



Major clinical research advances in gynecologic cancer in 2014

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In 2014, 9 topics were selected as major advances in clinical research for gynecologic oncology: 2 each in cervical and corpus cancer, 4 in ovarian cancer, and 1 in breast cancer. For cervical cancer, several therapeutic agents showed viable antitumor clinical response in recurrent and metastatic disease: bevacizumab, cediranib, and immunotherapies including human papillomavirus (HPV)-tumor infiltrating lymphocytes and Z-100. The HPV test received FDA approval as the primary screening tool of cervical cancer in women aged 25 and older, based on the results of the ATHENA trial, which suggested that the HPV test was a more sensitive and efficient strategy for cervical cancer screening than methods based solely on cytology. For corpus cancers, results of a phase III Gynecologic Oncology Group (GOG) 249 study of early-stage endometrial cancer with high-intermediate risk factors are followed by the controversial topic of uterine power morcellation in minimally invasive gynecologic surgery. Promising results of phase II studies regarding the effectiveness of olaparib in various ovarian cancer settings are summarized. After a brief review of results from a phase III study on pazopanib maintenance therapy in advanced ovarian cancer, 2 outstanding 2014 ASCO presentations cover the topic of using molecular subtypes in predicting response to bevacizumab. A review of the use of opportunistic bilateral salpingectomy as an ovarian cancer preventive strategy in the general population is presented. Two remarkable studies that discussed the effectiveness of adjuvant ovarian suppression in premenopausal early breast cancer have been selected as the last topics covered in this review.

Keywords: Angiogenesis Inhibitor; Breast Neoplasm; Early Detection of Cancer; Leiomyosarcoma; Ovarian Neoplasm; Poly (ADP-ribose) Polymerase

INTRODUCTION

Following the remarkable study of bevacizumab in recurrent and metastatic cervical cancer, several ingenious studies performed in 2014 demonstrated the efficacy of another antiangiogenic agent, cediranib, and immunotherapeutic

agents in patients with hitherto hopeless states of metastatic cervical cancer. Olaparib, a front-runner of poly (ADP-ribose) polymerase (PARP) inhibitors, was tested in various clinical settings, with promising results emerging from the phase II studies. Although there was no additional quality evidence in 2014, many clinical societies presented their position statements on the use of power morcellation in minimally invasive surgery (MIS) for presumed myoma. In **Table 1**, we have summarized 9 topics that are included in this review of the major clinical research advances in gynecologic cancer in 2014.

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Table 1. Nine topics of major clinical research advances in gynecologic cancer in 2014 according to the site of cancer

Site of cancer	Topic	Reference
Uterine cervix	1. Treatment of advanced or metastatic cervical cancer	
	1) Antiangiogenic targeted therapy: bevacizumab (GOG 240) and cediranib (CIRCCa trial)	[1,2]
	2) Immunotherapy: HPV-tumor-infiltrating lymphocytes and Z-100	[3,4]
	2. HPV test as a primary screening tool of cervical cancer	
	1) FDA approval of Cobas HPV test	[7]
Uterine corpus	2) Efficacy of HPV-based screening test: follow-up results of 4 RCTs in Europe	[12-16]
	3) Meta-analysis of self-collection versus clinician collection	[17]
	3. Update of adjuvant radiation therapy in endometrial cancer	
Uterine corpus	1) A phase III study of early stage endometrial cancer with high-intermediate risk factors (GOG 249)	[19]
	2) ASTRO new guidelines	[7]
Ovary	4. Uterine power morcellation: a hot potato in minimally invasive gynecologic surgery	[24,25,28-30]
	5. Update of PARP inhibitors in ovarian cancer	
	1) Olaparib maintenance therapy in PSROC	[33,34]
	2) Olaparib combined with chemotherapy in PSROC	[35]
	3) Combination of cediranib and olaparib in PSROC	[36]
	4) Other PARP inhibitors	[32]
	6. Pazopanib maintenance therapy for an effective survival prolongation in advanced ovarian cancer	[42]
	7. Tailored treatment according to the molecular subtype of high-grade serous ovarian cancer	[45,46]
8. Opportunistic bilateral salpingectomy for ovarian cancer risk-reducing procedure in the general population	[52,54]	
Female breast	9. Unveiled efficacy of ovarian suppression in premenopausal breast cancer	
	1) Adjuvant ovarian suppression in premenopausal early breast cancer	[56]
	2) Adjuvant aromatase inhibitor exemestane with ovarian suppression in premenopausal early breast cancer	[57]

ASTRO, American Society for Radiation Oncology; FDA, the US Food and Drug Administration; GOG, Gynecologic Oncology Group; HPV, human papillomavirus; PARP, poly (ADP-ribose) polymerase; PSROC, platinum-sensitive recurrent ovarian cancer; RCT, randomized controlled trial.

