JGOG International

2013 Nov.
No.8

Newsletter of the Japanese Gynecologic Oncology Group (JGOG)

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Join the power of young scientists and promote it to the world!

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

Eleven years have passed since the Japanese Gynecologic Oncology Group was reorganized into a non-profit organization. During this period, we have promoted new clinical studies to accumulate new evidence on gynecologic oncology. Due to our members' efforts, the dose-dense TC therapy developed in Japan is gaining acceptance as the standard treatment against ovarian cancer internationally. Supplementary clinical studies are being conducted in many countries of the world. Unfortunately, the results of MITO 7 presented at ASCO 2013 showed that there were no significant differences in progression-free survival (PFS) and overall survival (OS) between patients who received the dose-dense therapy and patients who received the control arm of triweekly TC. However, the MITO 7 experiments involved administering one-third of the standard triweekly doses of paclitaxel and cargoplatin every week instead of administering the entire doses every three weeks as in the control arm, and were thus rather "dose fractioned" than "dose dense", a condition proposed by the JGOG. We are waiting to see the results of on-going supplementary studies.

This series of studies was initiated by the Japan Kanto Tumor Board (JKTB), a regional group in Kanto. Then, JGOG took the initiative and spread the study nationwide, leading to the completion of the dose-dense TC protocol. This collaboration between an excellent local research group (JKTB) and the central organization (JGOG) is a wonderful model of task division. The flow of local research groups devising and investigating protocols and JGOG brushing up and proposing the excellent protocols to be studied nationwide and worldwide also increases the opportunities for young scientists to participate in worldwide research projects.

Excellent protocols are always presented in our Summer Seminar held every year for young gynecologic oncologists who are interested in clinical research. Some of the protocols have been adopted as topics of clinical studies by the JGOG. We are expecting the young power to rise, and JGOG needs the energy of young people for further development. I believe that we, including the readers of this brochure, can lay our hopes on the power of the young JGOG members.

JGOG1066: A phase II study of CCRT with HDR-ICBT in patients with locally advanced uterine cervical cancer

Takafumi Toita, M.D., Ph.D.
Studychairperson, JGOG1066 Trial

JGOG1066 was a multicenter phase II study designed to assess the toxicity, feasibility, and efficacy of concurrent chemoradiotherapy (CCRT) in patients with stage IIIb and IVA uterine cervical cancer. The protocol regimen consisted of weekly administration of cisplatin at 40mg/m2 and high-dose-rate intracavitary brachytherapy (HDR-ICBT) with a low cumulative radiation dose schedule (EQD2 = 62-65Gy). The background information and study objectives have previously been described in an earlier issue of the JGOG International (No. 5, 2011 Sept.).

Between March 2008 and January 2009, 72 patients were enrolled from 25 institutions. A total of 89% of the patients completed protocol treatment as planned. Although neutropenia ≥ grade 3 occurred in 44% of the patients, other toxicities were relatively mild and tolerable. Five courses of chemotherapy were successfully administered in 92% of the patients. With a median follow-up of 28 months, the 2-year progression-free survival rate (PFS) and pelvic disease progression-free rate (PDPF) were 66% (95% CI, 54% to 76%) and 73% (95% CI, 61% to 82%), respectively. There were decreases in both the PFS (P=0.036) and the PDPF (P=0.24) with increasing tumor diameter (assessed by MRI). The 2-year PFS and PDPF, respectively, were 77% and 85% for < 50mm, 69% and 72% for 50-70mm, and 39% and 54% for ≥ 70mm tumor diameter. With regard to late adverse events, toxicity ≥ grade 3 occurred only in 3 patients. The cumulative 2-year late complication rates were 9% for grade 1, 12% for grade 2, 3% for grade 3, and 0 for grades 4/5.

