

Newsletter of the Japanese Gynecologic Oncology Group (JGOG)

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The Ovarian Cancer Committee: Research results and future trials that we expect

Kazunori Ochiai, M.D., Ph.D. President, JGOG

The Ovarian Cancer Committee, which is among the JGOG tumor committees, has greatly contributed to gynecologic cancer therapy not only domestically but also internationally. What was remarkable may be results of JGOG3016. As you are aware, it is no exaggeration to say that the progress of standard chemotherapies in the ovarian cancer field is a history of chemotherapy itself. In other words, standard therapies comprise surgical therapy followed by chemotherapy whose efficacy itself directly affects progression free survival as well as overall survival. Nevertheless, progression free survival is set as primary endpoint in the majority of clinical trials. This endpoint setting is based on the view that verification of the efficacy of an experimental arm is invalidated if overall survival is an endpoint because survival is influenced by post-recurrence treatment. However, the ultimate objective of cancer therapy is an improvement of overall survival but not of progression free survival since cancer patients never expect cancer therapy to let them go into transient remission: they want it to extend their life span.

If so, then, among numerous ever tried clinical chemotherapies for ovarian cancer and the like, has any improved overall survival? Yes, it was an arm of paclitaxel + cisplatin of the GOG111 trial, which was significantly better than the conventional standard regimen of cyclophosphamide + cisplatin. Overall survival has been improved by the JGOG3016 trial as well. The dose-dense weekly TC of this trial significantly surpassed the conventional tri-weekly TC in overall survival. We

flatter ourselves that these results gave rise to controversy in the history of world-wide ovarian cancer chemotherapies. We hope studies equivalent to the JGOG3016 trial will be executed across the world to verify our results so that the JGOG3016 regimen will be established as standard therapy.



Report of the 9th Korea-Japan Gynecologic Cancer Joint Meeting

Joo-Hyun Nam, M.D., Ph.D. President, KGOG

The 9th Korea-Japan Gynecologic Cancer Joint Meeting was held in Seoul on November 3, 2011 just before the 2nd biennial meeting of Asian Society of Gynecologic Oncology (ASGO). Since the 1st Korea-Japan Gynecologic Cancer Joint Meeting in Seoul, October 22, 2002 during the 9th International Gynecologic Cancer Society (IGCS) meeting, Korea-Japan Gynecologic Cancer Joint Meetings have been held alternately in Korea and Japan every year until the 8th joint meeting in Tokyo in 2009. From the 9th joint meeting of this year on, Gynecologic Cancer Joint Meetings are supposed to be held in every other year together with the biennial meeting of ASGO at the same place.

In this joint meeting, one each protocol from two countries in cervix, ovary and uterine corpus cancer were introduced and discussed. The agenda of the meeting is shown below. We could reach the conclusion that two countries will be able to participate in some interesting protocols each other, particularly JGOG 3019/iPocc trial and KGOG 1029.

I'd like to cite "DISCUSSION AND FUTURE PERSPECTIVES" by professor Hee-Sug Ryu and Toru Sugiyama which was recently published in Journal of Gynecologic Oncology, January 2012.

There are several trials proposed by Korean Gynecologic Oncology Group (KGOG). Two trials of cervical cancer were initiated by Dr. Sang Young Ryu, GOG 263, and TACO trial. GOG 263 is a randomized phase III trial of adjuvant radiation versus chemoradiation in intermediate risk, stage I/IIA cervical cancer treated with initial radical hysterectomy and pelvic lymphadenectomy. TACO