TREATMENT OF ADVANCED OR METASTATIC CERVICAL CANCER

1. Antiangiogenic targeted therapy: bevacizumab and cediranib

At the 2014 European Society for Medical Oncology (ESMO) Congress held in Madrid, Spain, 2 oral abstracts were presented on the use of antiangiogenic-targeted agents in cervical cancer under the theme of "Precision Medicine in Cancer Care." The first abstract summarized the final overall survival (OS) results from the Gynecologic Oncology Group (GOG) 240, a phase III randomized trial of bevacizumab for the treatment of recurrent and metastatic cervical cancer, as reported by Tewari et al. [1]. Briefly, a total of 452 women with metastatic, recurrent, or persistent cervical cancers that were incurable with standard treatment options were randomized to 1 of 4 treatment arms: (1) cisplatin (50 mg/m²) plus paclitaxel alone (135–175 mg/m²), or (2) with bevacizumab 15 mg/kg, or (3) topotecan (0.75 mg/m² on days 1–3) plus paclitaxel alone (175 mg/m² on day 1), or (4) with bevacizumab. The second interim

analysis after 271 deaths revealed a significant difference in median OS between bevacizumab and non-bevacizumab groups (hazard ratio [HR], 0.71; 95% confidence interval [CI], 0.54 to 0.95; 1-sided p=0.0035); the OS difference remained significant at the time of March 7, 2014, when 348 deaths occurred (16.8 months vs. 13.3 months; HR, 0.765; 95% CI, 0.62 to 0.95; p=0.0068). Similar results were obtained for both chemotherapy regimens. This report confirmed a >50-month sustained clinical benefit with the incorporation of bevacizumab into chemotherapy for advanced cervical cancer. However, more severe toxicity profiles were observed with the addition of bevacizumab, including 3.2% gastrointestinal (GI) perforation rate, a higher incidence of GI-vaginal fistulae (8.2% vs. 0.9%), and higher incidence of ≥ grade 3 thromboembolic events (10.6% vs. 5.4%).

The second abstract on an antiangiogenic targeted agent in cervical cancer presented in the 2014 ESMO Congress was the CIRCCa trial [2]. In the CIRCCa trial, 69 women with primary metastatic or relapsed cervical cancer were randomized (1:1) to receive carboplatin (area under the curve [AUC], 5) plus pa-

clitaxel (175 mg/m² tri-weekly) for a maximum of 6 cycles plus cediranib (20 mg/day; n=34); a potent tyrosine kinase inhibitor of vascular endothelial growth factor receptor (VEGFR) 1, 2, and 3; or placebo (n=35) concurrently with chemotherapy, and later as maintenance therapy until progression. A total of 79% of the patients completed 6 cycles of chemotherapy, 22% stopped placebo and 17% stopped cediranib during the study period. Median progression-free survival (PFS) of cediranib group was superior to that of placebo group (35 months vs. 30 months; HR, 0.61; 80% CI, 0.41 to 0.89; p=0.046). However, as CIRCCa closed prematurely owing to the cessation of commercial production of cediranib, the statistical analysis of the difference in median OS between the two groups was underpowered for comparison (59 weeks vs. 63 weeks; HR, 0.93; 80% CI, 0.64 to 1.36; p=0.401). Typical toxicities of antiangiogenic and tyrosine kinase inhibitor were more frequently observed in the cediranib group than in the placebo group: grade 2 to 4 diarrhea (50% vs. 18% during chemotherapy and 19% vs. 9% during the maintenance period), and grade 2 to 4 hypertension (34% vs. 12%). Although the results were inconclusive, the CIRCCa trial demonstrated the effectiveness of cediranib in advanced cervical cancer, which deserves a phase III study.

2. Immunotherapy: human papillomavirus-tumor-infiltrating lymphocytes and Z-100

Immunotherapy is still in the early developmental stages for use in cervical cancer therapy. In 2014, there were some promising study results for immunotherapy in the treatment of cervical cancer: human papillomavirus (HPV)-targeted tumor-infiltrating lymphocytes (TIL) in metastatic disease; Z-100 in locally advanced cervical cancer (LACC). The first study was a small, proof-of-concept study presented by Christian S. Hinrichs at the annual meeting of the American Society of Clinical Oncology (ASCO) in Chicago in July 2014 [3]. In the clinical trial (NCT01585428), nine patients with metastatic cervical cancer were treated with an infusion of HPV-TIL selected for HPV E6- and E7-reactivity after non-myeloablative conditioning with cyclophosphamide (60 mg/kg × 2 days) plus fludarabine (25 mg/m² × 5 days) and followed by a high-dose aldesleukin bolus. Except for two patients who showed no HPV reactivity, which was assessed by ELISPOT, interferon-γ production, and CD137 expression assays, the infused cells showed reactivity against high-risk HPV E6 and/or E7 in six patients. However, objective clinical response that was greater than partial response was observed only for three patients: two patients achieved complete response (CR; >22 and >15 months) and one patient showed partial response (3 months). Of the two CRs, one patient had chemotherapy-refractory HPV-16+

squamous cell carcinoma and the other had chemoradiation-refractory HPV-18+ adenocarcinoma. Both patients demonstrated prolonged repopulation with HPV-reactive T cells following treatment. All participants experienced ≥ grade 3 cytopenia, and 6 experienced infection, as demonstrated by positive blood culture.