The JGOG1066 demonstrated that CCRT consisting of HDR-ICBT and a standard weekly dose (40mg/m^2) of cisplatin was feasible with acceptable toxicity in Japanese women with cervical cancer. The treatment regimen in this study will be adopted for the protocol designed for the control patient cohort in the JGOG's future randomized clinical trials. The study also demonstrated that CCRT with a low cumulative dose radiation schedule of (EQD2= 62-65Gy) achieved comparable outcomes to those achieved by global standard dose schedules (EQD2=85Gy) with less late toxicities. Radiotherapy dose escalation in patients with bulky cervical tumors as well as effective systemic strategies to prevent distant metastases might further improve patient outcomes and present upcoming challenges for CCRT in patients with locally advanced uterine cervical cancer.

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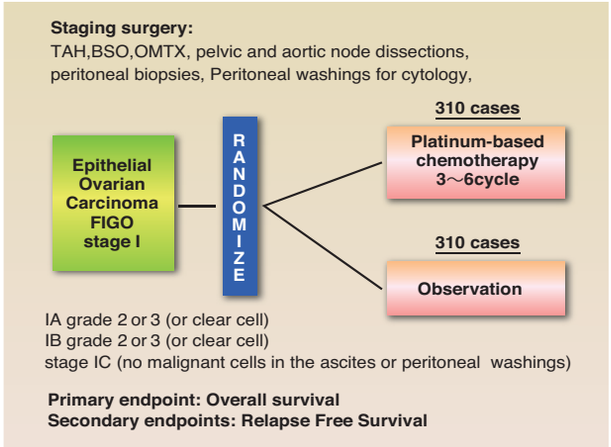
A phase III randomized clinical trial to investigate the necessity of adjuvant chemotherapy for surgical stage I epithelial ovarian cancer: JGOG 3020

Hiroshi Tanabe, M.D., Ph.D.
Studychairperson, JGOG3020 Trial

JGOG (Japanese Gynecologic Oncology Group) has been promoting since July 2012 the enrollment for a new study:, a phase III randomized clinical trial for surgical stage I epithelial ovarian cancer, to investigate the requirement for adjuvant chemotherapy.

Although the prognosis of patients with stage I ovarian cancer is fairly good nevertheless, additional adjuvant chemotherapy has been standardized treatment. Two large-scale comparative studies, EORTC-ACTION and ICON1, have explored the efficacy of adjuvant chemotherapy in early-phase ovarian cancer. When the findings from these two studies were combined and analyzed together, the 5-year overall survival (OS) of 82% was better in the adjuvant chemotherapy group than in the non-adjuvant chemotherapy group (74%; hazard ratio, 0.67). However, when

the analysis was restricted to a subset of groups 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 may not necessarily be efficacious for surgically-proven phase I ovarian cancer. If this were true, avoidance of unnecessary adjuvant chemotherapy would benefit the patient's QOL as well as medical economics. We were thus prompted to organize this clinical trial which is expected to define indications of adjuvant chemotherapy in cases with stage I epithelial ovarian cancer, thus resolving the this issue. We believe that this clinical trial would produce important findings that would greatly benefit patients by improving their QOL.



JGOG's Clinical Study topics

JGOG2048S study: A multi-institutional retrospective analysis of uterine carcinosarcoma

Kenichi Harano, M.D.
Study chairperson, JGOG2048S Trial

Carcinosarcomas (CS) of the uterus, also known as malignant mixed mullerian tumors (MMMTs), are rare neoplasms of the uterus. They only account for 2-5% of all uterine cancers, with an estimated annual incidence of less than two per 100,000 women. There were 258 reported cases of uterine CS in 2008 in Japan according to the survey of the Japan Society of Obstetrics and Gynecology. Uterine CS is an aggressive uterine cancer with poor survival rates, even when presented at an early stage. Previous studies have estimated that the median overall survival is approximately 21 months, and less than 1 year in advanced or recurrent disease. More than 40% of women with uterine CS have advanced-stage disease, and more than 50% of patients will recur.

