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Major clinical research advances in gynecologic cancer in 2011

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The annual review of 2011 comprised 11 themes of major research achievements in gynecologic oncology including breast cancer. A potential paradigm shift in the management of ovarian cancer was reviewed through comprehensive genomic analyses and a tumor-specific new intraoperative fluorescence imaging technique using folate receptor-α targeted agent, which is expected to improve intraoperative staging and more radical cytoreduction. In addition, updates of bevacizumab and poly (ADP-ribose) polymerase inhibitors, risk-reducing salpingo-oophorectomy, and risk evaluation of pelvic mass were discussed. Regarding cervical cancer, this review covered new findings on human papillomavirus vaccines and human papillomavirus tests as well as the current status of clinical trials on locally advanced cervical cancer. The promising role of sentinel lymph node biopsy in the management of early stage endometrial cancer was followed by two notable clinical researches on: exemestane, an aromatase inhibitor, for the prevention of breast cancer and eribulin, a non-taxane microtubule dynamics inhibitor for the treatment of metastatic breast cancer. Lastly, in premenopausal women with breast cancer, the effect of gonadotropin-releasing hormone analogue on the occurrence of chemotherapy-induced early menopause was discussed.

Keywords: Breast cancer, Comprehensive genomic analyses, Gynecologic oncology, Human papillomavirus vaccines, Poly (ADP-ribose) polymerase inhibitors

INTRODUCTION

Since 2007, the *Journal of Gynecologic Oncology* has published the annual review, "Major Clinical Research Advances in Gynecologic Cancer" in every December issue. Starting with the present review of 2011, the annual review will be included in the January issue of the next year, in this case, 2012.

Several outstanding research studies were found in our search of major journals and presented abstracts in the same manner as previously described [1], which were then categorized into 11 themes: five are on ovarian cancer, three are on cervical cancer, one is on endometrial and two are on breast cancer. Notably, we included research advances in breast cancer in the review for the first time. Because breast cancer is associated with gynecologic cancers, particularly endometrial cancer, and thus, because gynecologic oncologists often manage patients with a history of breast cancer, updates of the current trends in breast cancer management are important. In this review, we summarized the valuable data of noteworthy clinical trials and translational researches that are potentially practice changing in the field of gynecologic oncology.

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PARADIGM SHIFT IN MANAGEMENT OF OVARIAN CANCER

Two large studies were published in 2011, both of which were heralded by many researchers as laying the foundation for a paradigm shift in the management of ovarian cancer.

The first study was conducted by The Cancer Genome Atlas (TCGA) Research Network [2]. In this comprehensive study, genomic and epigenomic abnormalities were measured on clinically annotated high-grade serous ovarian cancer (HGS-OvCa) to identify the molecular mechanism of the pathophysiology that constitutes effective therapeutic targets. TCGA project has analyzed messenger RNA expression, microRNA expression, promoter methylation, and DNA copy number in 489 HGS-OvCa in addition to the DNA sequences of exons from coding genes in 316 of these tumors. The project reported 96% of a *TP53* mutation rate. *BRCA1* and *BRCA2* were mutated in 22% of tumors owing to a combination of germline and somatic mutations. Six other statistically recurrently mutated genes were also identified, but only in 2-6% of HGS-OvCa: *RB1, NF1, FAT3, CSMD3, GABRA6, and CDK12*. They also identified, they believe, rare but important driver mutations in HGS-OvCa because of transforming activity: *BRAF, PIK3CA, KRAS, and NRAS*. The study found 113 significant focal somatic copy number alterations (SCNAs), the most common focal amplifications of which encoded *CCNE1, MYC, and MECOM* as well as promoter methylation events involving 168 genes. A high prevalence of mutations and promoter methylation in putative DNA repair genes, including a homologous recombination component, might explain the high prevalence of SCNAs. Homologous recombination defects might be present in approximately half of all HGS-OvCa cases, providing a rationale for clinical trials of poly (ADP-ribose) polymerase (PARP) inhibitors. Finally, different mutation spectrums between ovarian cancer histological subtypes were suggested as a rationale of subtype-specific care. Examples are few *TP53* mutations but recurrent *ARID1A* and *PIK3CA* mutations in clear-cell ovarian cancer; frequent *CTNNB1, ARID1A*, and *PIK3CA* mutations in endometrioid ovarian cancer; and *KRAS* mutations in mucinous ovarian cancer.