The subject of immunotherapy in cervical cancer was covered by another Japanese GOG study, a randomized phase III trial for LACC using immunomodulator Z-100, which is a hot-water extract from human tuberculosis bacilli that contains polysaccharides such as arabinomannan and mannan [4]. The authors of the Z-100 study had previously conducted a phase II study (2 μg vs. 20 μg vs. 40 μg) with radiotherapy, and a double-blind randomized phase III trial (40, lead of the phase II study vs. 0.2 μg, substitute with placebo) with radiotherapy for stage III cervical cancer [5,6]. The unexpected lead agent of the phase III trial, 0.2 μg of Z-100, was selected for the subsequent phase III placebo-controlled double-blind randomized trial of radiotherapy for LACC with or without Z-100. In this study, a total of 249 patients with stage IIB-IVA squamous cell carcinoma of the cervix were randomly assigned to receive 0.2 μg of Z-100, or placebo subcutaneously twice a week during radiotherapy, followed by maintenance therapy of once every 2 weeks until progression. Z-100 showed a trend of OS improvement compared with placebo (5-year OS rate, 75.7% vs. 65.8%; HR, 0.65; 95% CI, 0.40 to 1.04; p=0.07) regardless of whether the cohort received chemoradiation or radiotherapy alone. There were no significant differences in adverse events between the two groups. Based on the promising results of OS improvement potential and tolerable side effects in the Z-100 group, they concluded that additional validation should be made in the near future regarding the survival benefit of Z-100 in cervical cancer.

HPV TEST AS A PRIMARY SCREENING TOOL OF CERVICAL CANCER

1. FDA approval of Cobas HPV test

Of the several HPV tests for high-risk HPV approved by the US Food and Drug Administration (FDA), the Cobas HPV test (Roche Molecular Systems, Pleasanton, CA, USA) received FDA approval for the first time for use as a primary screening tool of cervical cancer for women 25 and older in April, 2014, based on the results of the ATHENA trial [7]. The Cobas HPV test is a fully automated qualitative *in vitro* test for the detection of HPV in 3 separate variants: HPV16, HPV18, and a pool of 12 other HPV genotypes (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) using amplification of target DNA by the polymerase

chain reaction (PCR) and nucleic acid hybridization. Until now, the HPV test had been used primarily as a follow-up test to resolve ambiguous Pap results, or used jointly with Pap testing. Current United State guidelines recommend that women 30 to 65 years undergo either co-testing with both HPV and Pap every 5 years or Pap testing alone every 3 years [8]. Women 21 to 30 years are expected to undergo Pap testing every 3 years. The ATHENA study for HPV DNA tests versus liquid-based cytology for cervical cancer screening demonstrated that the Cobas HPV test outperformed Pap testing alone in detecting precancerous lesions and its performance was comparable to the hybrid test [9,10]. In women who had colposcopy, the Cobas HPV test was more sensitive than liquid-based cytology for detection of cervical intraepithelial neoplasia (CIN) ≥ 3 (92.0%, 95% CI, 88.1 to 94.6 vs. 53.3%, 95% CI, 47.4 to 59.1; difference 38.7%, 95% CI, 31.9 to 45.5; $p < 0.0001$). Addition of liquid-based cytology to HPV testing increased sensitivity for CIN ≥ 3 to 96.7% (95% CI, 93.9 to 98.3), but increased the number of screened positives by 35.2% compared with HPV testing alone. They concluded that Cobas HPV testing with distinct HPV16 and HPV18 detection could provide an alternative, more sensitive, and efficient strategy for cervical cancer screening than methods based solely on cytology.

2. Efficacy of HPV-based screening test: follow-up results of 4 randomized trials in Europe

A recently published follow-up study of 4 European randomized controlled trials of HPV-based screening for cervical cancer versus cytology-based screening underscores the importance of HPV-based screening [11]. Ronco et al. [11] followed up a total of 176,464 women aged 20–64 years from the 4 previous studies: Swedescreen [12], POBASCAM [13,14], ARTISTIC [15], and NTCC [16], for a median 6.5 years and calculated the cumulative and study-adjusted rate ratio of incidence of invasive cervical cancer. The overall rate ratio for invasive cervical carcinoma was 0.60 (95% CI, 0.40 to 0.89), however, the rate ratio in women with a negative screening test at entry was 0.30 (95% CI, 0.15 to 0.60). The cumulative incidence of invasive cervical carcinoma in women with negative entry tests was 4.6/10⁵ (95% CI, 1.1 to 12.1) and 8.7/10⁵ (95% CI, 3.3 to 18.6) at 3.5 and 5.5 years, respectively, in the HPV-based group, and 15.4/10⁵ (95% CI, 7.9 to 27.0) and 36.0/10⁵ (95% CI, 23.2 to 53.5), respectively, in the cytology-based group. They concluded that HPV-based screening was 60% to 70% more effective in reducing the incidence of invasive cervical carcinomas than cytology-based screening.

3. Meta-analysis of self-collection versus clinician collection

Finally, the clinical accuracy of HPV testing on self-collected

versus clinician-collected vaginal samples was systematically reviewed in the recent meta-analysis by Arbyn et al. [17]. They showed that the pooled sensitivity (ratio 0.88 [95% CI, 0.85 to 0.91] for CIN ≥ 2 and 0.89 [95% CI, 0.83 to 0.96] for CIN ≥ 3) and specificity (ratio 0.96 [95% CI, 0.95 to 0.97] for CIN ≥ 2 and 0.96 [95% CI, 0.93 to 0.99] for CIN ≥ 3) of HPV testing on self-samples was lower than those on clinician-collected samples. Compared with the lower sensitivity and specificity of HPV testing with signal-based assays on self-versus clinician-collected samples, some PCR-based HPV tests showed similar sensitivity on self- and clinician-collected samples. Accordingly, the vaginal samples for signal-based HPV screening tests should be collected by a clinician. However, PCR-based HPV test on self-collected samples could be considered as an additional strategy for increasing screening coverage.

