

Review Article



Major clinical research advances in gynecologic cancer in 2018

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ABSTRACT

Nineteen topics were selected as major clinical research advances in gynecologic oncology in 2018. For cervical cancer, the importance of human papillomavirus (HPV) testing alone as primary cervical cancer screening method and negative survival impact of minimally invasive surgery in early-stage cervical cancer were addressed. For ovarian cancer, cost-effectiveness of genetic testing to prevent cancer, use of analgesics and oral pill to reduce cancer risk, efficacy of secondary cytoreductive surgery and hyperthermic intraperitoneal chemotherapy, update in the use of poly (ADP-ribose) polymerase inhibitor, and efficacy of anti-angiogenic targeted treatments, including bevacizumab and tyrosine kinase inhibitors, were reviewed. For corpus cancer, sentinel lymph node mapping technique, adjuvant therapy in high-risk endometrial cancer (PORTEC-3), and targeted therapy in recurrent disease were covered. For the field of radiation oncology, survival outcomes of chemoradiation compared with chemotherapy alone in metastatic cervical cancer and new findings regarding the use of neoadjuvant chemotherapy in locally advanced cervical cancer were introduced. Lastly, for breast cancer, the use of talazoparib in patients with germline *BRCA1/2* mutation, ovarian suppression for premenopausal patients, adjuvant chemotherapy guided by 21-gene assay, and combination therapy of atezolizumab and nab-paclitaxel for triple-negative cancer as well as promising overall survival results of palbociclib and fulvestrant in advanced breast cancer were briefly mentioned.

Keywords: Minimally Invasive Surgical Procedures; Uterine Cervical Neoplasms; Poly(ADP-ribose) Polymerase Inhibitors; Ovarian Neoplasms; Endometrial Neoplasms; Breast Neoplasms

INTRODUCTION

Among the 19 topics in this series of major clinical research advances in 2018, 2 have drawn much attention. One is a randomized trial of laparoscopic or robotic vs. abdominal radical hysterectomy in patients with early-stage cervical cancer [1]. The study results dealt a great blow to gynecologic cancer surgeons who have favorably performed minimally invasive surgery (MIS) over open surgery for the treatment of early-stage cervical cancer. The other is greater expansion of targeted therapy including poly(ADP-ribose) polymerase (PARP)

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inhibitors, which has led to remarkable survival improvement in patients with gynecologic cancer. The SOLO1 study [2] noted that patients with advanced-stage ovarian cancer (OC) who carry *BRCA* mutation (*BRCAm*) had an outstanding increase in progression-free survival (PFS) if they received maintenance olaparib therapy following successful first-line chemotherapy.

We summarized 19 topics for major clinical research advances in gynecologic cancer in 2018 with placing more weight on these 2 topics (**Table 1**).

CERVICAL CANCER

1. Update on cervical cancer screening

Despite multiple lines of favorable results of cervical cancer screening using human papillomavirus (HPV) testing [3], guidelines so far did not recommend a stand-alone test for high-risk HPV (hrHPV) as primary screening for cervical cancer. For the first time, the US Preventive Services Task Force (USPSTF) now recommends HPV test alone every 5 years in women aged 30–65 years (grade A recommendation) [4]. The HPV FOCAL randomized clinical trial by Ogilvie et al. [5] was among the four randomized clinical trials on hrHPV primary screening, which were included in the updated evidence report and systematic review [6]. In this study, 19,009 women aged 20–65 years with no history of cervical intraepithelial neoplasia (CIN) 2+ in the past 5 years were randomized into two groups: those who underwent primary hrHPV testing alone (intervention group, n=9,552) and those who underwent liquid-based cytology (control group, n=9,457). Primary and secondary outcomes were the cumulative incidences of CIN 3+ and CIN 2+ 48 months following randomization, respectively. At 48-month exit, both groups underwent hrHPV and liquid-based cytology co-testing. While women in the intervention group who had negative results returned to the clinic within 48 months for exit co-testing, women in the control group with negative results returned for liquid-based cytology at least within a 24-month interval. At 48 months, significantly fewer CIN 3+ were detected in the intervention group than in the control group,

Table 1. Nineteen topics of major clinical research advances in gynecologic cancer in 2018

