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Newsletter of the Japanese Gynecologic Oncology Group (JGOG)

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Greetings from the President

Toru Sugiyama, M.D., Ph.D. President, JGOG

The non-profit Japanese Gynecologic Oncology Group (JGOG) is a clinical research group that works with major universities and cancer centers throughout the country in an effort to establish the optimal and latest diagnostic and therapeutic methods for patients with gynecologic malignancies.

The JGOG conducts collaborative studies with clinical research groups, including the Gynecologic Oncology Group (GOG) of the United States and the Gynecologic Cancer Intergroup (GCIG), a global association of organizations. High-quality data from these studies have appeared in treatment guidelines around the world and have become recognized as standard therapies.

I believe we can propose the evidence with impact from Asia to worldwide if cooperative studies are conducted in Asian major countries.

JGOG accumulates, manages, and stores anonymized patient data securely and with the patients' consent at the Data Center (Kitasato Academic Research Organization), which is independent of the JGOG. The analyzed results are disclosed to researchers after the trial is complete. Then, we present the results at conferences and in the literature to disseminate the findings to the world.

If we can obtain statistically better therapeutic results than those in the past, the new therapy becomes the new standard treatment. The purpose of our clinical studies, which are conducted rigorously from the multi-occupational perspectives of patients, researchers (health practitioners), clinical research coordinators (CRCs), and biostatisticians at the Data Center, as well as commercial and business professionals, is to deliver the most effective treatment to the patients.

Despite its long history, since 2002, the JGOG has been promoting restructuring as a non-profit organization in Tokyo, and reinforcing its activities as a more rigorous clinical

research group.

As of January 2015, the JGOG is comprised of 1000 members and 197 participating institutions that have met the most stringent standards for certification. As mentioned above, the most significant role of the JGOG is to conduct multi-institutional clinical research projects, or, in other words, to conduct clinical research of significance and provide the patients around the world who suffer from gynecologic malignancies with better treatment options.

To be more specific, the research projects consist of committees, including the Cervical Cancer (Vulva Cancer) Committee, Uterine Cancer Committee, and Ovarian Cancer Committee, as well as the Supportive and Palliative Care Committee, Radiotherapy Committee, and Pathology Review Committee, that create stricter protocols by working with the Data Center and considering the patients' perspectives. Internally, the Protocol Review and Evaluation Committee and independent inspectors enter the participating institutions periodically to determine if the appropriate protocol treatments are being provided. This is a similar approach as that of collaborative trials with the American GOG and the GCIG.

A second goal of the JGOG is to provide educational projects for young clinical researchers. Each year, we select a number of young researchers to participate in a 3-day seminar where they participate in heart-to-heart discussions on such issues as "What is clinical research?," "How do we conduct clinical research?" and "What are medical ethics?". In addition, during the seminar, young doctors create protocols.

Further, the JGOG provides short-term overseas training for young physicians, open lectures, and support for events including "the Gynecologic Cancer Conference," which promotes clinical studies. Our fostering of young investigators of gynecologic cancers is making solid progress, and this effort can be expected to lead to better health care in the future. Clinical studies require substantial funding, and, in Western countries, public funds are provided after rigorous screening.

In contrast, the injection of public funds is limited under the current Japanese system. In addition to membership fees, donations from businesses (supporting members) that understand the significance of our clinical studies become the primary source of the project funds, such as the costs of the Data Center, the Head Office, and educational projects. In recent years, we have read disturbing reports of misconduct in clinical research. However, the researchers and supporting businesses involved in JGOG clinical research are prohibited from managing or analyzing its data.

We receive the securely-managed results from the Data Center and deliver them to the patients. These high-quality data is the valuable treasure that is returned to future patients and to us as researchers, and is our motivation in these endeavors. JGOG hopes to reinforce its structure, to raise the awareness of its members and institutional personnel, and to achieve maximum results from the limited resources available.

The third goal of the JGOG is to share all perspectives. I would like to ask for further efforts by all persons concerned, as well as for the understanding of my fellow citizens.

Finally, I would like to introduce a quote from Inazo Nitobe, a native of Iwate, that agrees with JGOG's ideals and goals:

"We must show the world that even if we do not have abundant funds, things done out of the right motivation will succeed handsomely in this manner."

