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Newsletter of the Japanese Gynecologic Oncology Group (JGOG)

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Have the action goals set up five years ago been met?

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

I set up ten action goals in an article titled "The Future of JGOG" in the domestic journal of JGOG, "Karyo News," published five years ago on June 25, 2009, six months since I became president. I would like to reflect back on the extent to which the goals have been met and prepare for the coming five years.

1) Have attractive protocols been made?

The studies that we have started in the past five years include seven studies in the Cervical Cancer Committee, one study in the Uterine Cancer Committee, and four studies in the Ovarian Cancer Committee. Among them includes the JGOG3020 study (A phase III randomized clinical trial to investigate the necessity of adjuvant chemotherapy for surgical stage I epithelial ovarian cancer), which was initiated by a young physician at the summer educational seminar conducted to foster young gynecologic oncologists. Further, JGOG3016 study (Long-term follow-up of a randomized trial comparing conventional paclitaxel and carboplatin with dose-dense weekly paclitaxel and carboplatin in women with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer), which has been presented twice at the American Society of Clinical Oncology (ASCO), had been published in Lancet Oncology and attracted worldwide attention. JGOG3017 study (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) has also been raised during an oral session at ASCO and has drawn attention as the first phase III study to be specific to histologic type.

2) Has awareness of the JGOG members as clinical researchers been raised?

I have asked the constituent members of JGOG for awareness and responsibility. For this purpose, we have set up opportunities for self-study at the Annual Conference, Gynecologic Cancer Conference, etc. so that the members can perform clinical studies as

researchers with high ethical standards. We have also prepared, as well as properly managed, a policy regarding the members' conflict of interest (COI).

3) Has the quality of the institutions participating in the JGOG studies improved?

The institutions performing the JGOG clinical studies are required to meet the institutional standards and undergo periodic audit. The number of institutions that have been subject to audit during the past five years was a total of 80 institutions, and three of them had serious problems pointed out. Guidance was provided to the institutions that had problems, and either the problems were improved or re-inspection was carried out a few years later. This seems to have clearly improved the quality of clinical studies at the institutions.

4) Have we participated in international trials?

JGOG has been affiliated with and playing active roles in international clinical research organizations, including the Gynecologic Oncology Group (GOG) and Gynecologic Cancer Intergroup (GCIG). The numbers of GOG and GCIG studies that JGOG has worked on during the past five years were nine and four studies, respectively. To take part in international studies, the standards of institutions and researchers need to comply with the international standards. In that sense, there is no doubt that the quality of the institutions and researchers has inevitably improved by participating in international studies. In addition, it is particularly worth noting that, in JGOG3017, we conducted a Japan-led international randomized, controlled, phase III study before other domestic research organizations. The roles that the JGOG Data Center played in this study were tremendous.

5) Have we promoted education of young gynecologic oncologists?

The Gynecologic Cancer Conference was started ten years ago as a conference on ovarian cancer on the initiative of Professor Sugiyama of Iwate Medical University. As a study group specific to clinical studies, the conference is helping to train young physicians. Also, the Educational Seminar, which is held every summer, has been held eight times, with a total of 162 participants to date. Former participants of this seminar have now become leaders, teaching young gynecologic oncologists, and this system is the way JGOG should always be. It is not a dream that the JGOG executives will one day be occupied by the former participants of the seminar.

6) Have we supported the clinical research support division?

The Pathology Review Committee and Radiotherapy Committee are very important in conducting clinical research and in terms of quality control of clinical research as well. JGOG is striving to run the committee activities smoothly while limiting the number of permanent committee members, trying to cut back its expenses. However, the above committees are accepting many members. This is precisely because we are aware of their importance in maintaining the quality of research.

7) Have we promoted public relations activities?

We have published the JGOG News Letter domestically four times a year, informing the members about key issues in accordance with the changes in the times, as well as conveying various voices of the members. Internationally, we have published the JGOG International once a year, conveying the activities of JGOG abroad.

8) Have we promoted interactions with patients?

We have had patients participate in the JGOG Ethics & COI Committee and Clinical Trial Review Committee as members so that we could look at our research from a patient's perspective and obtain feedback. Also, we participated in Globe-athon, a global-scale movement for raising awareness of gynecological cancers, in a 24-hour walk around

the Imperial Palace with patients and advocates of these activities.