Site of cancer	Topic	Reference
Uterine cervix	Update of cervical cancer screening	[4-7]
	Minimally invasive surgery in early stage cervical cancer	[1,8]
Ovary	Genetic testing for OC risk	[12,13]
	Analgesics and oral pills use and OC risk	[14-18]
	Surgical treatment update: secondary cytoreductive surgery	[21]
	Surgical treatment update: HIPEC	[22]
	PARP inhibitor: update of clinical outcomes (SOLO-1)	[2-31]
	Resistance to PARP inhibitor: methylation of <i>BRCA1</i> copies and <i>PARP1</i> mutation	[32,35]
	Anti-angiogenic treatment in combination with chemotherapy: bevacizumab and others	[42-45]
Uterine corpus	Update of clinical outcomes using sentinel lymph node mapping	[47]
	Adjuvant therapy in high-risk endometrial cancer: PORTEC-3 vs. GOG-258	[48]
	Targeted therapy in recurrent endometrial cancer	[51,52,56]
Radiation oncology	Pelvic radiotherapy vs. chemotherapy in metastatic cervical cancer	[58]
	Neoadjuvant chemotherapy in locally advanced cervical cancer	[59,60]
Breast cancer	Talazoparib and germline <i>BRCA</i> mutation	[61]
	Adjuvant endocrine therapy for premenopausal breast cancer	[64]
	Adjuvant chemotherapy based on Oncotype DX: TAILORx trial	[65]
	Combination of atezolizumab and nab-paclitaxel in advanced triple-negative cancer: Impassion130	[66]
	Overall survival results of palbociclib and fulvestrant in advanced breast cancer: PALOMA-3 study	[67]

HIPEC, hyperthermic intraperitoneal chemotherapy; OC, ovarian cancer; PARP, poly(ADP-ribose) polymerase.

incidence rate/1,000 with 95% confidence interval (CI) were 2.3 (1.5–3.5) vs. 5.5 (4.2–7.2) and relative risk (RR) with 95% CI was 0.42 (0.25–0.69). Among women with negative results at baseline, CIN3+ RR (0.25) of the intervention group was lower than that of the control group (95% CI, 0.13–0.48). They concluded that primary HPV testing resulted in a significantly lower likelihood of CIN 3+ than cytology at 48 months.

In addition, a decision analysis was performed to determine the benefits and harms of various cervical cancer screening strategies: cytology alone, hrHPV testing alone, and co-testing [7]. Strategies involving primary hrHPV testing and alternative co-testing were associated with slightly greater effectiveness and greater harms than current guideline-based cytology alone in terms of conducting more tests (screening tests/life-year gained), colposcopies (colposcopy/life-year gained), and false-positive results (colposcopy/cervical cancer case averted). Primary hrHPV testing every 5 years was efficient as the switch age extended from 25 to 30 years although the efficiency of triage options depended on which outcome was used as a proxy for harm. With cytology triage; for example, colposcopy/life-year gained of 5-year primary hrHPV testing when switching from cytology to hrHPV testing at ages 30, 27, and 25 years were 73, 143, and 195, respectively. In most analyses, however, strategies involving co-testing were inefficient compared with those involving hrHPV testing alone, notably including one currently recommended in the US (consisting of cytology testing every 3 years starting at age 21 years, switching at age 30 years to co-testing every 5 years) [7]. Therefore, the final update of USPSTF recommendation statement continues to recommend co-testing every 5 years as an “alternative” strategy as opposed to the “preferred” use of cytology or hrHPV testing alone [4].