Dies Faustus, January 2015

JGOG's activities

Report of the 13th Annual Meeting of JGOG

Nobuhiro Takeshima, M.D., Ph.D. Vice President, JGOG

The Japanese Gynecologic Oncology Group (JGOG) held its 13th annual meeting on December 5, 2014 in Kokuyo hall (Shinagawa, Tokyo). Dr. Kazunori Ochiai, President of JGOG, delivered the opening address.

In the morning, several committee reports were presented. The educational committee suggested possible new clinical trials, for various gynecologic malignancies, that had been discussed among young doctors. Then, the financial committee reported the end of year figures for 2014 and the new budget for 2015 was approved. The financial position in 2014 was tight, but these financial difficulties are expected to be reduced next year.

In the afternoon, the current state of international clinical trials was presented (GOG Japan, GCIG, AGOG etc), and future plans for these trials were discussed. Then, JGOG domestic clinical trials were reviewed and their progress was thoroughly analysed. New clinical trials were also presented in relation to ovarian cancer, endometrial cancer, cervical cancer, and anti-nausea drugs. An open discussion was then held on these new ideas. At the end of the meeting, a seminar on ethics was conducted. The seminar was performed by Dr. Tamura and focussed on the genetics of cancer treatment.

The meeting progressed smoothly despite having a tight schedule. Two hundred and twenty doctors from all over the country participated in this meeting. In the closing remarks by Dr. Junzo Kigawa, Dr. Toru Sugiyama was introduced as the new president of JGOG.

JGOG's activities

Recent Activity of the JGOG: Publications, ongoing and recently closed studies

Takayuki Enomoto, M.D., Ph.D., Vice President, JGOG

Since last year (2014), six papers have been published from JGOG studies (three clinical trials, two surveillance studies and one translational research study) (**Table 1**).

From the Cervical Cancer Committee, four papers have been published. Mikami *et al.* conducted a survey of current operative management protocols for bulky uterine cervical cancers (FIGO stages IB2, IIA2 and IIB) being practiced at active JGOG member institutions. They found that surgery was being performed for stage IIB cervical cancer at 54% (88 of 164) of our institutions, which appears to be more frequently than in most other equivalent countries. Adjuvant chemotherapy was given to intermediate risk patients at 20% of JGOG institutions, and given to high risk patients at 33% of institutions.

Iwata *et al.* evaluated high-risk HPV DNA testing for high-grade cervical intraepithelial neoplasia (CIN) lesions using the cobas® HPV Test and diagnostic HPV16/18 genotyping in Japanese women with low-grade squamous intraepithelial lesions. They concluded that high-risk HPV16/18 genotyping, used for women older than 40, who are at increased risk of high-grade CIN lesions, might help them avoid undergoing unnecessary colposcopy or overtreatment of non-progressive lesions.

Table 1　JGOG - Publications since 2014

Protocol No.	Site	Title	Type of Research	Author and Journal
DT105	Cervix	Human Papillomavirus test for triage of Japanese women with low-grade squamous intraepithelial lesions.	Clinical Trial	Iwata T et al. Reprod Sci 2015; Jun 19. pii:193371911 5589408.
1073	Cervix	Performance of p16INK4a/Ki-67 immunocytochemistry for identifying CIN2+ in atypical squamous cells of undetermined significance and low-grade squamous intraepithelial lesion specimens: a Japanese Gynecologic Oncology Group study.	Translational Research	Fujii T et al. Int J Clin Oncol 2015; 20:134-42.
1069S	Cervix	Surgical principles for managing stage IB2, IIA2, and IIB uterine cervical cancer (bulky tumors) in Japan: a survey of the Japanese Gynecologic Oncology Group.	Survey	Mikami M et al. Int J Gynecol Cancer 2014; 24:1333-40.
DT101	Cervix	Phase III placebo-controlled double-blind randomized trial of radiotherapy for stage IIB-IVA cervical cancer with or without immunomodulator Z-100: a JGOG study.	Clinical Trial	Sugiyama T et al. Ann Oncol 2014; 25:1011-7.
2048S	Corpus	Prognostic factors in patients with uterine carcinosarcoma: a multi-institutional retrospective study from the Japanese Gynecologic Oncology Group.	Survey	Harano K et al. Int J Clin Oncol 2015; DOI 10. 1007/s10147-015-0859-7
3016 Additional Analysis	Ovary	Quality-of-life outcomes from a randomized phase III trial of dose-dense weekly paclitaxel and carboplatin compared with conventional paclitaxel and carboplatin as a first-line treatment for stage II-IV ovarian cancer: Japanese Gynecologic Oncology Group Trial (JGOG3016).	Clinical Trial	Harano K et al. Ann Oncol 2014; 25:251-7.