9) Has JGOG become open?

Convening of each committee, including the JGOG Board of Directors, is notified to the members, and attendance is voluntary. Also, the minutes of all meetings are made public, and the members can access them. However, in reality, only a few request for attendance, and more ingenuity is required in order to realize an open JGOG.

10) Have the JGOG projects been sorted out? Has it been reflected in the articles of association?

All existing articles of association, terms of agreements, bylaws, etc. have been reviewed and adjusted to fit the reality. However, since we need to act flexibly according to enactments and revisions of the national guidelines, etc., we would like to work towards review on a continuous basis.

These are my report on how we have tackled the ten action goals. There is another thing that I, as president, have been working on as a matter of the highest priority. That is restructuring and reinforcement of the Head Office. Although the reform, including personnel affairs, is still in its infancy, I would like to assure you that we will strive to make the Head Office live up to the members' expectations.

JGOG's activities

Report of the 12th Annual Meeting of JGOG

Junzo Kigawa, M.D., Ph.D. Vice President, JGOG

The Japan Gynecologic Oncology Group (JGOG) held its 12th annual meeting on November 29, 2013 in Kokuyo hall (Tokyo). The meeting was smoothly with an excellent agenda despite a tight schedule. The number of institutions are190.

Table 1

JGOG1071S	Observational study to explore the possibilities of limited operations for stage Ia2 squamous cell carcinoma of the cervix.
JGOG1076S	Retrospective study of influences of platinum-containing drug-free periods on chemotherapeutic efficiency in recurrent cervical cancer.
JGOG2046	A feasibility study of hysterectomy and bilateral salpingo-oohorectomy after preoperative chemotherapy for stage IVb endometrial cancer
JGOG3018	Randomized phase III trial comparing pegylated liposomal doxorubicin at 50mg/m^2 versus 40mg/m^2 in patients with with platinum-refractory and -resistant Mullerian carcinoma (epithelial ovarian, fallopian tube, or primary peritoneal carcinoma)
JGOG3019/GOTIC	IntraPeritoneal therapy for Ovarian Cancer with Carboplatin (GOTIC-001 / JGOG3019) 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
JGOG3020	A phase III randomized clinical trial to investigate thenecessity of adjuvant chemotherapy for surgical stage I epithelial ovarian cancer: JGOG 3020
JGOG3022	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

Table 2

JGOG1073	Performance of p16INK4a/Ki-67 immunocytochemistry for identifying CIN2+ in atypical squamous cells of undetermined significance and low-grade squamous intraepithelial lesions specimen
JGOG1074	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
JGOG1075S	Clinicopathologic Features and Treatment Outcomes of Vulva Cancer in Japan
JGOG2047	A Randomised Phase II/III trial Comparing Dose-dense Weekly Paclitaxel plus Carboplatin Versus Triweekly Paclitaxel plus Carboplatin in Patients with Stage I-IV or Metastatic Uterine Carcinosarcoma
JGOG9001	Randomized trial of anti-emetic therapy for chemotherapy of gyencologic malignancy
JGOG3021	Everolimus in Patients With Reccurent Ovarian Clear cell Carcinoma

The 2013 business report which included reports from each committee covering a period of October of 2012 to September of 2013 was discussed. And all the committee reports and the business report were approved.

The most important goal of the JGOG is "to execute high-quality clinical trials" more efficiently and continuously produce results that are acceptable as international standards. Multiple working groups worked to promote our goals.

An outline of clinical trial status is shown in **Table 1** and clinical trials being currently planned are listed in **Table 2**.

JGOG's topics

Report of the presentation of the JGOG 3017/GCIG results at the ASCO2014.

Aikou Okamoto, M.D., Ph.D.
Director, JGOG ASCO Oral presenter, JGOG3017 Trial

I had the pleasure of making a presentation describing the results of the phase III randomized-controlled trial (JGOG 3017/GCIG) at the Oral Abstract Session of the ASCO on May 31 this year. This trial was performed to examine whether or not the regimen of paclitaxel + carboplatin (TC) or the one of irinotecan + cisplatin (CPT-P) would be efficient as the first-line therapy for the treatment of ovarian clear cell adenocarcinoma. This year's ASCO has reached its 50 year milestone, which was one reason

that the Oral Abstract Session, which was started in the afternoon, was overwhelmed by contiguous hot discussions and the atmosphere became almost oppressed with the discussers' sense of tension and vitality. It was a honor for me to make a presentation in such atmosphere. My presentation there is described succinctly below.