2. MIS in early-stage cervical cancer

In 2018, there were two notable studies regarding surgical approach for the treatment of cervical cancer, both of which indicated inferior survival outcomes of MIS to open surgery [1,8]. After its first release at the Society of Gynecologic Oncology (SGO) Annual Meeting in New Orleans, results of the phase III randomized trial of laparoscopic or robotic vs. abdominal radical hysterectomy in patients with early-stage cervical cancer (LACC) was published in *The New England Journal of Medicine* [1]. The LACC trial showed that the minimally invasive surgical approaches negatively affected oncologic outcomes for women with early-stage cervical cancer both in terms of disease-free survival (DFS) and overall survival (OS). LACC trial, an international multi-institutional collaboration study with 33 centers worldwide, opened in 2008 and was designed to randomize 740 women with early-stage (1A1 with lymphovascular space invasion [LVSI], 1A2, or 1B1) cervical cancer to undergo either minimally invasive or open radical hysterectomy (1:1 ratio). The primary outcome was DFS at 4.5 years, with non-inferiority margin of –7.2% points for the difference in DFS at 4.5 years. In 2017, however, with 631 patients enrolled (319 in MIS group and 312 in open surgery group), the study was halted because of a notice of safety from the data and safety monitoring committee. Minimally invasive radical hysterectomy was associated with a lower rate of DFS than open surgery (3-year rate, 91.2% vs. 97.1%; hazard ratio [HR] for disease recurrence or death=3.74; 95% CI=1.63–8.58). The 3-year OS was also significantly lower in the minimally invasive group than that in the open surgery arm (3-year rate, 93.8% vs. 99.0%; HR for death from any cause=6.00; 95% CI=1.77–20.30). There were several limitations and criticisms of the LACC trial [1,9-11]. It did not reach the 84% power to declare non-inferiority due to not reaching its final intended enrollment and short follow-up period. Similarly, because of weak power, the study results could not be generalized to all patients with low-risk cervical cancer <2 cm. Other criticisms included not enough number of minimal cases for quality

surgeon criteria, extraordinarily low recurrence rate in the open surgery group, no subgroup analysis according to possible risk factors, and no information of potential causes of the inferior survival rate such as intracorporeal colpotomy or uterine manipulator, etc. Despite the criticisms, the LACC trial was the first to prospectively compare the 2 surgical approaches and evaluate oncologic outcomes, including DFS, OS, and recurrence rates.

There was a retrospective epidemiologic study that reinforced the LACC trial findings [8]. According to the National Cancer Database, 2,461 women who underwent radical hysterectomy for stage 1A2 or 1B1 cervical cancer in 2010–2013 were included. Of them, 1,225 (49.8%) and 1,236 (50.2%) underwent MIS and open surgery, respectively. The majority (79.8%) of patients in the MIS group underwent robot-assisted laparoscopy. Initially, the histopathological variables and demographic variables appeared unevenly distributed; that is, the MIS group had smaller, lower-grade tumor and adenocarcinoma and higher income and educational levels than the open surgery group. These variables were well balanced in the propensity-weighted matched cohort. After median 45 months of follow-up, 4-year mortality was significantly higher in women who underwent MIS than those who underwent open surgery (9.1% vs. 5.3%; HR=1.65; 95% CI=1.22–2.22; $p=0.002$). In addition, the researchers performed an interrupted time-series analysis and found a 0.8% decline in 4-year relative survival rate (95% CI=0.3–1.4) per year after 2006 when the MIS was adopted in the US ($p=0.01$). An important limitation of the retrospective study was the inability to explain why minimally invasive radical hysterectomy was associated with inferior survival. Although subgroup analyses showed greater relative hazard for death, which was more strongly associated with MIS than with open surgery and was evident across histologic subtypes and tumor size (<2 vs. ≥ 2 cm), the researchers could not make a precise estimation on the associations between MIS and all-cause mortality among subgroups due to the small number of deaths in women with tumors <2 cm. Hence, further studies are needed to determine the causes of the decrease in the survival rate in patients with early-stage cervical cancer who underwent MIS. Patients who are scheduled to undergo radical hysterectomy for the treatment of early-stage cervical cancer should be informed about these study results and the risks and benefits with respect to MIS compared with open surgery should be discussed.

OVARIAN CANCER

1. Genetic testing for OC risk

Obstetrician-gynecologists play a key role in identifying women with hereditary cancer syndromes including gynecologic cancer. The American College of Obstetricians and Gynecologists newly reported a Committee Opinion for genetic testing for women in blood relatives of individuals with known hereditary genetic mutations [12]. The committee emphasized the clinical implications of “cascade testing,” which refers to the genetic counseling and testing in blood relatives of known hereditary genetic mutation carriers. They stated that the cascade testing results in better health and quality of life for these family members and is cost-effective than whole-genome sequencing. Obstetrician-gynecologists are required to know the exact candidates for cascade testing and should offer it to them. However, clinical criteria/family history (FH)-based testing may not be fully effective to identify mutations and to rule out the absence of one. This disadvantage of clinical criteria/FH-based testing can be overcome by population-based testing. Cost-effectiveness analysis of testing for high- and moderate-penetrance OC gene mutations in general population women was recently reported [13]. Using a decision-analytic model, researchers showed