The second major study was by van Dam et al. [3] and concerned a new intraoperative imaging technique using a folate receptor-α (FR-α) targeted fluorescent agent. The researchers tried to develop a real-time tumor-specific surgical visualization system with a detection power up to the submillimeter level because the degree of cytoreduction is one of the most important prognostic factors in ovarian cancer. This study used 10 subjects that comprised four ovarian cancers (two serous carcinomas, one undifferentiated and one mucinous carcinoma), one serous borderline tumor, and five benign ovarian tumors (two fibrothecomas, one cellular fibroma, one cystic teratoma, and one benign multicystic ischemic ovary). Using flourescein isothiocyanate conjugated folate (folate-FITC) for targeting FR-α, which was overexpressed in 90-95% of malignant tumors, fluorescence was detectable intraoperatively in all patients with a malignant tumor and FR-α expression, but not in those with benign tumors. Thus, the real-time image-guided excision of fluorescent tumor deposits of size <1 mm was feasible. Tumor-specific fluorescent signals could be detected from two to eight hours after injection of folate-FITC intravenously. Van Dam et al. [3] suggested several advantages of the intraoperative fluorescence imaging system: avoiding needless extensive surgical procedures and associated morbidity thanks to a large field of view for inspection and staging; contributing to more efficient cytoreduction and ultimately improving the effect of adjuvant chemotherapy in patients with reduced tumor burden. It was true particularly when combined with hyperthermic intraperitoneal chemotherapy (HIPEC) [4]. The promising value of an intraoperative imaging system appeared valid even in a laparoscopic setting and interval debulking surgery after chemotherapy because FR-α expression in the remaining vital tumor tissue was not significantly altered after chemotherapy.

The diagnostic and therapeutic values of integrated genomic approaches and intraoperative tumor-specific fluorescence imaging in staging and debulking surgery for ovarian cancer need confirmation by further studies.

UPDATES OF BEVACIZUMAB IN OVARIAN CANCER

Unfortunately, no final report on international, multicenter, randomized controlled trials for antiangiogenic agents in ovarian cancer was published in full this year. However, three important updates of previously reported phase III studies were presented at the American Society of Clinical Oncology (ASCO) Annual Meeting in 2011. First, updates of two front-line bevacizumab studies were presented. The independent radiologic review of GOG 218 confirmed a preliminary result of a study published last year. In other words, the addition of 15 mg/m^2 of bevacizumab every 3 weeks during both 6 cycles of paclitaxel (175 mg/m^2)/carboplatin (AUC 6) and 16 cycles of maintenance drug alone (16 months of total duration) (arm III) prolonged progression-free survival (PFS) of paclitaxel/carboplatin alone (arm I) by 6 months (hazard ratio [HR], 0.63; p< 0.0001) [5]. The second updated study was a subgroup analysis of poor prognosis patients by International Collaborative Ovarian Neoplasm (ICON) 7 [6]. Based on the mature results of PFS benefit (p=0.0041, a 15% improvement at 12 months and 1.5 months overall) and preliminary overall survival (OS) data (HR, 0.81; 95% confidence interval [CI], 0.63 to 1.04; p=0.098) of last year, the overall trend for improvement in OS due to the administration of bevacizumab continued in the highest risk group of patients, which had large volumes of residual

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disease and stage IV (HR, 0.64; 95% CI, 0.48 0.85; p=0.002). According to Gaitskell et al.'s meta-analysis of two trials [7], GOG 218 and ICON 7, of women who received both concurrent and maintenance bevacizumab in addition to chemotherapy had significantly lower risk of disease progression compared with women who received concurrent and maintenance placebo or no further treatment in addition to their chemotherapy (HR, 0.75; 95% CI, 0.68 to 0.83). However, meta-analysis found no statistically significant difference in OS between women who received concurrent and maintenance bevacizumab in addition to chemotherapy, and women who received concurrent and maintenance placebo or no further treatment in addition to chemotherapy (HR, 0.87; 95% CI, 0.73 to 1.03).

Lastly, Aghajanian et al. [8] reported the preliminary results of the OCEANS trial, which was the first phase III trial of an antiangiogenic agent to demonstrate a clinical benefit to platinum-sensitive recurrent epithelial ovarian cancer (EOC), primary peritoneal (PPC), and fallopian tube cancer (FTC). A total of 484 patients were evenly randomized to arm A (control group), who received 6 cycles of gemcitabine (1,000 mg/m^2, day 1 and 8), carboplatin (AUC 4, day 1), and placebo (day 1) every three weeks, which was followed by tri-weekly maintenance placebo until disease progression, and arm B (experimental group), who received 6 cycles of gemcitabine/carboplatin with bevacizumab (15 mg/kg, day 1) every three weeks, which was followed by tri-weekly maintenance bevacizumab until disease progression. During the median follow-up of 24 months, arm B significantly increased PFS compared to arm A (12.4 vs. 8.4 months; HR, 0.484; p<0.0001). Despite the immature OS data, the bevacizumab group showed a comparably higher overall response rate (78.5% vs. 57.4%; p<0.0001) and longer duration of response (10.4 vs. 7.4 months; p<0.0001) without any new safety concerns.