Table 2　JGOG - Active clinical trials and surveys

Protocol No.	Study Name	Site	Study Design
1074	Multicenter randomized Phase III trial of Concurrent Chemoradiotherapy (CCRT) with cisplatin versus CCRT with cisplatin and paclitaxel for locally advanced adenocarcinoma of the uterine cervix	Cervix	Randomized P III
1075S	Clinicopathologic features and treatment outcomes of vulvar cancer in Japan	Cervix	Survey
2046	A feasibility study of hysterectomy and bilateral salpingo-oophorectomy after preoperative chemotherapy for stage IVB endometrial cancer	Corpus	Feasibility Study
2049S	A retrospective cohort study about uterine leiomyosarcoma in Japan	Corpus	Survey
3018	Randomized phase III trial comparing pegylated liposomal doxorubicin at 50 mg/m^2 versus 40 mg/m^2 in patients with platinum-refractory and -resistant Mullerian carcinoma (epithelial ovarian, fallopian tube, or primary peritoneal carcinoma)	Ovary	Randomized P III
3019	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	Ovary	Randomized P II-III
3020	A phase III randomized clinical trial to investigate the necessity of adjuvant chemotherapy for surgical stage I epithelial ovarian cancer	Ovary	Randomized P III
3022	Prospective cohort study of Bevacizumab plus standard platinum based chemotherapy as front-line treatment for advanced epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer	Ovary	Prospective Cohort
3023	An open-label, randomized, phase II trial evaluating the efficacy and safety of standard of care with or without Bevacizumab in platinum-resistant ovarian cancer patients previously treated with Bevacizumab for front-line or platinum-sensitive ovarian cancer	Ovary	Randomized P II

Fujii *et al*. analyzed the comparative accuracy of p16(INK4a)/Ki67 immunocytochemistry and high-risk HPV16/18 genotyping for evaluating CIN2+ lesions. They found that, as the triage test for evaluating CIN2+ lesions in ASCUS and LSIL specimens, the immunocytochemistry was more accurate than HPV genotyping.

Sugiyama *et al*. conducted a placebo-controlled double-blind randomized trial of the immunomodulatory drug Z-100 (polysaccharides extracted from bacillus tuberculosis) in patients with locally advanced cervical cancer who also received radiation therapy, based on results from a previous study which showed better overall survival (OS) with a low-dose (0.2μg) of Z-100 compared to a high-dose (40μg). Patients with stages IIB-IVA squamous cell carcinma of the uterine cervix were randomly assigned to receive low-dose Z-100 or a placebo. Sugiyama *et al*. concluded that treatment with low-dose Z-100 did show a trend towards OS improvement for locally advanced cervical cancer, although the statistical power was less than anticipated.

From the Corpus Cancer Committee, Harano *et al*. performed a retrospective study to establish better prognostic

Table 3 JGOG - Recently closed clinical trials and surveys

Protocol No.	Study Name	Site	Study Design
1067	A phase II study of adjuvant chemotherapy with Irinotecan (CPT-11) plus Nedaplatin (NDP) for stage IB2 or IIA	Cervix	P II
2043	A randomized phase III trial of AP (doxorubicin plus cisplatin) versus DP (docetaxel plus cisplatin) or TC (paclitaxel plus carboplatin) as post-operative chemotherapy in patients with high and high-intermediate risk group of endometrial carcinoma	Corpus	Randomized P III
1067S	Retrospective study of influences of platinum-containing drug-free periods on chemotherapeutic efficiency in recurrent cervical cancer	Cervix	Survey

markers for uterine carcinosarcomas. They surveyed 486 cases and concluded that tumor stage, performance status, CA125 level, lymphovascular space invasion, and myometrial invasion were each associated with poor prognoses.