UPDATE OF ADJUVANT RADIATION THERAPY IN ENDOMETRIAL CANCER

1. A phase III study of early stage endometrial cancer with high-intermediate risk factors (GOG 249)

The GOG 249 conducted a randomized phase III trial of pelvic radiation therapy (RT) versus vaginal cuff brachytherapy (VCB) followed by paclitaxel/carboplatin chemotherapy (VCB/C) in patients with high risk, early stage endometrial cancer, based on the promising results of a phase II trial of VCB followed by chemotherapy in early endometrial cancer patients with high-intermediate risk factors [18]. The results were first presented as a late-breaking abstract in the Annual Meeting of the Society of Gynecologic Oncology (SGO) in Tampa, FL, USA [19]. According to the high intermediate risk factors in GOG 99, the eligibility criteria of GOG 249 were based on age, tumor grade, depth of invasion, and presence of lymphovascular space invasion (LVSI), stage II, or stage I–II serous or clear cell tumors. A total of 601 patients were randomized to pelvic RT group (n=301) or VCB/C group (n=300, vaginal brachytherapy followed by paclitaxel (175 mg/m², 3 hours) plus carboplatin (AUC=6; q 21 days for 3 cycles). Additional VCB was optional for patients with serous or clear cell tumors or stage II disease. Recurrence-free survival (RFS) was the primary endpoint. Although acute toxicity was observed more frequently in the VCB/C group, a majority of the patients in both groups completed the therapy (91% pelvic RT and 87% VCB/C). With a median follow-up of 24 months, RFS of pelvic RT group was similar to that of VCB/C group (82% vs. 84%; HR, 0.97; 95% CI, 0.64 to 1.43). Thus, they failed to demonstrate the RFS superiority of VCB/C to pelvic RT. Based on the similar RFS and tolerability for both groups, the authors concluded that pelvic

RT and VCB/C appeared to be a well-tolerated adjuvant treatment option in women with high-risk endometrial cancer.

2. New guidelines from ASTRO

The SGO recently stated that the American Society for Radiation Oncology (ASTRO) had issued guideline recommendations along with 5 key questions Regarding postoperative adjuvant RT in patients with endometrial cancer [7]. During the process of drafting these recommendations, they considered that data from the literature did not support an OS benefit for adjuvant RT in all patients; however, there was some evidence of increased risk of second malignancy in women <60 years of age at diagnosis, who received pelvic RT with VCB compared with those received VCB only [20]. The first key question sought to identify the patients with endometrioid endometrial cancer who did not require adjuvant therapy after hysterectomy. Foregoing adjuvant RT is a reasonable option for patients with no residual disease in the hysterectomy specimen despite positive biopsy, or grade 1 or 2 cancers with either no invasion or <50% myometrial invasion, especially when no other high-risk features were present. Patients with grade 3 cancers without myometrial invasion or grade 1 or 2 cancers with <50% myometrial invasion and higher risk factors such as age >60 years and/or LVSI could reasonably be treated with or without VCB. The second key question sought to identify the patients with endometrioid endometrial cancer who should receive VCB. The recently released GOG 249 results of the aforementioned questions provide substantial evidence supporting the effectiveness of VCB as pelvic RT for preventing vaginal recurrence in patients with high-intermediate risk factors. They stated that VCB was superior to pelvic RT in patients with these risk factors, particularly in patients who have undergone pelvic and para-aortic lymph node dissection. The third key question sought to identify the women who should receive adjuvant pelvic RT; patients with stage I, grade 1 or 2 with >50% myometrial invasion, and other risk factors such as age >60 years or LVSI, or grade 3 with >50% myometrial invasion may benefit from the reduced risk of pelvic recurrence. Patients with stage II with cervical stroma invasion could also benefit from pelvic RT. For stage III disease with lymph node metastasis or involved uterine serosa, ovaries/fallopian tubes, vagina, bladder, or rectum, pelvic RT should be included in postoperative adjuvant treatment together with adjuvant chemotherapy. The fourth key question addressed when VCB should be used in addition to external pelvic RT. Given the lack of substantive evidence favoring the use of VCB after pelvic RT, VCB may not generally be warranted in patients who are also undergoing external pelvic RT, unless the risk factors for vaginal recurrence

are present. The fifth key question concerned how RT and chemotherapy should be integrated in the management of endometrial cancer. The best available evidence that the panel concurred on was for concurrent chemoradiation followed by adjuvant chemotherapy in the advanced-stage endometrial cancer patients with positive nodes or involved uterine serosa, ovaries/fallopian tubes, vagina, bladder, or rectum. Alternative sequencing strategies with external pelvic RT and chemotherapy could provide another option.

UTERINE POWER MORCELLATION: A HOT POTATO IN MINIMALLY INVASIVE GYNECOLOGIC SURGERY

Uterine leiomyosarcoma is a rare but highly aggressive tumor of the uterus [21]. Even when complete resection is achieved for uterine sarcomas that are confined in the uterus, the prognosis remains very poor. The problematic part of the management of leiomyosarcoma is that there are no reliable methods to preoperatively detect the tumor; these tumors are usually identified incidentally after review of the surgical specimen of presumed uterine myomas [22]. However, rapidly and widely adopted MIS techniques such as intracorporeal power morcellation have further confounded the dilemma because of the potential risk of morcellation-associated cancer dissemination [21,23]. Although this is not a new issue in 2014, a series of announcements from reputable academic societies and the FDA since the SGO's position statement in December 2013 have intensified social attention on the morcellation issue.