In contrast to the OCEANS trial in platinum-sensitive cancers is the ongoing phase III trial of bevacizumab in platinum-resistant settings, namely AURELIA, which is a multicenter, open label, randomized, two-arm phase III trial of bevacizumab plus chemotherapy versus chemotherapy alone in patients with platinum-resistant EOC, FTC, or PPC. All patients enrolled in the AURELIA trial receive chemotherapy with either paclitaxel or topotecan or liposomal doxorubicin. Of those, bevacizumab (10 mg/kg bi-weekly or 15 mg/kg tri-weekly) is injected concomitantly only in the patients randomized to arm 2. The primary endpoint is PFS. The release of preliminary data is expected soon. At present, no sufficient evidence has confirmed whether there is a survival benefit from the use of bevacizumab in the treatment of ovarian cancer.

NEW HOPE FOR TREATMENT OF OVARIAN CANCER

Despite the somewhat disappointing results of phase III trials of molecular targeted agents in ovarian cancer, some promising reports of phase I-II studies keep alive the hope for treatment of ovarian cancer.

PARP facilitates DNA repair by binding to DNA breaks and attracting DNA repair proteins to the site of damage. Two pivotal experimental studies in 2005 showed preclinical efficacy of PARP inhibitors in tumors with homologous DNA repair defects, such as those arising in *BRCA1* or *BRCA2* mutation carriers with ovarian cancer [9,10]. Subsequent phase I and II studies of *BRCA1* or *BRCA2* mutations carriers have confirmed the activity of the PARP inhibitor, olaparib, with an objective response rate of 33% in patients with ovarian cancer [11,12]. However, the efficacy of PARP inhibitors was established only in a population with germline mutations in the *BRCA1* and *BRCA2* genes, which accounted for only about 10% of epithelial ovarian cancer [13]. In 2011, two phase II studies showed the activity of olaparib in women with high-grade serous ovarian cancer who did not have germline *BRCA1* or *BRCA2* mutations. The first study was a phase II, multicenter, open-label, non-randomized study with 91 patients (65 ovarian and 26 breast cancer) [14]. Objective response rates by the Response Evaluation Criteria in Solid Tumors (RECIST) were 41% (7/17) and 24% (11/46) in patients with and without *BRCA1* or *BRCA2* mutations, respectively. No serious adverse events were observed. The second study was presented by Ledermann [15] at the ASCO Annual Meeting in 2011. A total of 265 patients with platinum-sensitive relapsed serous ovarian cancer were randomized regardless of *BRCA1* or *BRCA2* mutations status (136 to oral olaparib 400 mg bid and 129 to placebo). PFS by RECIST was significantly longer in the olaparib than the placebo group (HR, 0.35; 95% CI, 0.25 to 0.49; p<0.00001; median 8.4 versus 4.8 months). The majority of adverse events were CTCAE grade 1 or 2, nausea, fatigue, vomiting, and anemia. Additional phase II trials of the PARP inhibitor, iniparib, in combination with gemcitabine/carboplatin in patients with platinum-sensitive and platinum-resistant recurrent ovarian cancer were also presented at the ASCO Annual Meeting in 2011 [16,17]. Compared with data from previous studies, the preliminary analyses of 17 patients with platinum-sensitive recurrent ovarian cancer and 19 patients with platinum-resistant recurrent ovarian cancer demonstrated increased overall response rates (70.6% vs. 47.2% and 31.6% vs. 11.7%, respectively) without unexpected toxicities. These findings confirm the hypothesis that patients with common sporadic tumors can be targeted effectively with PARP inhibitor therapy [13]; thus, further assessment of the drug in clinical trials is needed.

Finally, a phase I trial of another molecular targeted option, the AKT inhibitor (GSK2141795) was presented at the European Multidisciplinary Cancer Congress, 2011, in Stockholm, Sweden [18]. This small study showed 3 responses, one of which was a patient with clear cell carcinoma who had mutations of the PI3/AKT pathway. Considering that clear cell carcinoma is one of the most difficult subtypes to treat, the AKT inhibitor needs to be studied in further clinical trials because clear cell carcinoma has a high frequency of the mutation.

QUALITY OF LIFE OF POST-RISK-REDUCING SALPINGO-OOPHORECTOMY SURVIVORS

Risk-reducing salpingo-oophorectomy (RRSO) is currently recommended for *BRCA* 1/2 mutation carriers at the completion of the childbearing years between the ages of 35 and 40 or younger in carriers with a familial cancer history of early onset [19-21]. According to the report from a research group at the MD Anderson Cancer Center, the majority of women who were at high risk for breast and ovarian cancer were satisfied with their choice of a risk-reduction strategy [22], the standard practice of RRSO according to the recommendation has increased the number of post-RRSO survivors who are at risk of primary peritoneal cancer, bone loss, and menopausal symptoms [23]. However, there is a lack of post-RRSO health care guidelines for this cohort of patients.