This study (JGOG 3017/GCIG) was a phase III multilateral randomized-controlled trial to examine which regimen was eligible for first-line therapy for ovarian clear cell adenocarcinoma, TC or CPT-P therapy. This study was planned based on two previous studies targeting ovarian clear cell adenocarcinoma: a retrospective study [1, 2] and a phase II randomized-controlled trial, [3] both suggesting CPT11's potential therapeutic efficiency for the carcinoma. Six-hundred nineteen chemotherapy-naïve patients with stage I – IV ovarian clear cell adenocarcinoma were allocated to postoperative TC therapy (305 cases) or CPT-P therapy (314). Primary endpoints were progression-free survival (PFS) while secondary endpoints were overall survival (OS) and adverse events. (**Fig. 1**) Advanced stage I patients accounted for 66.4% of the registered cases and 87.9% of those patients had undergone total extirpation of the lesions. As shown in **Figure 2**, there was no significant difference in PFS or OS between the two groups, not verifying CPT-P's superiority over TC in the cancer treatment. Grade 3 or 4 adverse events including leukopenia/neutropenia, thrombocytopenia, neuropathy and arthralgia occurred more often in the

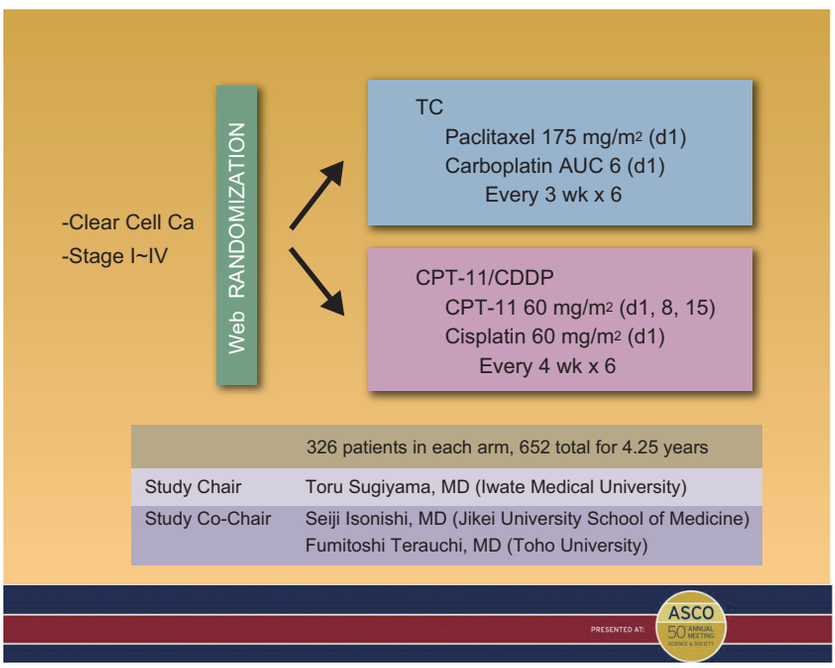


Figure 1 JGOG 3017/GCIG: Schema

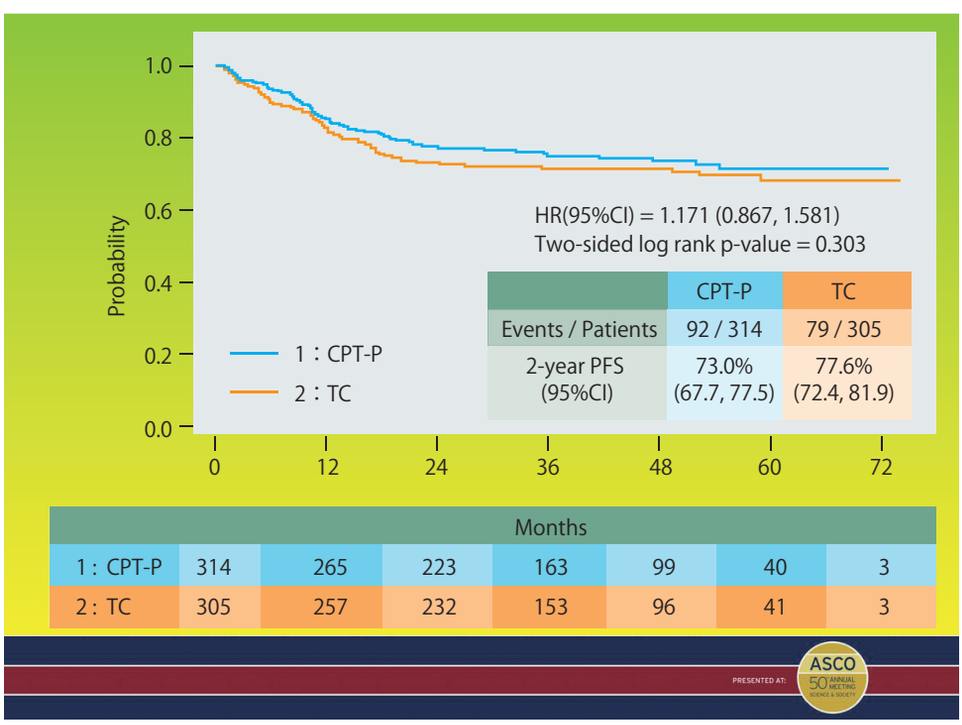


Figure 2 JGOG 3017: 2-year PFS for TC vs CPT-P

TC group while those including febrile neutropenia, nausea, vomiting and diarrhea were seen more often in the CPT-P group.

Discussions arose as follows. Though significant results were expected because this trial was the first phase III trial to treat specific type ovarian cancer and because it was the first multilateral study, in that Japan played a leading role in the gynecological field, it failed to verify CPT-P therapy as a new useful regimen. Therefore, TC therapy was considered to remain as standard therapy for ovarian