(GCIG/KGOG 1027) is a randomized trial of weekly versus tri-weekly cisplatin based chemoradiation in locally advanced cervical cancer. Dr. Sokbom Kang and Professor Noriaki Sakuragi are collaborating for a cross-validation study to develop preoperative criteria identifying for low-risk group of lymph node metastasis in endometrial cancer. Regarding ovarian cancer, professor Byoung-Gie Kim suggested a translational research on clear cell carcinoma, which needs consortium of several countries with high prevalence of the disease, and sharing of tissue samples and co-work between Japan, Taiwan, and Korea. Lastly, future perspectives of this Korea-Japan Joint meeting include: deepening our friendships, sharing other's scientific achievements, co-work for mutual clinical protocols, developing cancer treatment guidelines together, and exchange programs for faculties and residents. I would like to express my heartiest gratitude to Japan Gynecologic Oncology Group (JGOG) who graciously accepted our invitation to share their expertise in the field of gynecologic oncology (presented by Professor Hee-Sug Ryu). JGOG desires to work together with KGOG more closely through this Korea-Japan Gynecologic Cancer Joint Meeting. In Korea and Japan, neoadjuvant chemotherapy followed by radical hysterectomy for stage I/II cervical cancer with

Agenda of the 9th Korea-Japan Gynecologic Cancer Joint Meeting

Opening remarks & introduction

Joo-Hyun Nam (*President of KGOG, Univ. of Ulsan*) & Kazunori Ochiai (*President of JGOG, The Jikei Univ.*)

Part 1: Ovary session

Chaired by Byoung-Gie Kim (*Sungkyunkwan Univ.*) & Mitsuaki Suzuki (*Jichi Medical Univ.*)

- KGOG 3022: Multi-center, retrospective study of image-based prediction model for surgical cytoreduction in advanced ovarian cancer, Sokbom Kang (*National Cancer Center*)
- JGOG 3019/iPocc trial: A randomized phase II/III trial of weekly IV versus tri-weekly IP carboplatin both in combination with weekly IV paclitaxel for newly diagnosed epithelial ovarian, fallopian tube, and primary peritoneal cancer, Keiichi Fujiwara (*Saitama Med Univ. Int Med Center*)

Part 2 : Cervix session

Chaired by Sang Young Ryu (*Korea Cancer Center Hospital*) & Mikio Mikami (*Tokai Univ.*)

- KGOG 1029: A randomized controlled trial comparing radical hysterectomy plus tailored adjuvant therapy versus primary chemoradiation therapy in bulky early-stage cervical cancer, Jeong Yeol Park (*Univ. of Ulsan*)
- JGOG 1065: The utility of neoadjuvant chemotherapy using irinotecan hydrochloride (CPT-11) and nedaplatin (NDP) for the bulky but operable cancer with the uterine cervix, Ken Takizawa (*The Cancer Institute Hospital of JFCR*)

Part 3 : Uterine corpus session

Chaired by Jae Weon Kim (*Seoul National Univ.*) & Toshiaki Saito (*National Kyushu Cancer Center*)

- KGOG 2006: Management of endometrial hyperplasia with a levonorgestrel-releasing intrauterine system: single arm, prospective multicenter study, Seok-Ju Seong (*CHA Univ.*)
- Japanese trial: A randomized phase II/III trial of dose-dense weekly paclitaxel plus carboplatin versus tri-weekly paclitaxel plus carboplatin in chemo-naive patients with stage I-IV, persistent, or recurrent carcinoma of the uterus, Takeo Otsuki (*Tohoku Univ.*)

Discussion and future perspectives

Hee-Sug Ryu (*Ajou Univ.*) & Toru Sugiyama (*Iwate Medical Univ.*)

Closing remarks

Ikuo Konishi (*Kyoto Univ.*) & Soon-Beom Kang (*Seoul National Univ.*)