In 2011, several studies focused on post-RRSO care. An abstract regarding the impact of hormone replacement therapy (HRT) on the risk of breast cancer in post-RRSO survivors was presented at the ASCO Annual Meeting in 2011 [24]. In 1229 BRCA1 (n=795) and BRCA2 (n=504) mutation carriers, HRT following RRSO was not associated with an increased risk of breast cancer compared with those with no RRSO (HR, 0.46, 95% CI, 0.28 to 0.76 vs. HR, 0.51, 95% CI, 0.32 to 0.80). In BRCA1 mutation carriers, HRT used both with (HR, 0.52) and without (HR, 0.29) RRSO was associated with a decreased risk of breast cancer. Another study, conducted by Challberg et al. [25], used a questionnaire. They evaluated menopausal symptoms and bone health in 212 questionnaire respondents (response rate 73%) who underwent RRSO before the age of 48. The percentage of patients currently on HRT who experienced "very much" or "quite a bit" appeared to be less for hot flushes, night sweats and vaginal dryness than those who had never used HRT or previous HRT users. Bone loss with a T score of less than -1.0 was present in 5 out of 31 (16%) women with no period of estrogen deprivation before 50 years compared with 37 out of 78 (47%) of those with more than 24 months of estrogen deprivation (p=0.03). They recommended that women undergoing RRSO before 50 years should be counseled concerning the risk and benefits of HRT because the risks of breast cancer from estrogen-only HRT appeared to be relatively small. Cohen et al. [26] also reported high rates of osteopenia and osteoporosis in a cohort of BRCA1/2 mutation carriers with breast cancer undergoing RRSO prior to 50. However, six of 10 (60%) patients who reported no history of dual-energy X-ray absorptiometry (DXA) bone scan said that their non-use was because the "MD did not recommend screening," and two out of six (33%) patients with menopausal symptoms not receiving HRT and with no known contraindication to its use were advised against HRT by their physicians [23]. Based on this study's result, therefore, Chapman et al. [23] concluded that the inconsistent post-RRSO care was attributed to the lack of post-RRSO health care guidelines and proposed guidelines. Further work on the development of standardized post-RRSO health care guidelines is therefore necessary.

THE RISK OF OVARIAN MALIGNANCY ALGORITHM (ROMA): HE4 AND CA-125

According to the final report in 2011 of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, simultaneous screening with CA-125 and transvaginal ultrasound compared with usual care did not reduce ovarian cancer mortality [27]. However, we are currently expecting the final results of the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS), which is based on the promising preliminary findings of 2009 regarding the prevalence screening of ovarian cancer [28].

Apart from effective screening of the general population, risk evaluation for epithelial ovarian cancer in women with pelvic mass was another important issue to be established. Since the first report of the good performance of the dual marker combination of human epididymis protein 4 (HE4) and CA-125 for risk prediction of ovarian malignancies by Moore et al. [29] in 2009, the performance of the combination of HE4 and CA-125 values has been investigated for effective triage of women with a pelvic mass: risk of ovarian malignancy algorithm (ROMA).

A prospective validation study of ROMA analyzed the performance of HE4, CA-125, and ROMA of 389 patients with a pelvic mass [30]. The study failed to demonstrate better performance of ROMA than CA-125 alone (receiver operator characteristic-area under curve [ROC-AUC], 0.898 vs. 0.877). Despite the excellent ability of HE4 to discriminate between endometriosis and ovarian cancer, ovarian cancer will cause a raised CA-125 and HE4, whereas endometriosis will only cause

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a raised CA-125. Even for pre-menopausal patients, HE4 and ROMA did not perform better than CA-125. This is in contrast to the previous results of Moore et al. [29], who found that a combination of CA-125 and HE4 performed better than CA-125 alone. Furthermore, they suggested the chances of HE4 or ROMA as a successful screening marker were low because very high specificities were required in screening for low prevalent disease.

Another large study on ROMA was conducted by Bandiera et al. [31], who analyzed the performance of HE4 and ROMA with preoperative serum samples from 419 women, of which 140 were healthy controls, 131 were ovarian benign cysts, 34 were endometriosis, and 114 were epithelial ovarian cancers. For the discrimination of benign masses from epithelial ovarian cancers in premenopausal women, the sensitivity and specificity were 92.3% and 59.4% for CA-125, 84.6% an 94.2% for HE4, and 84.6% and 81.2% for ROMA, whereas in postmenopausal women, the sensitivity and specificity were 94.3% and 82.3% for CA-125, 78.2% and 99.0% for HE4, and 93.1% and 84.4% for ROMA. Multivariate analysis revealed that elevated HE4 and ROMA were independent prognostic factors for shorter OS and PFS. The inconsistency of these results provides a rationale for researchers to perform multicenter studies in order to draw firm conclusions.