From the Ovarian Cancer Committee, Harano *et al.* reported results regarding the quality-of-life (QoL) from the JGOG 3016 Trial. The trial assessed for QoL using the Functional Assessment of Cancer Therapy (FACT)-General scale (FACT-G), and the FACT-Taxan (FACT-T) and FACT-Ovary (FACT-Ov) subscales; they concluded that weekly dose-dense paclitaxel and carboplatin did not decrease overall QoL, compared with conventional tri-weekly paclitaxel and carboplatin.

Ongoing JGOG studies and recently closed JGOG studies are listed separately in **Tables 2** and **3**, respectively.

JGOG's topics

An open-label, randomized, phase II trial evaluating the efficacy and safety of standard of care with or without Bevacizumab in Platinum-resistant ovarian cancer patients previously treated with Bevacizumab for front-line or Platinum-sensitive ovarian cancer (JGOG3023 trial)

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Background

Significant extension of progression-free survival (PFS) was confirmed by the GOG0218 trial (the initial treatment for ovarian cancer)[1], the OCEANS trial (for platinum-sensitive recurrent ovarian cancer)[2], and the AURELIA trial (for platinum-resistant recurrent ovarian cancer)[3]. The AURELIA trial compared the standard therapy (single-agent chemotherapy alone) and single-agent chemotherapy plus bevacizumab in cases with platinum-resistant recurrent ovarian cancer, reporting for the first time that the combination therapy improved treatment outcomes.

Bevacizumab beyond Progressive Disease (PD)

In ML18147, a prospective, randomized, controlled Phase III trial of colorectal cancer, continuous administration of bevacizumab in the first- and second-line settings, in combination with standard chemotherapeutic regimens, extended overall survival[4]. PFS extension was also confirmed in patients with recurrent breast cancer in the TANIA trial[5]. The MITO16/MaNGO trial of bevacizumab beyond PD for ovarian cancer is underway overseas in patients receiving bevacizumab as initial treatment for platinum-sensitive recurrent ovarian cancer[6]. However, no studies are currently being planned for platinum-resistant recurrent ovarian cancer.

JGOG3023 trial

Under these circumstances, we have designed an investigation designated JGOG3023. In this study, we will investigate the efficacy and safety of single-agent chemotherapy plus bevacizumab versus single-agent chemotherapy alone in patients with platinum-resistant recurrent ovarian cancer with a previous history of receiving bevacizumab treatment. Based on the results of the Phase III study, single-agent chemotherapy plus bevacizumab is expected to improve therapeutic effects in patients receiving initial treatment as well as in those with platinum-sensitive recurrent ovarian cancer. Since the treatment is expected to be used in clinical settings, it is significant to generate clinical results for bevacizumab beyond PD particularly in patients with platinum-resistant recurrent ovarian cancer who have had poor treatment outcomes. The subjects to be enrolled in this study are patients who received 3 or more cycles of treatment with bevacizumab plus platinum-based combination chemotherapy and experienced recurrence or exacerbation during chemotherapy or within 6 months after the final date of treatment with the platinum agent. We have planned a superiority study with the hypothesis that PFS would become longer in patients receiving single-agent chemotherapy plus bevacizumab than in patients receiving single-agent chemotherapy alone (**Fig. 1**).

Group A will receive single-agent chemotherapy combined with bevacizumab and Group B will receive single-agent chemotherapy alone. The chemotherapy agent will be chosen by an attending physician from the following four regimens: pegylated liposomal doxorubicin, topotecan, paclitaxel, and

gemcitabine injection. The dosing schedule for each chemotherapy regimen will be as follows: pegylated liposomal doxorubicin injection will be administered intravenously (i.v.) at 40 mg/m^2 or 50 mg/m^2 on Day 1 (with 28 days as one cycle); topotecan will be administered i.v. at 1.25 mg/m^2 on Days 1, 2, 3, 4, and 5 (with 21 days as one cycle); paclitaxel injection will be administered i.v. at 80 mg/m^2 on Days 1, 8, and 15 (with 21 days as one cycle); and gemcitabine injection will be administered i.v. at 1000 mg/m^2 on Days 1 and 8 (with 21 days as one cycle). Each cycle will be repeated until disease progression. The treatment regimen of bevacizumab that will be given in combination with chemotherapy will be as follows: bevacizumab will be administered i.v. at 15 mg/kg on Day 1 (with 21 days as one cycle) .
The primary endpoint of this study is PFS, and the secondary endpoints are safety, objective response rate, overall survival, frequency of abdominal paracentesis, and response rate by tumor marker CA125.