a bulky mass and chemoradiation for advanced disease have been important subjects for research (JGOG 1065, KGOG 1029, and GOG 263). JGOG 2043, a randomized study on adjuvant chemotherapy of Paclitaxel/Carboplatin and Docetaxel/Cisplatin compared with a control therapy Adriamycin/Cisplatin in endometrial cancer, is in the process of being analyzed. The results are expected to have a great impact on the management of endometrial cancer around the world. In ovarian cancer, we have completed an international cooperative phase III study of clear cell carcinoma of ovary (JGOG 3017) in cooperation with KGOG and expect the analysis results will be presented at American Society of Clinical Oncology 3 years later. Another clinical trial of ovarian clear cell carcinoma, GOG 268, is now underway in full scale. In addition, based on the promising result of phase II clinical trial of Olaparib, a phase III clinical trial of ovarian cancer for poly (ADP-ribose) polymerase (PARP) inhibitor was proposed. Professor Fujiwara remarked our effort for the standardization of intraperitoneal chemotherapy in ovarian cancer (JGOG 3019/iPocc trial). Finally, we expect the ceaseless collaboration between KGOG and JGOG to be much closer in the future (presented by Professor Toru Sugiyama).

Strategy against gynecologic cancer: past, present, and future.
-Ovarian Cancer Committee-



The past trials of the ovarian cancer committee

Fumitaka Kikkawa, M.D., Ph.D. Former Chairperson, Ovarian Cancer Committee

Six studies have been conducted by the ovarian cancer committee since 2002, as shown in the table. Four finished studies were reported at international meetings and in journals, and two studies are now ongoing.

Protocol No.	Study name	Phase
JGOG3014	Randomized phase II trial of paclitaxel plus carboplatin therapy versus irinotecan plus cisplatin therapy as first-line chemotherapy for clear-cell adenocarcinoma of the ovary.	II
JGOG3015	Phase II study of irinotecan / docetaxel in paclitaxel / carboplatin or cisplatin-resistant ovarian cancer	II
JGOG3016	Randomized phase III trial of conventional paclitaxel and carboplatin (c-TC) versus dose-dense weekly paclitaxel and carboplatin (dd-TC) in women with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer:	III
JGOG3017	Randomized phase III trial of paclitaxel plus carboplatin (TC) therapy versus irinotecan plus cisplatin (CPT-P) therapy as a first-line chemotherapy for clear-cell carcinoma of the ovary	III
JGOG3018	Randomized comparative phase III study of liposomal doxorubicin (PLD) at 40 and 50 mg/m ² for platinum-resistant mullerian carcinoma	III
JGOG3019	Phase II/III study of weekly paclitaxel and triweekly intravenous carboplatin or intraperitoneal carboplatin for epithelial ovarian cancer, fallopian tube cancer, and primary peritoneal cancer	II/III

The incidence of ovarian clear-cell adenocarcinoma of the ovary accounts for 20%-25% of epithelial ovarian cancer in Japan. This tumor is resistant to anticancer drugs, and even a gold standard regimen (paclitaxel + carboplatin) has little effect on survival. Therefore, we conducted a phase II trial, listed as JGOG3014 (cisplatin + irinotecan vs paclitaxel + carboplatin). This trial showed that the progression-free survival tended to be longer in the cisplatin + irinotecan group compared to the paclitaxel + carboplatin group in patients with clear cell adenocarcinoma of the ovary, although the difference was not statistically significant. The results of JGOG3014 were published in the *International Journal of Gynecological Cancer* (2010; 20: 240-47). The Gynecologic Cancer Intergroup recognized the possibility

of this protocol for clear-cell adenocarcinoma and started an international study, known as GCIG/JGOG3017, in April 2009.

Paclitaxel is a very promising anticancer drug that was under development for a long time as part of an effort to develop a new generation of clinically effective anticancer drugs that could supplement the platinum drugs. Therefore, we chose to administer higher doses of paclitaxel (dose-dense) in a randomized phase III trial, known as JGOG3016, which was conducted to compare weekly paclitaxel + carboplatin (conventional) and paclitaxel + carboplatin (dose-dense). The results showed that the median progression-free survival was longer in the dose-dense group than in the conventional group (28.0 months vs 17.2

months, $p=0.0015$), and the study was published in *Lancet* (2009;374:1331-8). This study impacted on the study groups on gynecological oncology worldwide, and other groups have planned the same study to verify our data.