RATIONALES OF PROMOTION OF HPV VACCINE COVERAGE IN LOW-RESOURCE REGIONS

In 2011, three influential study results gave an additional explanation for the reason that we should focus human papillomavirus (HPV) vaccination efforts in low-resource regions to reduce cervical cancers efficiently: cross-protective efficacy; the efficacy of fewer than three doses of a bivalent HPV 16/18 vaccine; and early effect of the HPV vaccination program. A pair of four-year end-of-study analyses of the randomized, double-blind Papilloma Trial against Cancer in Young Adults (PATRICIA) trial reported strong evidence for near 100% prophylactic vaccine efficacy in HPV-naive women at any age and cross-protective efficacy of the HPV 16/18 vaccine [32,33]. A total of 46,402 healthy women aged 15-25 years with no more than six lifetime sexual partners were randomized to HPV 16/18 vaccine or a control hepatitis A vaccine and analyzed to estimate the extent of cross-protection. Vaccine efficacy was evaluated against six-month persistent infection, cervical intraepithelial neoplasia 2 or greater (CIN II+) associated with 12 non-vaccine HPV types, and CIN III+ associated with the composite of 12 non-vaccine HPV types. Consistent vaccine efficacy of the HPV 16/18 vaccine against persistent infection and CIN II+ was seen for HPV-33, 31, 45, and 51, which showed cross-protective efficacy of the HPV 16/18 vaccine against four oncogenic non-vaccine HPV types.

Kreimer et al. [34] evaluated the vaccine efficacy of fewer than three doses of the HPV 16/18 vaccine in the Costa Rica vaccine trial. Because many of the 7,153 women missed one or more of three doses of a randomly assigned HPV16/18 vaccine or control (hepatitis A) vaccine, vaccine efficacy was evaluated in each dosage group by determination of the number of newly detected HPV 16 or HPV 18 infections that persisted at least one year. They found that incident HPV 16 or HPV 18 infections that persisted for 1 year were not related to dosage of the control vaccine. Specifically, vaccine efficacy was 80.9%, 84.1%, and 100% for three, two, and one dose(s) of the HPV vaccine, respectively. They concluded that two doses of the HPV 16/18 vaccine, and maybe even one dose, were as protective as three doses in protecting against persistent HPV 16/18 infections.

Lastly, an Australian ecological study reported the early effect of the HPV vaccination program on cervical abnormalities [35]. They compared the incidence of high-grade cervical abnormalities (HGAs) and low-grade cytological abnormalities (LGAs) before and after the vaccination program began. A decrease in the incidence of HGAs by 0.38% (95% CI, 0.61 to 0.16) in girls younger than 18 years was observed after the introduction of the vaccination program. However, no similar temporal decline was recorded for LGAs or in older age groups. This study was the first to report the effect of a national HPV vaccination program on cervical abnormalities at a population level. The fact that the decrease in the incidence of HGA in young women soon after the implementation of the vaccination program suggested that we should begin screening women at a young age because of the high cost-effectiveness of this young age group. From a public health perspective, the cost-effectiveness of increasing HPV vaccine coverage seems very important in preventing cervical cancer in low-resource settings. These three findings in 2011 support the evidence for improving cost-effectiveness.

Of note were efficacy and safety reports of quadrivalent HPV vaccine against anal HPV infection and anal intraepithelial neoplasia [36]. Of 602 men who have sex with men, 432 (71.8%) had completed the protocol. Each 299 were vaccinated with quadrivalent HPV vaccine and with placebo, respectively. Efficacy of the quadrivalent HPV vaccine against anal intraepithelial neoplasia associated with HPV 6, 11, 16, or 18 was 50.3% in the intention-to-treat population and 77.5% in the per-protocol efficacy population. No vaccine-related serious adverse events were observed.

EVIDENCE OF SAFETY AND FEASIBILITY IN HPV-BASED CERVICAL CANCER SCREENING

Based on the better sensitivity of the HPV test than cervical cytology for the detection of CIN II, CIN III and cancer, co-screening with HPV and a papanicolau (Pap) test every three years for women with normal cytology and negative HPV test results is currently recommended by the American Cancer Society and American College of Obstetricians and Gynecologists guidelines [37]. However, only 19% of US clinicians would recommend the three-year follow-up with co-screening for these women because of the concern about the cancer risk accrued over three years [38].

Several studies in 2011 yielded safety and feasibility evidence for HPV-based cervical cancer screening. The most influential was a population-based study in routine clinical practice by Katki et al. [39], who showed safety in routine clinical practice of three-year screening with HPV test and Pap test for women testing negative for HPV with normal cytology (HPV-negative/Pap-negative) with 331,818 eligible women aged 30 years and older. The five-year cervical cancer risk in HPV-negative/Pap-negative women was 0.016% (3.2/100,000/year), only slightly smaller than 0.019% (3.8/100,000/year) risk in HPV-negative women (p=0.800). In comparison, the five-year cervical cancer risk in Pap-negative women was 0.037% (7.5/100,000/year; p=0.300). The results indeed provided support for three-year HPV alone-based screening of HPV-negative women because they had an extremely low risk of developing cervical cancer over five years. On the other hand, abnormal Pap test greatly increased the five-year cancer risk for the 16,757 HPV-positive women (12.1% vs. 5.9%, p<0.0001). In the HPV-positive women, Pap test had a significant role in further triage. Interestingly, a higher percentage of disease outcomes was shown in HPV-positive/Pap-negative women than in HPV-negative/Pap-positive women for CIN III or adenocarcinoma in situ (35% vs. 4%, p<0.0001), adenocarcinoma in situ (44% vs. 4%, p<0.0001), total cancers (29% vs. 10%, p=0.004), and especially adenocarcinoma (63% vs. 0%, p<0.0001). It suggested that incorporating HPV testing with cytology could earlier detect women at high risk of cervical cancer, especially adenocarcinoma, which was poorly identified by Pap tests.

