bleomycin from days 1 to 5, 0.7 mg/m² vindristine on day 5, 7 mg/m² mitomycin on day 5 and 14 mg/m² cisplatin from days 1 to 5) q21 days for two to four cycles followed by RH (NAC arm) or undergo RH (RH arm). Patients with positive surgical margins, metastatic nodes, parametrical involvement and/or deep stromal invasion received post-operative irradiation. The primary endpoint was OS. Totally, 134 patients (67 NAC and 67 RH) were randomized between December 2001 and August 2005. The first planned interim analysis was performed in July 2005 using data from 108 patients registered as of November 2004. We are now preparing to publish the results of the interim analysis and the final analysis.

JCOG0505: Phase III Trial of Paclitaxel Plus Carboplatin Versus Paclitaxel Plus Cisplatin in Stage IVB, Persistent or Recurrent Cervical Cancer (11)

Paclitaxel and cisplatin is the standard regimen for treating patients with Stage IVB, persistent or recurrent cervical cancer who are not amenable to curative treatment with local therapy. However, carboplatin is expected to be more feasible than cisplatin in terms of effectiveness and toxicity management. Therefore, the aim of this randomized trial was to compare the efficacy of paclitaxel and carboplatin (TC) with that of paclitaxel and cisplatin (TP) as a control. This trial was designed to evaluate the non-inferiority of TC compared with TP. The primary endpoint is OS. The secondary endpoints are PFS, response rates, adverse events, severe adverse events and the proportion of non-hospitalization periods compared with planned treatment periods served as an indicator of quality of life. Planned accrual was completed in November 2011. Follow-up data are now being accumulated.

JCOG0806A: Multicenter Retrospective Study for Clinical and Pathological Analyses for Stage IB1 Small (<2 cm) Uterine Cervical Cancer

This study has been performed as JCOG accompanying study since 2008. The study was designed to reveal clinical outcomes and pathological findings of Stage IB1 uterine cervical cancer. Final reports of the results were issued by the data center of JCOG in August 2010. We are now preparing to publish the results as well as for a prospective study to prove the efficacy of less-invasive surgery for patients with Stage IB1 small (<2 cm) uterine cervical cancer.

Multicenter Retrospective Study for Pulmonary Metastasectomy for Uterine Cervical Cancer (12)

This study evaluated the results of the resection of pulmonary metastases from cervical cancer. Among 7748 patients with primary Stage IB or II cervical cancer who underwent curative initial treatment consisting of radical hysterectomy
or radiotherapy in 22 hospitals, pulmonary metastases detected after a disease-free period were resected from 29 (0.37%) patients with the intention to cure by 30 June 1998. The 5-year disease-free survival rate (DFS) after pulmonary metastasectomy for all patients was 32.9%. Patients with one or two pulmonary metastases had a 5-year DFS of 42.2% compared with 0% for patients with three or four metastases \( (P = 0.0003) \). Patients with squamous cell cancers (SCC) had a 5-year DFS of 47.4% compared with 0% for patients with adenosquamous cell cancers or adenocarcinoma \( (P = 0.0141) \). In multivariate analysis, the significant prognostic variables for DFS were less than or equal to two metastases \( (P = 0.0232) \) and SCC \( (P = 0.0168) \). Cervical cancer patients with pulmonary metastases after successful initial treatment can be expected to achieve long-term DFS by pulmonary metastasectomy when there are less than or equal to two metastases and the histology is SCC.

**Endometrial Cancer**

**Multicenter Retrospective Study for Conservative Therapy for Endometrioid Adenocarcinoma and Atypical Endometrial Hyperplasia of the Endometrium in Young Women (13)**

Thirty-nine patients with endometrioid adenocarcinoma (EA) and atypical endometrial hyperplasia (AH) of the endometrium who received conservative treatment to preserve fertility were collected from member institutions of the GCSG. The institutional diagnosis of EA in 29 patients was changed to AH in 10, complex hyperplasia in 3 and atypical polypoid adenomyoma in 3; the diagnosis of AH in 10 patients was changed to EA in 1 and simple hyperplasia in 1 by a central pathological review. Nine of 12 women (75%) with EA and 15 of 18 women (83%) with AH had initially responded to medroxyprogesterone acetate (MPA) treatment. Two of nine responders with EA later developed relapse and one of them had a lymph node metastasis. Two became pregnant and one delivered one full-term infant. One of the responders with AH had a relapse in the endometrium. Five became pregnant and four delivered four normal infants. Young women with EA localized in the endometrium who wish to preserve their fertility may be treated as successfully with MPA as those with AH. Based on the results, we conducted the Phase II study presented below.

**Multicenter Phase II Study of Fertility-sparing Treatment with MPA for EA and AH in Young Women (14)**

This multicenter prospective study was carried out at 16 institutions to assess the efficacy of fertility-sparing treatment using MPA for EA and AH in young women. Twenty-eight patients presumed to have Stage IA EA and 17 patients with AH who were <40 years of age were enrolled. All patients were given a daily oral dose of 600 mg MPA with low-dose aspirin. This treatment continued for 26 weeks as long as the patients responded. Either estrogen–progestin therapy or fertility treatment was provided for the responders after MPA therapy. The primary endpoint was a pathological CR rate. Toxicity, pregnancy rate and PFS were the secondary endpoints. CR was found in 55% of EA cases and 82% of AH cases; the overall CR rate was 67%. Neither therapeutic death nor irreversible toxicities were observed. During the 3-year follow-up period, 12 pregnancies and 7 normal deliveries were achieved after MPA therapy. Fourteen recurrences were found in 30 patients (47%) between 7 and 36 months. The efficacy of fertility-sparing treatment with a high dose of MPA for EA and AH was proven by this prospective trial. However, even in responders, close follow-up is required because of the substantial rate of recurrence.

**Future Perspectives of the GCSG of the JCOG**

We are now planning to conduct several studies such as less invasive surgery for Stage IB1 uterine cervical cancer, maintenance chemotherapy following concurrent chemoradiotherapy for locally advanced uterine cervical cancer and chemotherapy for uterine leiomyosarcoma. So far, we have not had an opportunity to collaborate with foreign societies. However, in the future, we would like to make a protocol that interests foreign societies. We hope that the GCSG will develop better treatments for women who suffer from gynecologic cancer via unique and high-quality clinical trials.

**Participating Institutions (As of 31 May 2011)**

Hokkaido University, Sapporo Medical University, Iwate Medical University, Tohoku University, University of Tsukuba, National Defense Medical College, Saitama Cancer Center, Saitama Medical Center, The Jikei University Kashiiwa Hospital, National Cancer Center Hospital, Tokyo Metropolitan Cancer and Infectious diseases Center Komagome Hospital, The Jikei University School of Medicine, Cancer Institute Hospital, The University of Tokyo, Juntendo University, NTT Medical Center Tokyo, Kitasato University, Niigata Cancer Center Hospital, Shinshu University, Aichi Cancer Center, Nagoya University, Kyoto University, Osaka City University, Kinki University, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka City General Hospital, Sakai Hospital Kinki University Faculty of medicine, Hyogo Cancer Center, Tottori University, National Hospital Organization Kure Medical Center, National Hospital Organization Shikoku Cancer Center, National Hospital Organization Kyushu Cancer Center, Kurume University, Kyushu University, Saga University, Kumamoto University, Kagoshima City Hospital and University of the Ryukyus.

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Conflict of interest statement

None declared.

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