Histologically, CS displays both epithelial and sarcomatous differentiation. The most common epithelial component is serous, followed by endometrioid histology. The sarcomatous component has been subdivided into homologous (leiomyosarcoma, fibrosarcoma, malignant fibrous histiocytoma, or undifferentiated sarcoma) or heterologous (rhabdomyosarcoma, chondrosarcoma, osteosarcoma, or liposarcoma) tumors. However, recent histogenetic analyses suggest that most of CS derive from a monoclonal origin, and they are currently classified as metaplastic carcinomas. Clinically, the behavior of uterine CS is more similar to that of carcinomas than to the sarcomas in terms of dissemination and sensitivity to cisplatin-based chemotherapy. The staging system for uterine CS is same as that of endometrial carcinoma according by revised International Federation of Gynaecology and Obstetrics (FIGO) 2009 guidelines.

Surgery is the cornerstone of treatment for uterine CS; however, because of the rarity of the disease, there is no existing consensus for optimal surgical treatment. Surgery typically consists of hysterectomy, bilateral salpingo-oophorectomy, and resection of gross abdominal tumor. Studies have suggested that lymphadenectomy is not only a diagnostic tool but that it also has a therapeutic role. It was reported that lymphadenectomy was associated with improved overall survival for patients with stage I to III disease.

The high rate of recurrence underlines the need for effective adjuvant treatment. However, data on the adjuvant treatment is scarce, and there is no standard treatment. The Gynecologic Oncology Group (GOG) 150 study compared adjuvant ifosfamide and cisplatin to whole abdominal radiotherapy and found similar outcomes, but showed a trend towards superior survival with chemotherapy. Current guidelines recommend adjuvant chemotherapy in all stages, and tumor-directed RT in selected early stage cases. The prognosis of advanced or recurrent disease remains poor. Only cisplatin, ifosfamide, and paclitaxel have demonstrated significant activity and have been evaluated in subsequent phase III trials. A combination of cisplatin and ifosfamide treatment was reported to result in a statistically significant improvement over ifosfamide alone in median progression-free survival (6 months vs 4 months), but the overall survival was not statistically significantly different. An ifosfamide and paclitaxel combination demonstrated a statistically significant improvement of overall survival over ifosfamide alone, and thus this combination is currently the standard treatment. Given the substantial toxicity and inconvenience of ifosfamide-based therapy, there has been a great interest in developing other treatments. A phase II GOG trial of carboplatin and paclitaxel that included 46 patients reported a high response rate of 54%. A phase II/III trial that examines the effectiveness of treatments including carboplatin and paclitaxel is now planned in JGOG.

Tailored management based on predictive/prognostic factors could probably help to better define the subset of patients who could benefit from treatment. Several studies have suggested that factors such as stage, lymphovascular space invasion, age, depth of myometrial invasion, tumor histology, and performance of lymphadenectomy influence survival. Nonetheless, results are often contradictory and most studies include only a small num-

ber of patients.

The aim of the present study is to assess prognostic factors and outcome in Japanese patients with uterine CS. Data of the patients with newly diagnosed uterine CS between 2007 and 2012 were retrospectively evaluated. The study included 500 patients from 184 facilities that joined the JGOG. Data analysis is in progress.

JGOG's activities

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

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

The Japan Gynecologic Oncology Group (JGOG) held its 11th annual meeting on November 30, 2012. The meeting went smoothly with an excellent agenda despite a tight schedule. First, 32 new directors were elected (**Table 1**), and the JGOG principal investigators elected Kazunori Ochiai, MD, to a second term as Group Chair. Dr. Ochiai is Professor and head of the Department of Ob-Gyn, Jikei University.