Treatment for platinum-resistant recurrent ovarian cancer is either single-agent chemotherapy or palliative care at present, and the prognosis is very poor. This study is expected to lead to the establishment of a new therapy for these patients, and it is very significant for Japan to share data with the global research community.

Reference

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[4] Bennouna J, et al. Continuation of bevacizumab after first progression in metastatic colorectal cancer(ML18147): a randomized phase 3 trial. Lancet Oncol. 2013 Jan;14(1):29-37.
[5] von Minckwitz G et al. Bevacizumab plus chemotherapy versus chemotherapy alone as second-line treatment for patients with HER2-negative locally recurrent or metastatic breast cancer after first-line treatment with bevacizumab plus chemotherapy(TANIA): an open-label, randomised phase 3 trial. Lancet Oncol. 2014 Oct;15(11):1269-78.
[6] Bevacizumab Beyond Progression in Platinum Sensitive Ovarian Cancer. MITO16/MANGO2b /ClinicalTrials.gov Identifier: NCT01802749

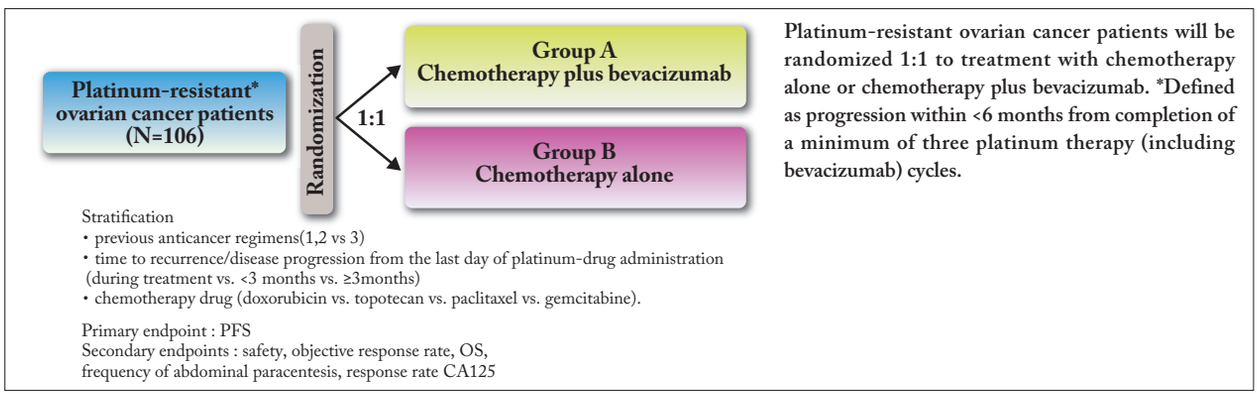

Fig.1 JGOG3023 Schema

Editorial postscript

Great Buddha of Kamakura

JGOG has started with a new system from 2015 under a new President, Toru Sugiyama. We have taken over the organization and ideals established by the previous president Kazunori Ochiai, and drawn up measures in order to advance further.
Molecular target therapeutic agents such as bevacizumab and pazopanib used in the treatment fields of gynecological malignancy in Japan have been covered by insurance and there has been a slight increase in the choice of treatment, but in future, therapies such as molecular-targeted therapy and immunotherapy will increase at the medical facilities. The next problem is how to provide these therapies safely to the patients and increase the therapeutic effect. We believe that it is the responsibility of JGOG to continue to practice the therapies through the planning and implementation of clinical research, and providing education on the treatment of gynecologic neoplasm.
Moreover, JGOG has not limited itself to clinical trials within Japan, but also actively cooperates in international clinical trials. It is considered that these global clinical trials have become increasingly important in order to accumulate more cases quickly.
The concept of clinical trials' quality is of course important, but it is not an overstatement to say that it is secured by the data centers. It is also a fact that maintenance of data centers is very expensive. The clinical trial groups in Japan have been able to subsidize a major part of the revenue with donations from drug manufacturers, but that source is almost closed as it ran into some issues. The situation is grave, though we sincerely want to perform clinical trials with the intention of making current and future patients happy. We hope that the current situation improves at least a little. However, even in such a difficult state, we expect JGOG to continue and move forward with the efforts of the members so that we are able to collect at least some evidence.

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