Evidence for the feasibility of HPV-based cervical cancer screening was provided by studies for HPV self-sampling, which was counted as alternative strategy of non-attendees for cervical cancer screening. According to a recent survey, reasons for non-attendance of cervical screening included the unpleasant/embarrassing nature of examination, practical issues such as lack of time, problems with transport, making appointments, and perceptions of being at low risk for disease [40]. A recent randomized controlled trial showed a low attendance rate (4.5%) for cytology screening in the control group versus a higher total response rate (10.2%) in the self-sampling group, which suggested that self-sampled HPV tests could be an option for increasing participation in cervical cancer screening [40]. In addition, many community-based randomized controlled trials showed the higher sensitivity of the self-sampled HPV test than clinic-based cervical cytology to detect invasive cervical cancer (odds ratio [OR], 4.2 [41], 5.4 [42], and 2.8 [43]). Therefore, we can overcome some of the practical and emotional barriers to screening attendance by means of a self-sampled HPV test in both developed countries and low resource regions with a lack of infrastructure to maintain high quality laboratory results.

TREATMENT OF LOCALLY ADVANCED CERVICAL CANCER

Since the paradigm change in 1999 for the treatment of locally advanced cervical cancer from radiation therapy alone to cisplatin-based chemoradiation [44], no study has suggested an adjuvant therapeutic regimen that showed additional survival benefits in patients with locally advanced cervical cancer until a recent phase III randomized trial by Duenas-Gonzalez et al. [45]. They demonstrated that gemcitabine-cisplatin chemoradiation followed by brachytherapy and adjuvant gemcitabine-cisplatin chemotherapy (arm A) improved both PFS (HR, 0.68; 95% CI, 0.49 to 0.95; p=0.022) and OS (HR, 0.54; 95% CI, 0.37 to 0.79; p=0.001) compared with cisplatin-based chemoradiation followed by brachytherapy alone (arm B). Grade 3 and 4 toxicities, most commonly hematologic toxicities, neutropenia, were more frequent in arm A than arm B (86.5% vs. 46.3%, respectively; p<0.001). Of the three deaths that occurred in arm A during or within 30 days of the study treatment, two were possibly related to study treatment toxicity. Therefore, concerns about treatment-related deaths make this regimen difficult to accept as a standard-of-care without a more careful study regarding late toxicity [46].

We expect positive results from three Gynecologic Cancer Intergroup (GCIG) clinical trials for locally advanced cervical cancer, which have just begun or are just going to begin: OUTBACK, INTERLACE (Induction Chemotherapy in Locally Advanced Cervical Cancer), and TACO (Tri-weekly Administration of Cisplatin in Locally Advanced Cervical Cancer) trials. First, the OUTBACK trial is a phase III trial of adjuvant chemotherapy following chemoradiation as the primary treatment for patients with stage IB1 and positive LNs, IB2, II, IIIB or IVA cervical cancer compared with chemoradiation alone. Led by the Australia & New Zealand Gynecological Oncology Group

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(ANZGOG), the OUTBACK trial opened to recruitment in March 2011 with OS as the primary endpoint. The recruitment target is 780 participants. Second, the INTERLACE trial, which is led by the Medical Research Council/National Cancer Research Institute (NCRI), is a phase III multicenter trial of weekly induction chemotherapy (paclitaxel 80 mg/m^2 plus carboplatin AUC2) followed by standard chemoradiation versus standard chemoradiation alone in patients with locally advanced cervical cancer. INTERLACE opened to recruitment July 2011. Lastly, the TACO trial was proposed by both by Dr. Ryu of the Korean Gynecologic Oncology Group (KGOG) and by Dr. Wilailak of the Thai Gynecologic Cancer Society (TGCS) (KGOG 1027/THAI 2012). It is based on the positive results of five-year survival of a pilot randomized trial of weekly versus tri-weekly cisplatin-based chemoradiation in locally advanced cervical cancer (88.7% vs. 66.5%, respectively; HR, 0.375; 95% CI, 0.154 to 0.914; p=0.03) [47]. The principal investigators are now preparing to launch the TACO trial as an international, multicenter, randomized phase III trial comparing six cycles of weekly cisplatin 40 mg/m^2 with three cycles of tri-weekly cisplatin 75 mg/m^2 for chemoradiation in locally advanced cervical cancer. We expect new treatment regimens to bring significant improvement in the near future to the survival rates of patients with locally advanced cervical cancer.