The SGO asserted that morcellation is generally contraindicated in the presence of documented or highly suspected malignancy, and may be inadvisable in premalignant conditions or risk-reducing surgery [24]. The point of contention lies in determining the lowest incidence where the risk of occult sarcoma is acceptable. Many single-center retrospective studies have reported that the risk of uterine sarcoma during morcellation ranges from 0.09% to 0.49% [22,23,25-27]. Other than the wide range of risk of occult sarcoma during morcellation of presumed myoma, there is lack of consensus on the acceptable range of risk. The author of an editorial in *Lancet Oncology* argued that a 1 in 400 risk of morcellating an occult tumor was unacceptable [28]. In contrast, Goff [29], the previous president of the SGO, emphasized the clear evidence of benefit from MIS, in minimizing the morbidity of a larger open incision, in hundreds of thousands of women. Nevertheless, in April, 2014, the FDA released an official statement regarding the morcellation issue and discouraged the use of laparoscopic power morcellation for the removal of the uterus or uterine fibroids, stating: "The FDA's primary concern as we

consider the continued use of these devices is the safety and well-being of patients" [30]. Despite the FDA's communication regarding this safety issue, American Association of Gynecologic Laparoscopists (AAGL), The European Society of Gastrointestinal Endoscopy (ESGE), and American Congress of Obstetricians and Gynecologists (ACOG) remain in agreement with the SGO: MIS, including power morcellation, continues to be an option for some patients undergoing hysterectomy or myomectomy. Primarily owing to the rarity of uterine sarcoma, only poor-quality retrospective data are available. Acknowledging the limited evidence for attaining the best balance of the benefit-to-harm for now, all of the societies concur on the need to adequately inform patients of the risks, benefits, and alternatives of MIS with power morcellation. More recently, the SGO released a statement addressing the FDA's safety concern [25], stating that: "As physicians we know we must strive to never harm any one of our patients. But banning morcellation may cause more harm to more women."

UPDATE OF PARP INHIBITORS IN OVARIAN CANCER

Since the initial observation of anticancer activity of PARP inhibitors in BRCA-related ovarian cancer [31], several PARP inhibitors, for example, olaparib (AZD2281), veliparib (ABT-888), niraparib (MK4827), and rucaparib (CO338), have been tested or are currently being tested in ovarian cancer patients as part of a phase I, II or III clinical trial [32].

1. Olaparib maintenance therapy in platinum-sensitive relapsed serous ovarian cancer

In 2014, there were publications of 3 randomized phase II studies of olaparib in patients with recurrent platinum-sensitive ovarian cancer. The first report was published after the 2013 ASCO presentation of the results of BRCA mutation status subgroup analysis from a randomized, phase II study that assessed maintenance therapy with olaparib (400 mg twice a day) versus placebo in patients with platinum-sensitive recurrent serous ovarian cancer who had received ≥ 2 platinum-based regimens and who had a partial or CR to their most recent platinum-based regimen; PFS and data from the second interim analysis of OS were reported [33]. A total of 265 patients were randomized to olaparib (n=136) and placebo (n=129). A significant improvement of PFS was observed in the olaparib group, which was most marked in patients with a germline BRCA mutation (11.2 months [95% CI, 8.3 to not calculable] vs. 4.3 months [95% CI, 3.0 to 5.4]; HR, 0.18 [95% CI, 0.10 to 0.31]; $p < 0.0001$), but also in patients with wild-type BRCA (7.4 months [95% CI, 5.5 to 10.3] vs. 5.5

months [95% CI, 3.7 to 5.6]; HR, 0.54 [95% CI, 0.34 to 0.85]; $p = 0.0075$). There was no significant difference in OS between the groups at the second interim analysis with 58% maturity (HR, 0.88; 95% CI, 0.64 to 1.21; $p = 0.44$); (HR, 0.73; 95% CI, 0.45 to 1.17; $p = 0.19$) for patients with BRCA mutation, and (HR, 0.99; 95% CI, 0.63 to 1.55; $p = 0.96$) for patients with wild-type BRCA. The quality of life sub-study data from this study were presented in the 2014 ESMO Congress in Madrid, Spain [34]. There was no detrimental effect of olaparib on quality of life during the course of maintenance therapy and it there were no differences depending on BRCA mutation status.