JGOG is the biggest among the Japanese study groups on gynecological oncology. We have aimed at assembling a high quality study group in order to present reliable data on ovarian cancer treatment to the scientific community, and several studies have been published in international journals. We will cooperate positively with the international study groups, and make further new data available in the future.

Strategy against gynecologic cancer: past, present, and future.
-Ovarian Cancer Committee-



Currently ongoing clinical trial
JGOG3019 (iPocc) Trial

Keiichi Fujiwara, M.D., Ph.D. Studychairperson, JGOG3019 (iPocc) Trial

I would like to introduce our new ovarian cancer study, the JGOG-3019 Trial (iPocc Trial), in which we are exploring the efficacy and safety of intraperitoneal chemotherapy in ovarian cancer. As all of you well know, the most significant characteristic feature of ovarian cancer is the intraperitoneal dissemination at an early stage. Therefore, it is reasonable to consider intraperitoneal (IP) chemotherapy for this disease entity.

The primary concept of IP chemotherapy is to expose the tumor tissue directly to an extremely high concentration of anticancer agents by perfusing inside the peritoneal cavity. IP chemotherapy has been investigated for many years. So far, there have been three large-scale randomized trials conducted in the US, and all of them

showed overall and/or progression-free survival benefits. To further explore these results, the National Cancer Institute (NCI) and GOG have conducted a meta-analysis [on the results] of these three US trials and other phase III trials of IP versus IV chemotherapy, which showed that IP therapy was associated with a significant improvement of survival. Based on this meta-analysis, NCI released a clinical announcement in 2006 that encouraged the gynecological oncology community to consider using IP chemotherapy with cisplatin as the standard treatment in advanced ovarian cancer patients in whom the residual disease was debulked to 1 cm or less. Unfortunately, however, IP chemotherapy has not been adopted as a standard care because several controversial issues have to be resolved.

The most significant survival benefit was shown in the GOG172 trial, however, a major drawback in this trial is that the agent for IP chemotherapy was cisplatin, which is more toxic and more difficult to manage compared to carboplatin. Therefore, it is important to explore whether carboplatin can replace cisplatin in the IP use. We have conducted several studies before the JGOG3019 trial was started. Those studies have demonstrated that the use of carboplatin in IP chemotherapy would be feasible.

Currently, three ongoing large-scale randomized trials examine the efficacy of carboplatin-based IP chemotherapy; they are named GOG252, OV-21, and iPocc. Among them, the simplest study is the iPocc Trial.

In the iPocc Trial, efficacy and toxicity of IP vs IV carboplatin are compared in combination with dose-dense weekly paclitaxel at 80 mg/m². Carboplatin is administered every 3 weeks at AUC 6. In this study, eligible patients are those with epithelial ovarian cancer at stages of II to IV, thus, this study will explore the potential of IP chemotherapy in suboptimal advanced ovarian cancer, not only in optimally debulked cases.

The classical concept of IP chemotherapy is a local therapy in which there is direct contact between cancer cells and anticancer drugs, and it is believed that direct penetration of

the agents is limited to a few millimeters from the tumor surface. However, it has been suggested that carboplatin administered into the IP cavity is absorbed from the peritoneal surface within 24 hours, and that serum platinum AUC is exactly the same as serum platinum AUC after IV administration, although platinum AUC in the IP cavity was 17 times higher when carboplatin was given IP than it was after IV administration. It has been demonstrated in a phase II trial that the use of IP carboplatin for suboptimal residual cases was also feasible; therefore, the iPocc Trial is also challenging this important scientific question.

The iPocc Trial has just opened to international study groups such as KGOG or AGO Austria. Our data center, Kitasato Clinical Trial Coordinating Center, has developed a Web-based registration-randomization system. Data entry will be electronically captured using the RAVE system. Contracts are also being processed with individual hospitals in Singapore, Australia, and Spain. The target accrual is 746 patients, and currently approximately 100 patients have been enrolled, and we encourage the international gynecologic oncology trial community to participate in this important trial.