SENTINEL-NODE BIOPSY IN EARLY STAGE ENDOMETRIAL CANCER

For early endometrial cancer, the prognostic relevance of assessing lymph node status by lymphadenectomy is still controversial although randomized controlled trials and a meta-analysis have shown that pelvic lymph node dissection (PLND) has no effect on patient survival and leads to a high incidence of related complications [48-50]. Therefore, tremendous effort has been concentrated on preoperative or intraoperative prediction of LN metastasis to identify the indication of systematic lymphadenectomy, but without success. A meta-analysis by Selman et al., suggested that sentinel node biopsy is more accurate than MRI and CT scan in assessing LN status in endometrial cancer [51]. The main interest in the sentinel-node concept for patients with early stage endometrial cancer is the reduction of the morbidity of extensive surgical staging by lymphadenectomy while accurately identifying patients who will benefit from adjuvant therapy.

A prospective multicenter study published in 2011 showed the detection rate and diagnostic accuracy of sentinel LN biopsy in early stage endometrial cancer (SENTI-ENDO) [52]. A total of 133 patients with stage I-II endometrial cancer had pelvic sentinel LN assessment via cervical dual injection with technetium and patent blue. In accordance with French guidelines, the extent of lymphadenectomy was determined according to preoperative pathological results [53]. All patients with type 1 endometrial cancer (endometrioid) had pelvic lymphadenectomy after removal of the sentinel LNs. A para-aortic lymphadenectomy was recommended if metastases were detected on intraoperative histology or after definitive histology; 15 (12%) patients underwent para-aortic lymphadnectomy. All patients belonged to one of the three risk groups defined by FIGO classification in 2009: 57 low risk-type 1 endometrial cancer, stage IA grade 1 or 2; 33 intermediate risk type 1 endometrial cancer, stage 1A grade 3, or stage IB grade 1 or 2; and 16 high risk type 1 endometrial cancer, sage IB grade 3, or type 2 endometrial cancer; or any stage and grade [54]. At least one sentinel LN was detected in 89% of eligible patients (111 of 125). The clinical value of sentinel LN biopsy is based on its reliable negative predictive value (NPV) and high sensitivity to detect metastatic disease [55]. In this study, NPV and sensitivity showed 100% for each hemipelvis as a unit. However, NPV dropped to 97%, but was still high when the patient was considered as the unit of analysis because sentinel LN was not involved in three of the 19 patients who had pelvic LN metastases (two in contralateral pelvic area and one in the para-aortic area). Of the 16 patients with positive sentinel LNs, 6, 5, and 5 occurred in patients with low, intermediate, and high risk endometrial cancer, respectively. Notably, no LN metastasis other than positive sentinel LN occurred in patients with low or intermediate risk endometrial cancer. The study suggested that sentinel LN biopsy alone was enough to justify adjuvant therapy without the need for complete pelvic lymphadenectomy in these patients. However, the high incidence of metastases in both sentinel and non-sentinel LNs in patients with high-risk endometrial cancer led to the performance of pelvic lymphadenectomy in high risk patients. This study seems quite meaningful in that it might suggest the important role of a sentinel LN biopsy in the triage for the extent of lymphadenectomy in early endometrial cancer.

EFFECTIVE STRATEGIES FOR PREVENTION AND TREATMENT OF BREAST CANCER

In 2011, two notable achievements in the field of breast cancer research were for the prevention and the treatment of metastatic disease, respectively.

The first study was a randomized, placebo-controlled, double-blind trial for the efficacy of exemestane, an aromatase inhibitor, in the prevention of breast cancer in postmeno-

pausal women [56]. This study was initiated to overcome the low acceptance of tamoxifene or raloxifene for reducing the risk of breast cancer, partly because of rare but serious toxic effects [57-61]. The eligibility criteria included postmenopausal women 35 years of age or older with at least one of the following risk factors: 60 years or older; Gail 5-year risk score greater than 1.66% (chances in 100 of invasive breast cancer developing within 5 years); prior atypical ductal or lobular hyperplasia or lobular carcinoma in situ; ductal carcinoma in situ with mastectomy. A total of 4560 women were randomized to exemestane (2,285 patients) or placebo (2,275 patients). The primary outcome was the incidence of invasive breast cancer. At a median follow-up of 35 months, 11 and 32 invasive breast cancers were diagnosed in the exemestane group and the placebo group, respectively (annual incidence, 0.19% vs. 0.55%; HR, 0.35; 95% CI, 0.18 to 0.70; p=0.002). Adverse events occurred in 5% or more of subjects, 88% in the exemestane group versus 85% in the placebo group (p=0.003). Arthritis (p=0.01) and hot flushes (p<0.001) were more common in the exemestane group. The major reason for early discontinuation of the protocol treatments were toxic effects (15.4% vs. 10.8%, p<0.001). However, the researchers concluded that, with its excellent safety profile, exemestane significantly reduced invasive breast cancers in postmenopausal women who were at moderately increased risk for breast cancer, based on the similarity between the two groups in terms of skeletal fractures, cardiovascular events, other cancers, or treatment related deaths.