2. Olaparib combined with chemotherapy in platinum-sensitive relapsed serous ovarian cancer

In the second report, the efficacy and tolerability of olaparib in combination with chemotherapy, followed by olaparib maintenance monotherapy, were compared with those of chemotherapy alone [35]. In this randomized phase II study in patients with platinum-sensitive recurrent high-grade serous ovarian cancer (HGSOC), a total of 162 women were randomly assigned to the olaparib (200 mg twice a day on days 1 to 10 of each 21-day cycle for the combination period, and 400 mg twice a day continuously until progression for maintenance monotherapy period) plus chemotherapy group (n=81), and the group that received chemotherapy alone (n=81). Chemotherapy comprised paclitaxel (175 mg/m² intravenous on day 1) and carboplatin (AUC=4; intravenous on day 1) for olaparib plus chemotherapy group, and paclitaxel (175 mg/m² intravenous on day 1) and carboplatin (AUC=6; intravenous on day 1) for the group that received chemotherapy alone. PFS was significantly longer in the olaparib plus chemotherapy group (median, 12.2 months [95% CI, 9.7 to 15.0]) than in the chemotherapy alone group (median, 9.6 months [95% CI, 9.1 to 9.7]; HR, 0.51 [95% CI, 0.34 to 0.77]; $p = 0.0012$), especially in patients with BRCA mutations (HR, 0.21; 95% CI, 0.08 to 0.55; $p = 0.0015$). The most common grade ≥ 3 adverse events during the combination period were neutropenia (43% vs. 35%) and anemia (9% vs. 7%). Thus, olaparib plus paclitaxel and carboplatin followed by maintenance monotherapy significantly improved PFS compared with paclitaxel and carboplatin alone, with an acceptable toxicity profile. The greatest clinical benefit was observed in patients with a BRCA mutation.

3. Combination of cediranib and olaparib in platinum-sensitive relapsed serous ovarian cancer

The last report evaluated a combination of olaparib and cediranib compared with olaparib alone in a randomized phase II study [36]. Improvements PFS and OS had previously been demonstrated in a randomized phase III trial of

cediranib in patients with relapsed platinum-sensitive ovarian cancer (ICON 6), and had been briefly reviewed in the major clinical research advances in gynecologic cancer in 2013 [37]. Cediranib plus olaparib showed activity against recurrent ovarian cancer in a previous phase I trial, with an objective response rate of 44% [38]. Based on these trial results, a phase II trial that evaluated a combination of cediranib and olaparib maintenance therapy versus olaparib alone was conducted. A total of 90 patients were randomly assigned to receive olaparib (400 mg twice a day alone; n=46), or to receive a combination of olaparib (200 mg twice a day) and cediranib (30 mg a day; n=44). An interim analysis after 50% of expected events showed significant improvement in PFS in the combination group (median 17.7 months [95% CI, 14.7 to not reached]), compared with olaparib alone group (median, 9.0 months [95% CI, 5.7 to 16.5]; HR, 0.42; 95% CI, 0.23 to 0.76; p=0.005). Grade ≥ 3 adverse events, including fatigue, diarrhea, and hypertension, were more common in the combination group than in the monotherapy group. These promising results warrant a phase III trial, evaluating the efficacy of the combination of olaparib and cediranib in recurrent platinum-sensitive ovarian cancer.

4. Other PARP inhibitors

In contrast to the promising phase II study results for olaparib, a phase II trial of veliparib failed to demonstrate PFS improvement in HGSOC [39]. In this trial, 75 patients with pretreated BRCA-mutant ovarian cancer, or patients with pretreated primary peritoneal, fallopian tube, or HGSOC were randomized to receive cyclophosphamide alone (n=38, 50 mg once a day) or with veliparib (n=37, 60 mg once a day) in 21-day cycles. There was no significant difference in median PFS between the 2 groups (2.3 months vs. 2.1 months). Stratification of patients by BRCA status did not reveal any significant improvement in PFS. Phase III studies of niraparib (NOVA, NCT01847274) and rucaparib (ARIEL3, NCT01968213) are currently accruing patients. Some of the current ongoing phase III studies of PARP inhibitors include patients with HGSOC, regardless of a germline BRCA mutation status. Notably, the possible responsiveness of non-HGSOC to PARP inhibitors would further broaden the population that might benefit from PARP inhibitors [40,41].

PAZOPANIB MAINTENANCE THERAPY FOR EFFECTIVE PROLONGATION OF SURVIVAL IN ADVANCED OVARIAN CANCER

The results of the AGO-OVAR 16 phase III randomized trial of pazopanib versus placebo in patients with advanced

ovarian cancer who showed no progression during first-line chemotherapy were published after the first presentation of incorporation of pazopanib in maintenance therapy of ovarian cancer at the 2013 ASCO annual meeting [42]. Pazopanib is an oral, multikinase inhibitor of VEGFR 1, 2, 3, platelet-derived growth factor receptor (PDGFR), and c-Kit. A total of 940 patients with cancer of the ovary, fallopian tube, or peritoneum, International Federation of Gynecology and Obstetrics (FIGO) stage II to IV who had received at least 5 cycles of platinum-taxane chemotherapy were randomly assigned (1:1) to receive pazopanib (800 mg/day; n=472), or placebo (n=468) for up to 24 months. Although interim survival analysis at the time of 35.6% events in the population did not show any significant difference, the group receiving pazopanib maintenance therapy showed a significantly better PFS than the placebo group (median 17.9 months vs. 12.3 months; HR, 0.77; 95% CI, 0.64 to 0.91; p=0.0021). The group receiving pazopanib maintenance therapy experienced grade ≥ 3 adverse events more frequently than the placebo group, especially adverse events that resulted in treatment discontinuation (33.3% vs. 5.6%), hypertension (30.8%), neutropenia (9.9%), liver-related toxicity (9.4%), diarrhea (8.2%), fatigue (2.7%), thrombocytopenia (2.5%), and palmar-plantar erythrodysesthesia (1.9%). In contrast to the Asian subgroup analysis results that found uncertain PFS superiority but similar toxicity s between the 2 groups [37], the results of significant PFS benefits, but higher toxicity incidence in the group that received pazopanib maintenance therapy compared to the placebo group warrant further analysis to identify subgroups of patients in whom improved efficacy may balance toxicity [42].