Strategy against gynecologic cancer: past, present, and future. -Ovarian Cancer Committee-



Future study

A phase III randomized clinical trial concerning the necessity of adjuvant chemotherapy for epithelial ovarian cancer surgically staged as I : JGOG 3020

Mitsuaki Suzuki, M.D., Ph.D. Chairperson, Ovarian Cancer Committee

Our committee is now planning a clinical trial for ovarian cancer, which is named “A randomized phase III comparative study to see a need for adjuvant chemotherapy in epithelial ovarian cancer cases surgically staged as I.”

The prognosis of patients with stage I ovarian cancer is fairly good. Nevertheless, additional adjuvant chemotherapy has been standardized. There are two large-scale comparative studies which explored the efficacy of adjuvant chemotherapy in early-phase (phase I or II) ovarian cancer: EORTC-ACTION and ICON1. When these two studies were analyzed together after their combination, the 5-year overall survival (OS) of 82% was better in the adjuvant chemotherapy group than OS of 74% in the non-adjuvant chemotherapy group (hazard ratio was 0.67). However, when analysis was restricted to the subset group that underwent staging surgery (34% of the total cases) in EORTC-ACTION, there was no significant

difference in OS between the adjuvant and non-adjuvant chemotherapy groups. Cochrane Reviews addressed this issue in 2009, concluding that adjuvant chemotherapy was hardly efficacious for surgically proven phase I ovarian cancer. If this were true, sparing such a case adjuvant chemotherapy would benefit the patient's QOL as well as medical economics. We were thus prompted to plan this clinical trial.

Eligibility criteria are either ‘Ia or Ib (grade 2/3) or Ic(b) among stage I epithelial ovarian cancers (FIGO, 1988)’ or ‘clear cell adenocarcinoma,’ and surgical staging including intraperitoneal cytology, peritoneal biopsies, and dissection of retroperitoneal lymph nodes inclusive of 326 b1 in addition to the basic surgical technique (TAH + BSO + omentectomy).

Cases that meet the above criteria are randomly allocated to two groups: an adjuvant chemotherapy (+) group that

are treated with carboplatin AUC6 + paclitaxel 175 mg/m² every 3 weeks for 3-6 cycles and an adjuvant chemotherapy (-) group. The primary end point is OS while the secondary end points are relapse free survival (RFS), the incidence of adverse events and complications etc.

This clinical trial is expected to define indications of adjuvant chemotherapy in cases with stage I epithelial ovarian cancer, thus solving the clinical question. We think it is a worthwhile clinical trial that will improve the patient's QOL.

Our committee is planning another clinical trial, which is a phase II clinical trial of an mTOR inhibitor (everolims) against recurrent clear cell ovarian cancer. We hope that clinical trials of molecularly targeted drugs will be started for the treatment of intractable ovarian cancer since our country is delayed in the introduction of molecularly targeted drugs.



Report of the 10th Annual Meeting of Japanese Gynecologic Oncology Group

Masayuki Hatae, M.D., Ph.D. Vice President, JGOG

We believe that the 10th annual meeting of JGOG was taken place smoothly with high-quality contents despite a short and heavy schedule. Although we think that the morning meeting was perfectly successful in what was business affairs as well as gaining approval in the general assembly, I have to admit that the schedule was so tight. Therefore, I should give the schedule careful reconsideration for the next annual meeting.

2011 business report

In the first session of the annual meeting, Dr. Udagawa, Vice President, presented 2011 business report which included reports from each committee covering a period of October of 2010 to September of 2011. All the business report was approved.

2012 business plan

We would like to explain about a proposal of the business plan of this year. The most important goal

of the JGOG is “to execute high-quality clinical trials.” We will promote the project of clinical trials more efficiently and continuously to produce results that are acceptable as international standards. An outline of clinical trial status is shown in Table 1 while clinical trials being currently planned are listed in Table 2.