clear cell adenocarcinoma. On the other hand, the two groups differed in toxicological profiles, showing that CPT-P therapy could be an alternate treatment. Regarding the future direction of clear cell cancer therapy, molecular-targeted agents are indispensable, and angiokinase inhibitors and mTOR inhibitors are promising agents. These agents are already under study in Japan (JGOG3021). Readers are encouraged to positively participate in the JGOG3020 which aims to examine whether or not adjuvant chemotherapy is necessitated for stage I cancer.

Several questions were raised by the audience. (i) Why was the percentage of stage I patients as large as 66%? (ii) Was there any difference in prognosis or in adverse events between Japanese and non-Japanese patients? (iii) How far have differences in responses to chemotherapy between Japanese patients and those of other human races studied at the genetic level? I felt that investigators had a tendency to place increasingly greater emphasis on having in mind racial differences in future clinical trials.

Last but not least, I express thanks to every trial participant from institutions of the JGOG (111 institutions), KGOG, GINECO, SGCTG/UK and MITO for cooperating with the registration to JGOG 3017/GCIG. I also thank Professor Tohru Sugiyama of PI and his associates for giving me the opportunity to make the presentation, the staff of the JGOG3017 Coordinating Center, and lastly the participating patients and their families.

References

[1] Takano M, et al., Oncol Rep, 2006; 16: 1301-6
[2] Takano M, et al., Int J Clin Oncol, 2007; 12: 256-60
[3] Takakura S, et al., Int J Gynecol Cancer, 2010; 20: 240-7

JGOG's topics

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: Japanese Gynecologic Oncology Group study (JGOG 3022)

Shinichi Komiyama, MD., and Ph.D.
Principal Investigator
Department of Gynecology, Toho University Ohashi Medical Center