TAILORED TREATMENT ACCORDING TO THE MOLECULAR SUBTYPE OF HIGH-GRADE SEROUS OVARIAN CANCER

Despite improvements in PFS, one of the major challenges in demonstrating OS improvement in clinical trials of new agents for the treatment of ovarian cancer is the lack of stratification of histologic subtypes, which dilutes the effectiveness of agents that might have shown benefit when tested in molecularly defined or genomically defined subgroups [43]. Although the achievement of significant PFS benefit has been endorsed as a reason for drug approval in the United States, therapeutic trials in ovarian cancer have started to recognize the histological and molecular subtypes of ovarian cancer [44]. In the 2014 ASCO Annual Meeting in Chicago, there were 2 presentations regarding the molecular subtypes of HGSOC as a predictor of outcome following bevacizumab in ICON7, an upfront study of bevacizumab in newly diagnosed ovarian

cancer [45,46].

Winterhoff et al. [46] attempted to determine if response to bevacizumab was associated with the molecular classification from the cancer genome atlas (TCGA): differentiated, immunoreactive, mesenchymal, and proliferative [47]. Using Quality Illumina Whole-Genome DASL HT global gene expression data from 455 ICON7 samples of German patients, 380 patients were stratified into 4 TCGA classifications: 86 differentiated (23%), 124 immunoreactive (33%), 73 mesenchymal (19%), and 97 proliferative (25%). Patients with serous carcinomas of mesenchymal subtype obtained the greatest benefit from bevacizumab, with an improvement of median PFS of 9.5 months (25.5 months [95% CI, 21.1 to not available] vs. 16 months [95% CI, 10.5 to not available]; $p=0.053$), compared with the other subtypes (median PFS 5.8 months in differentiated, $p=0.35$; 3.4 months in immunoreactive, $p=0.38$; 3.2 months in proliferative, $p=0.76$). Of note, patients with mesenchymal tumors or high risk clinical (suboptimal stage III or all stage IV) characteristics demonstrated an improvement of median PFS of 7.3 months with bevacizumab (19.8 months [95% CI, 18.3 to 23.7] vs. 12.5 months [95% CI, 10.1 to 16.2]; $p<0.01$).

Gourley et al. [45] of the second group used the Ovarian DSA microarray for transcriptional analysis of 283 ICON7 samples of patients from the United Kingdom. In contrast to the first group, they identified 3 subgroups using unsupervised hierarchical clustering: two proangiogenic (showing angiogenic gene upregulation) and 1 immune (showing angiogenic gene repression and immune gene upregulation). The OS for the immune subgroup was better than that of the other two proangiogenic subgroups (HR, 0.66; 95% CI, 0.46 to 0.94). For the immune group (41% of cases), the addition of bevacizumab was associated with a worse PFS (HR, 1.73; 95% CI, 1.12 to 2.68) and OS (HR, 2.00; 95% CI, 1.11 to 3.61) compared to chemotherapy alone. In the proangiogenic group, however, there was no significant improvement of PFS with the addition of bevacizumab.

Because the two study groups used different algorithms for defining their subtypes, there is no straightforward method of comparing the results. Nevertheless, the two studies are expected to drive the consideration of molecular-genomic diversity in future clinical trial design.

OPPORTUNISTIC BILATERAL SALPINGECTOMY FOR OVARIAN CANCER RISK-REDUCING PROCEDURE IN THE GENERAL POPULATION

Following the potential paradigm shift of the origin of HGSOE from ovarian capsule to fallopian tube [48], many gy-

necologic oncologists believe that bilateral salpingectomy (BS) could effectively reduce the risk of ovarian cancer [49]. Most physicians might concur on the performance of risk-reducing surgery in the form of BS in high-risk populations such as young BRCA mutation carriers who have a family history of breast cancer [49]. However, there is no prospective study demonstrating the HGSOE-preventive effect of opportunistic BS in the general population. There are only several instances of "primum non nocere" of opportunistic BS during surgery for other benign indications [50,51]. Direct supporting evidence for routine implementation of opportunistic BS can only be obtained from long-term follow-up data in a randomized prospective study. Instead, a large-scale population-based cohort study was conducted using data from the Swedish Cancer Registry on women with previous surgery on benign indication, including sterilization, salpingectomy, hysterectomy, and bilateral salpingo-oophorectomy (BSO; $n=251,465$) compared with the unexposed population ($n=5,449,119$) [52]. There was a significantly lower risk for ovarian cancer among women with previous salpingectomy (HR, 0.65; 95% CI, 0.52 to 0.81) compared with the unexposed population. Different degrees of risk reduction were observed with different types of surgery: hysterectomy (HR, 0.79; 95% CI, 0.70 to 0.88), sterilization (HR, 0.72; 95% CI, 0.64 to 0.81), and hysterectomy with BSO (HR, 0.06; 95% CI, 0.03 to 0.12). In addition, BS was associated with more effective risk reduction of ovarian cancer than unilateral salpingectomy (HR, 0.35; 95% CI, 0.17 to 0.73; and HR, 0.71; 95% CI, 0.56 to 0.91, respectively). These results suggest that opportunistic salpingectomy, even at least unilateral removal of fallopian tube, could be an effective preventive strategy of ovarian cancer in the general population.