Table 1 Director list

President	Kazunori Ochiai		
Vice President	Junzo Kigawa,	Keiichi Fujiwara	
Directors			
Daisuke Aoki,	Yoichi Aoki,	Kimihiko Ito,	
Takayuki Enomoto,	Masahide Omichi,	Hidetaka Katabuchi,	
Noriyuki Katsumata,	Shoji Kamimura,	Toshiharu Kamura,	
Kaneyuki Kubushiro,	Toshiaki Saito,	Satoru Sagae,	
Toru Sugiyama,	Nao Suzuki,	Mitsuaki Suzuki,	
Masahiro Takeuchi,	Nobuhiro Takeshima,	Kazuhiro Takehara,	
Hiroshi Tsuda,	Takafumi Toita,	Toru Nakanishi,	
Masayuki Hatae,	Yasuyuki Hirashima,	Hisaya Fujiwara,	
Mikio Mikami,	Etsuko Miyagi,	Nobuo Yaegashi,	
Hiroyuki Yoshikawa			

Table2 Honorary and Service list

Honorary member		
Fumitaka Saji,	Naohiko Umesaki,	Hiroshi Hoshiai,
Makoto Yasuda,	Masamichi Hiura,	Noriyuki Inaba
Service member		
Issei Higuchi,	Ken Takisawa	

The numbers of principal investigators and institutions are 933 and 183, respectively.

In the first session of the annual meeting, Dr. Udagawa, Vice President, presented the 2012 business report, which included reports from each committee. 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.

Honorary members and service members were commended. Those members are shown in **Tables 1** (service members) and **2** (honorary and service members)

JGOG's activities

Introduction to the JGOG Education Seminar

Nobuo Yaegashi, M.D., Ph.D. Chairperson of the Education Committee

The Education Committee holds an education seminar for young doctors every year in August at a hotel in Tokyo. This year is the 7th staging of the annual seminar which started in 2007. Its purpose is to have young doc-

tors create a protocol concept from scratch in an active learning program to understand the basic points of the clinical research. I think this program enhances the quality of JGOG clinical researches in the long term, leading to grooming new leaders who will serve as the backbone of future gynecological oncology.
Applications for the seminar participation are open to JGOG facilities. In the participant selection stage, the Committee gives consideration to not only applicants' backgrounds and achievements but also points, social positions and regional characteristics of their facilities. About 20 seminar participants from across the nation were divided into 3 groups (cervical cancer, uterine cancer and ovarian cancer) to carry out tasks from early in the morning until late at night for 3 consecutive days (Friday through Sunday) locking themselves in the hotel. On the last day, they present protocol concepts that they have completed as an indication of their progress.

Although the 3-day seminar seems to be a long program, it is actually known as a pretty hard seminar both mentally and physically because they have to design a new clinical research during the limited period and present it in a comprehensive way, and because they have to answer tough questions as well as opinions from the advisors and staff along the way.

On the other hand, each group is always accompanied by 2-3 tutoring advisors while biostatistics specialists and medical oncologists serve as a consultant as needed. Moreover, the JGOG Administration Office is confined to the seminar place during the 3-day period to support the management of the seminar, so seminar participants can concentrate exclusively on their tasks. Therefore, you should make pretty big profits from the seminar where you can get full support.

Results (protocol concepts of newly designed clinical trials) are presented by seminar participants themselves at the Education Committee at the time of the annual JGOG General Assembly. Some of their results have been adopted as a JGOG protocol, which encourages seminar participants. I hear that many members of each group have built up a sense of continuing solidarity. I consider such solidarity as a secondary effect of the seminar. This seminar is also characterized by some seminar participants becoming advisors.

I expect JGOG's passion for the development of young investigators to be diffused all over the country.

JGOG's topics

Globe-athon Japan 2013

Keiichi Fujiwara, M.D., Ph.D. Vice President, JGOG

Globe-athon is a combination of the words "globe" and "marathon", the latter of which means running long distance. So, Globe-athon means running or walking long distance that is performed all over the world.

Why did we do this? For the following cause.