Second was the phase III open-label randomized study, which focused on eribulin monotherapy versus treatment of physician's choice (TPC) in patients with metastatic breast cancer (EMBRACE) [62]. It was not until EMBRACE that a biological agent showed significant improvement of OS in patients with heavily pretreated metastatic breast cancer. Eribulin mesilate is a non-taxane inhibitor of microtubule dynamics in the halichondrin class of antineoplastic drugs. Based on the promising results of phase II eribulin studies, EMBRACE enrolled a total of 762 women who were randomly allocated to either the eribulin group (508 patients) or the TPC group (254 patients). In particular, EMBRACE used the TPC group as a control group in order to mirror clinical practice at the time in this setting. OS for eribulin was significantly increased compared with TPC group (HR, 0.81; 95% CI, 0.66 to 0.99; p=0.041), with median OS 13.1 and 10.6 months in patients receiving eribulin and those assigned TPC, respectively. While asthenia and fatigue were the most common adverse events in both groups, peripheral neuropathy was the most common adverse event leading to the discontinuation of eribulin (5%). Considering its manageable toxicity profile, relative ease of administration, short infusion time, and no requirement for premedication to prevent hypersensitivity, eribulin was suggested by this study as a new potential standard drug for women with heavily pretreated metastatic breast cancer.

PREVENTION OF CHEMOTHERAPY-INDUCED EARLY MENOPAUSE IN BREAST CANCER

Approximately 6% of women with breast cancer are diagnosed before age of 40 years [63]. Premenopausal women with breast cancer are at high risk of early menopause because most of young patients with breast cancer receive a certain combination of systemic chemotherapy and hormonal therapy considering the adverse outcome of young patients [64]. Gerber et al. [65] made a rough estimate that each month of chemotherapy translated into 1.5 years of lost reproductive life. Based on the promising results of preclinical and early clinical data of ovarian protective effect of a gonadotropin-releasing hormone (GnRH) analogue during chemotherapy [66,67], a randomized, phase 3 superiority trial was conducted: Prevention of Menopause Induced by Chemotherapy: A Study in Early Breast Cancer Patients-Gruppo Italiano Mammella 6 (PROMISE-GIM6) [63]. Of 281 premenopausal women with stage I-III breast cancer, 133 and 148 were allocated to receive chemotherapy alone and chemotherapy plus GnRH analogue, triptorelin, respectively. Triptorelin was administered intramuscularly at a dose of 3.75 mg at least 1 week before chemotherapy and then every 4 weeks for the duration of chemotherapy. Primary endpoint was early menopause which was defined as no resumption of menstrual activity and postmenopausal levels of follicle-stimulating hormone and estradiol 1 year after the last cycle of chemotherapy. The rate of early menopause was 25.9% in the chemotherapy-alone group and 8.9% in the chemotherapy plus triptorelin group with OR for treatment-related early menopause 0.28 (95% CI, 0.14 to 0.59; p<0.001).

The role of GnRH analogue in preserving ovarian function during chemotherapy for breast cancer is still controversial [68]. Despite the lack of data concerning the long-term maintenance of ovarian function and veiled mechanisms of action of GnRH analogues preserving ovarian function, PROMISE-GIM6 is the largest study that showed temporarily suppressing ovarian function by administering triptorelin reduced the incidence of chemotherapy-induced early menopause in premenopausal women with early-stage breast cancer.

CONCLUSION

Despite enormous efforts in research, the prognosis of ovar-

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ian cancer is still very poor. However, integrated genomic analyses of ovarian cancer by TCGA might yield opportunities to improve the prognosis of ovarian cancer through subtype-specific etiological approaches. Moreover, maximal cytoreduction through a real-time tumor-specific surgical visualization system using a FR-α targeted fluorescent agent might enhance the therapeutic effect of conventional cytoreductive surgery as well as subsequent chemotherapy. For cost-effectiveness in low resource settings, HPV vaccination could be recommended more actively in order to reduce the high incidence of cervical cancer. We hope that SENTI-ENDO study will be influential in suggesting guidelines for the management of PLND in patients with early-stage endometrial cancer. Regarding breast cancer, the agents, exemestane and eribulin, are expected to be effective in reducing the incidence of breast cancer and improving the poor prognosis of heavily treated metastatic breast cancer, respectively. Furthermore, GnRH analogues might be offered with solider evidence to premenopausal patients with breast cancer who wish to decrease the risk of premature ovarian failure associated with chemotherapy. Finally, we expect that more practice-changing studies will be performed in the field of gynecologic oncology in the coming year.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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