Table 1 List of clinical trials (JGOG clinical trials now in the process of case enrollment)

Protocol No.	Target cancer	Therapy	Trial period	Target number of patients
JGOG1067	Uterine cervical cancer Stage Ib/IIa. Lymph node metastasis (+)	Phase II trial of adjuvant chemotherapy using irinotecan hydrochloride hydrate (CPT-11)/nedaplatin (NDP)	January 2010 to December 2011	63
JGOG3018	Recurrent platinum-resistant Mullerian carcinoma (epithelial ovarian cancer, primary fallopian tube cancer, peritoneal cancer)	Phase II randomized comparative study: 50 vs. 40 mg/m ² of liposomal doxorubicin (PLD)	February 2010 to January 2013	206 for each group 412 in total
JGOG3019	Epithelial ovarian cancer, fallopian tube cancer, primary peritoneal cancer	Phase II/III randomized trial: i.v. paclitaxel every week plus i.v. carboplatin every 3 weeks vs. i.v. paclitaxel every week plus intraperitoneal carboplatin every 3 weeks.	May 2010 to April 2013 (scheduled)	60 for each group (phase II, 120 in subtotal) 313 for each group (phase III, 626 in subtotal) 746 in total
				As of December 5, 2011

Table 2 JGOG clinical trials under contemplation

Uterine cervical cancer				
Protocol No.	Study name	Phase	Outline	Target number of patients
JGOG1068	Phase I clinical trial of adjuvant chemotherapy combined with CPT-11-NDP(Nedaplatin) in patients with local advanced uterine cervicalcancer (Ib2-IVa) post-concurrent chemoradiotherapy	I	Exploration of recommended doses for chemotherapy post-RT or -CCRT	Up to 24
Endometrial cancer				
Protocol No.	Study name	Phase	Outline	Target number of patients
To be assigned	Phase II clinical trial of tumor resection after chemotherapy-induced remission in endometrial cancer in the stage of FIGO IVb	II	Verification of efficacy and safety of tumor resection in advanced endometrial cancer after remission introduced by chemotherapy	40
To be assigned	Phase II/III randomized clinical comparative trial of adjuvant chemotherapy and post-recurrence chemotherapy using dose-dense TC or conventional TC regimen	II and III	Efficacy comparison between dose-dense and conventional TC regimens in adjuvant and post-recurrence chemotherapy	400
Ovarian cancer				
Protocol No.	Study name	Phase	Outline	Target number of patients
JGOG3020	Phase III randomized clinical trial to explore the necessity of adjuvant chemotherapy in epithelial ovarian cancer in the surgical stage I	III	Comparison of CP regimen as adjuvant chemotherapy with no further treatment	610
To be assigned	Phase II clinical trial of everolimus in recurrent ovarian clear cell adenocarcinoma	II	Exploration of clinical efficacy of everolimus in recurrent clear cell adenocarcinoma	30

Editorial postscript



The cherry blossoms in Kyoto

The morbidity rate of ovarian cancer has been increasing in Japan. Since most cases of this disease are diagnosed at an advanced stage, gynecological oncologists depend on chemotherapy for treatment of patients with ovarian cancer. The Ovarian Cancer Committee of JGOG has conducted several studies in order to establish a better regimen of chemotherapy. In this issue, we focus on past, present, and future activities of the Ovarian Cancer Committee. Six studies were conducted, and the results of JGOG3014 and 3016 were published in the *International Journal of Gynecological Cancer* and in *Lancet*. Recently, JGOG has joined the international trials, and proposed our study plan. JGOG3017 was accepted by the Gynecologic Cancer Inter Group (GCIG) as an international study (GCIG/JGOG3017). We are very pleased with this acceptance. Our ongoing and future studies are also promising trials for treatment of ovarian cancer patients.

Fumitaka Kikkawa, M.D., Ph.D.
Chairperson, Public Relation Committee



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