The comprehensive global cancer statistics from the International Agency for Research on Cancer indicate that gynecological cancers accounted for 19% of the 5.1 million estimated new cancer cases, 2.9 million cancer deaths and 13 million 5-year prevalent cancer cases among women in the world in 2002. Cervical cancer accounted for 493,000 new cases and 273,000 deaths; uterine body cancer for 199,000 new cases and 50,000 deaths; ovarian cancer for 204,000 new cases and 125,000 deaths; and cancers of the vagina, vulva and choriocarcinoma together constituted 45,900 cases. More than 80% of the cervical cancer cases occurred in developing countries and two-thirds of corpus uteri cases occurred in the developed world. Even though large numbers of patients have suffered, far too little attention has been paid on gynecologic cancers, because the incidence is less than other major cancers, such as breast, colon, lung or stomach cancers.

The Globe-athon to End Women's Cancer is a call to action for advocacy groups, healthcare professionals, survivors and the lay public to unify their efforts globally in a common goal of fostering public awareness and education about gynecologic cancers.

The Globe-athon to End Women's Cancer was an unprecedented effort to expand public outreach and advocacy associated with gynecologic cancer on an international scale. Numerous scientific and medical leaders from around the world have voiced their sweeping enthusiasm for an event that will demonstrate international solidarity and commitment to raising public awareness about gynecologic cancers. In areas of the world where the incidence and mortality rates are the highest, there are few organized public awareness events aimed at education around screening and prevention of gynecologic cancers. In other developed countries, this event would provide multiple advocacy groups with an opportunity for greater collaboration and partnership.

We have been successful with commitment from 65 countries around the world. In addition, professional gynecologic cancer societies, advocacy groups and even government officials around the world have endorsed the international effort.

Dr. Larry Maxwell of Washington DC, the global leader of this event, invited us to join their efforts in January. Thus, in Japan, we at JGOG decided to host this event under the leadership of our president Dr. Kazunori Ochiai. JGOG hosted this event as an opportunity to expand the awareness of the importance of clinical trials in gaining new therapeutic evidence for these devastating diseases. The steering committee members are Ms. Miho Katagi and Ms. Hiromi Kawamura (patient advocacy), Drs. Etsuko Miyagi of Yokohama City University, Nao Suzuki of St. Marianna University, Noriyuki Katsumata of Nihon Medical University Musashikosugi Hospital, and Keiichi Fujiwara of Saitama Medical University International Medical Center.

We started walking from 5 pm on Saturday, September 28th to 5 pm on Sunday, September 29th, 2013. A total of 258 people including Dr. Robert Coleman of MD Anderson Cancer Center, patients, their families, trial coordinators, JGOG staff members, nurses, physicians, and many others marched around the Royal Palace (5.5 km) as a relay walk. The weather was perfect for 24 hours and no one dropped out.

We would like to thank the organizers and volunteers for this important event and hope to organize another Globe-athon next year too.

Please visit our Website and Facebook page for more information and wonderful pictures.
http://globeathon.jp/
https://www.facebook.com/globeathonjapan

Globe-athon US has even more interesting pictures and videos.
http://globeathon.com/
https://www.facebook.com/Globeathon

Editorial postscript

TOKYO SKYTREE

I am taking charge of editing JGOG International starting from this issue. As I have been involved in the editing work since launching of JGOG International, I will improve the Newsletter to surely inform the world of JGOG's achievements. The current issue carries up-to-date information on clinical trial which form the basis of JGOG's projects.

Specifically, it outlines the latest clinical trials for cervical cancer, uterine cancer and ovarian cancer. It also presents topics of the 2012 General Assembly as well as the 2013 Education Seminar. Moreover, I asked Dr. Keiichi Fujiwara, Chairman of the Executive Committee, to report the 1st 24-hour Walk Relay joined by patients and medical professionals to fight against gynecologic cancer (Globe-athon Japan 2013). The successfully-completed Relay was simultaneously held by over 60 countries in the world

By the way, the Public Relation Committee will choose such themes as can provide the readers with more and rich information. Members having the youngest mean age from the new Public Relation Committee will try hard to publish JGOG International issues comparable to those published by the senior Committee members who contributed enormously to JGOG International.

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

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