Vascular endothelial growth factor (VEGF) is a key promoter of angiogenesis and disease progression in epithelial ovarian cancer. Bevacizumab is a humanized anti-VEGF monoclonal antibody. Bevacizumab is currently the most widely administered antiangiogenic agent for the treatment of many solid malignancies including ovarian cancer. In November 2013, based on the GOG-0218 study, the Japanese Ministry of Health, Labour and Welfare approved the use of bevacizumab in addition to taxane and platinum for the treatment of patients with advanced ovarian cancer in Japan. GOG-0218 revealed that 1873 women with previously untreated advanced epithelial ovarian, primary peritoneal or fallopian tube cancer, who had already had surgery and who received bevacizumab in combination with paclitaxel and carboplatin, and continued use of bevacizumab alone, for a total duration of 15 months, had a median progression free survival (PFS) of 14.1 months compared to 10.3 months in women who received paclitaxel/carboplatin alone (HR= 0.72, p<0.0001). Gastrointestinal perforation, hypertension, proteinuria, venous thrombosis, wound-healing complications, or bleeding, were reported as significant adverse events related to bevacizumab therapy. However, this data was derived principally from American patients, and the safety of bevacizumab for Japanese patients is unclear. Thus, we aim to evaluate the safety and efficacy of bevacizumab in combination with standard taxane/platinum chemotherapy as a front-line treatment for Japanese patients with advanced epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer.

JGOG3022 is a prospective, single arm, cohort study, which is not intervened in knowledge of clinical details, treatment regimen or schedule. Main inclusion criteria are as follows: 1) Epithelial ovarian, primary peritoneal, or fallopian tube cancer, confirmed histologically, 2) Stage III – stage IV disease, 3) No concern with residual disease, 4) Interval debulking surgery following neoadjuvant chemotherapy without bevacizumab accepted. Main exclusion criteria are as follows: 1) Recurrent disease, 2) Bleeding disorders or coagulopathy, uncontrollable venous thrombosis including pul-

monary thromboembolus, severe urine protein, uncontrolled hypertension, 3) History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess, 4) Prior administration of bevacizumab or other anti-VEGF agents, 5) Prior abdominal radiotherapy. Patients will be enrolled using the JGOG Patient Registration Center System after primary surgery or interval surgery. Patients will receive standard taxane/platinum chemotherapy in combination with bevacizumab as front-line chemotherapy with following bevacizumab monotherapy for maintenance (**Figure 1**). Primary endopoint is incidence of specific adverse events related to bevacizumab or incidence of < grade3 adverse events. Secondary endopoints are PFS and overall response rate calculated in enrolled patients with measurable residuals. We plan to recruit a total of 400 patients in 2 years; 300 patients in the primary analysis cohort treated with paclitacel/carboplatin and bevacizumab, and 100 patients in the exploratory analysis cohort treated with other taxane/platinum and bevacizumab.

JGOG3022 is the first, large, Japanese study of bevacizumab containing with standard chemotherapy for patients with advanced epithelial ovarian cancer. Result of this trial will give us very important data for treatment of them. It should be accomplished as rapidly as possible.

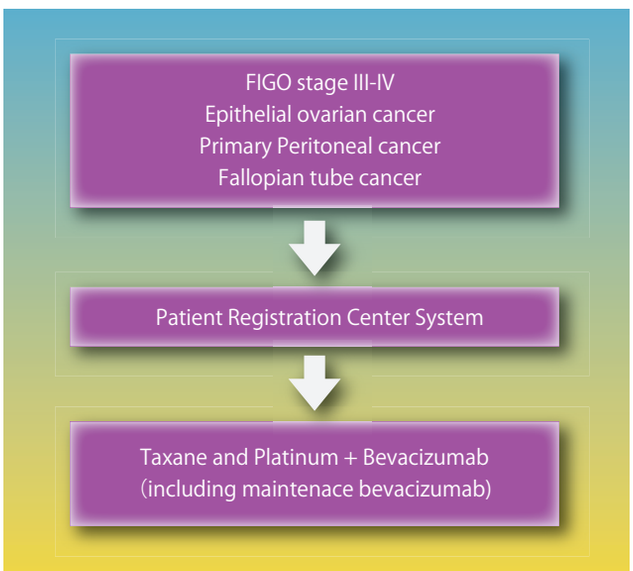


Figure 1. Study Schema of JGOG3022

International Symposium

International Symposium on the World's Immunization Policies: Cervical Cancer Prevention; Saving Lives and Families

Prof. Ryo Konno, M.D., Ph.D. Jichi Medical University Saitama Medical Center

We welcomed Professor David Salisbury from the United Kingdom, a leading country in the field of immunization, who was the formerly Director of Immunisation at the Department of Health.