Skepticism, if any, about the absolute benefit of opportunistic BS might arise from the increasing medical costs and potential complications associated with the additional procedure. Narod [53] estimated that 10,000 BS procedures would be required every year in British Columbia to reduce ovarian cancer incidence by 40%. Kwon et al. [54] conducted a cost-effective analysis of opportunistic BS using a Markov chain Monte Carlo simulation model to estimate the costs and benefits of the procedure in a hypothetical cohort of women undergoing hysterectomy for benign gynecologic conditions, or surgical sterilization, in the Canadian population. In this study, they concluded that BS with hysterectomy for benign conditions could reduce ovarian cancer risk at acceptable costs and it is a cost-effective alternative to tubal ligation for sterilization. The medical cost of BS might vary from country to country. Until the time that results of randomized prospective studies are available, opportunistic BS could be considered as an ovarian cancer preventive strategy on the basis of "at least, no harm."

UNVEILED EFFICACY OF OVARIAN SUPPRESSION IN PREMENOPAUSAL BREAST CANCER

1. Adjuvant ovarian suppression in premenopausal early breast cancer

Tamoxifen has been regarded as a standard adjuvant treatment for premenopausal women with hormone-receptor-positive breast cancer, for at least the past 5 years. As compared with tamoxifen, adjuvant therapy with an aromatase inhibitor was shown to improve survival outcomes of postmenopausal women with breast cancer. However, the clinical value of suppression of ovarian function in premenopausal women with breast cancer, with the adjuvant-supplemented tamoxifen or aromatase inhibitor exemestane therapy, was not clear. In order to answer this question, the International Breast Cancer Study Group initiated 2 randomized, phase III trials, the tamoxifen and exemestane trial (TEXT) and the suppression of ovarian function trial (SOFT), involving premenopausal women with hormone-receptor-positive early breast cancer [55]. In 2014, the results of the primary analysis in SOFT comparing adjuvant tamoxifen plus ovarian suppression with tamoxifen alone [56], and the combined analysis of data from TEXT and SOFT comparing adjuvant exemestane plus ovarian suppression with adjuvant tamoxifen plus ovarian suppression were released [57].

First, in SOFT, 3066 premenopausal women, stratified according to whether they received prior chemotherapy or not, were randomly assigned in a 1:1:1 ratio to receive 5 years of exemestane plus ovarian suppression (triptorelin, bilateral oophorectomy, or ovarian irradiation), tamoxifen plus ovarian suppression, or tamoxifen alone. In the overall study population, after a median follow-up of 67 months, there was no significant difference in the estimated disease-free survival (DFS) rate at 5 years between the tamoxifen-ovarian suppression group and the tamoxifen group (86.6% vs. 84.7%; HR, 0.83; 95% CI, 0.66 to 1.04; $p=0.10$). However, in a cohort of 1084 women who had sufficient risk of recurrence to warrant adjuvant chemotherapy and maintained premenopausal status despite chemotherapy, the multivariable Cox model showed that tamoxifen plus ovarian suppression resulted in a 22% reduction in the relative risk of breast-cancer recurrence, secondary invasive cancer, or death ($p=0.03$) as compared with tamoxifen alone. Given the younger age of this cohort compared with the no-chemotherapy cohort (median age, 40 years vs. 46 years; $p<0.01$), the results observed in this cohort in SOFT suggest that the addition of ovarian suppression to tamoxifen played

an important role in younger premenopausal patients with hormone-receptor-positive early breast cancer.

2. Adjuvant aromatase inhibitor exemestane with ovarian suppression in premenopausal early breast cancer

Next, Pagani et al. [57] reported the results of a comparison of adjuvant exemestane plus ovarian suppression with adjuvant tamoxifen plus ovarian suppression in premenopausal women with hormone-receptor-positive early breast cancer using the combined data from 4,690 patients in TEXT and SOFT. In TEXT, a total of 2672 premenopausal women underwent randomization to receive exemestane plus ovarian suppression or tamoxifen plus ovarian suppression for a period of 5 years. Although there were no significant differences in OS between the 2 groups, DFS at 5 years of the exemestane plus ovarian suppression group was significantly better than that of tamoxifen plus ovarian suppression group after a median follow-up of 68 months (HR for disease recurrence, secondary invasive cancer, or death 0.72; 95% CI, 0.60 to 0.85; $p<0.001$). Similar incidence of grade 3 or 4 adverse events including hot flashes, musculoskeletal symptoms, and hypertension was observed for both groups: 30.6% in the exemestane plus ovarian suppression group and 29.4% in the tamoxifen plus ovarian suppression group. Accordingly, they concluded that adjuvant treatment with ovarian suppression plus exemestane, which was recommended only for postmenopausal women until now, could become a new treatment option for reducing the risk of recurrence in premenopausal women with hormone-receptor-positive early breast cancer.

CONCLUSIONS

Following the FDA approval of bevacizumab as the first targeted agent for ovarian cancer, olaparib has emerged as a promising secondary targeted agent for the treatment of ovarian cancer, particularly for platinum-sensitive recurrent ovarian cancer in daily practice. Promising phase III study results for PARP inhibitors including olaparib are highly anticipated in the near future.

CONFLICT OF INTEREST

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

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4. **STROBE** (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for the reporting of observational studies
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