The symposium provided accurate, up-to-date information on public health and immunization policies in both the U.K. and of international organizations like WHO, as well as data on the safety and efficacy of HPV vaccines. The Aim of the symposium was to consider and discuss vaccinations that saves lives and families together with opinion leaders in the fields of policy development, health care, and the media.

- Date and Time: May 21 (Wed.), 2014, 5:30 p.m. to 7:30 p.m.
- Co-organizers: Japan Society of Obstetrics and Gynecology, Japan Association of Obstetricians and Gynecologists, Japan Society of Gynecologic Oncology, and the Japanese Expert Board for the Eradication of Cervical Cancer

▪ Venue: Iino Hall & Conference Center (Roof Gallery B-1 and B-2)

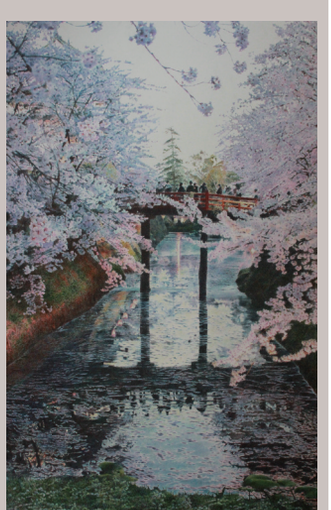
Program:

1. Opening Address
   Dr. Sadaomi Imamura, Executive Board Member, Japan Medical Association
2. Keynote Lecture: Immunization Policies and Practices in the U.K. and WHO with a Special Focus on HPV Vaccines (provisional title)
   Professor David Salisbury, former Director of Immunisation at the Department of Health, U.K., and advisor to WHO, PATH, and Bill and Melinda Gates Foundation
3. Concerns over HPV Vaccines in Japan: Background on the Side Effect Issue and Scientific Evidence on the Safety and Efficacy of HPV Vaccines
   Professor Ryo Konno, Department of Obstetrics and Gynecology, Jichi Medical University Saitama Medical Center
4. The Future of HPV Vaccination in Japan
   Professor Etsuko Miyagi, Oncology Division, Yokohama City University School of Medicine
5. Closing Address
   Dr. Katsuyuki Kinoshita, President, Japan Association of Obstetricians and Gynecologists

Summary: National education An HPV vaccine introduction educational strategy should be implemented nationally to increase community awareness. Carefully designed messages are essential to educate communities, parents, adolescents, mass media and other stakeholders. On the other hand, programs can quickly be undermined by rumors and misinformation disseminated via mass media, the internet and social media.

Vaccine programs should be managed using a transparent, scientific, evidence based policy, that includes safety and efficacy monitoring. WHO, FIGO, CDC, MHRA, EMA and other internationally respected organisations have considered all the available evidences on HPV vaccination and have concluded that HPV vaccines are safe. Epidemiological surveillance, both pre- and post-, vaccination is necessary for accurate analysis of causality between the vaccines and any adverse events. The best way to prevent erosion of confidence in immunization is clear and honest communication, with both the public and health professionals, combined with rapid, high level response and reassurance about vaccine safety.

Editorial postscript



A CHERRY TREE FESTIVAL

Recently there have been unfortunate series of news reports concerning inappropriate behavior by researchers in Japan, questioning the ethics of those in this field in this country. A sense of ethics or morality means “the way that ought to be followed as a person. Universal criterion in the judgment of good and evil, and right and wrong. Morality. Moral.” Today, medical sciences are continuously making progress based on a concept of the Evidence-based medicine (EBM), which is of the central importance in medical treatment. No matter how far medical sciences has progressed, trust between patients and doctors, which is the most important factor in medical treatment, should not be broken as a result of misconducts in EBM. JGOG is determined not to permit unethical behavior to continue in Japan any longer. JGOG is willing to take the lead in progressing gynecological clinical trials not only in Japan but in the world, guided always by a strong sense of morality.

The main topics in this issue are the international joint trial JGOG3017/GCIG, which was reported at this year’s ASCO, and anti-cervical-cancer preventive vaccine, for which active encouragement is temporarily suspended in Japan. Also, the first report of a new clinical trial, JGOG3022, appears in this issue. In order for the JGOG to continue delivering new gynecological findings to the world “JGOG International” has the responsibility to play a large role

Nao Suzuki, M.D., Ph.D.
Chairman of the JGOG Publicity Committee

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