that clinical criteria/FH-based *BRCA1/BRCA2/RAD51C/RAD51D/BRIP1/PALB2* testing was more cost-effective than clinical criteria/FH-based *BRCA1/BRCA2* testing (life-expectancy gained: 0.04 days). Moreover, a population-based testing for *BRCA1/BRCA2/RAD51C/RAD51D/BRIP1/PALB2* mutations is the most cost-effective strategy compared with clinical criteria/FH-based testing. Population-based *BRCA1/BRCA2/RAD51C/RAD51D/BRIP1/PALB2* testing can prevent 1.91% of breast cancer and 4.88% of OC cases in women in the US; thus, a total of 655 OC cases and 2,386 breast cancer cases were prevented per million. Therefore, health policies need to support increased access to use of genetic testing for the general population.

2. Analgesics and oral pill and OC risk

Although daily low-dose aspirin is considered to be helpful in reducing the risk of heart attacks and strokes, it has not been well recognized in the OC field until now. Trabert et al. [14] suggested that women who take aspirin daily have a lower risk of OC according to a large prospective analysis of 13 studies in the OC Cohort Consortium. The study included 758,829 women who had self-reported analgesic use and revealed that 3,514 of these women were diagnosed with OC. Women taking aspirin almost daily had a 10% lower OC risk than infrequent users/never-users (HR=0.90; 95% CI=0.82–1.00; $p=0.05$). However, this study did not show the effect of “low-dose” aspirin use on OC risk. Barnard et al. also investigated whether aspirin or non-aspirin nonsteroidal anti-inflammatory drug (NSAID) use is associated with reduced OC risk [15]. This prospective case-control cohort study based on Nurses' Health Study (NHS) and NHS II cohorts, which are ongoing prospective studies of 121,700 and 116,429 US nurses, respectively, with completed biennial questionnaires, showed a 23% lower OC risk in current low-dose (≤ 100 mg) aspirin users than non-users (HR=0.77; 95% CI=0.61–0.96). However, current use of NSAIDs was associated with a 19% higher OC risk compared with non-use (HR=1.19; 95% CI=1.00–1.41). Using the cohorts of NHS and NHS II, Merritt et al. [16] showed the association between aspirin, non-aspirin NSAID, and paracetamol use before and after OC diagnosis and OC-specific survival in *Lancet Oncology*. A total of 1,031 women were included in the pre-diagnosis exposure analysis and 964 in the post-diagnosis exposure analysis. Compared with never-users, current users of aspirin (HR=0.68; 95% CI=0.52–0.89) and non-aspirin NSAIDs (HR=0.67; 95% CI=0.51–0.87) had an improved OC-specific survival 2 years after diagnosis.

Oral contraceptive use is common among women in the reproductive age; however, further studies are warranted to evaluate the impact of oral contraceptive use on ovarian carcinogenesis. Current oral contraceptive users showed higher risk of breast cancer, and lower risks for ovarian, endometrial, and likely colorectal cancers associated with increasing duration of oral contraceptive use. Michels et al. [17] presented the results of a large population-based study analyzing the associations between duration of oral contraceptive use and several cancer risks in *JAMA Oncology*. All analyses included at least 100,000 women with self-reported oral contraceptive use. Long-term oral contraceptive use (≥ 10 years) reduced the OC risk, and relative risk decreased with increasing oral contraceptive use (HR=0.60; 95% CI=0.47–0.76; $p<0.001$ for trend). Furthermore, another nationwide prospective study showed that contemporary combined oral contraceptives reduced the OC risk [18]. OC risk is lower in current or recent users compared with never-users (HR, 0.58; 95% CI, 0.49–0.68). Risk reduction gradually decreased based on the duration of oral contraceptive use ($p<0.001$ for trend). However, this study did not show the cancer prevention effect of progestogen-only products. Researchers assumed that combined oral contraceptive suppress ovulation and protect against neoplastic development. However, the exact mechanisms on how oral contraceptives reduce OC risk remained unclear.

3. Surgical treatment update: secondary cytoreductive surgery

Almost all patients with advanced OC develop peritoneal carcinomatosis. Primary cytoreductive surgery followed by six cycles of intravenous platinum-based chemotherapy (PBC) is considered as the most effective treatment in advanced OC. Alternatively, 3 cycles of PBC followed by interval cytoreductive surgery is another therapeutic choice. For women with recurrent OC, secondary cytoreductive surgery resulted in significant increase in PFS in women with OC who experienced their first relapse at least 6 months after completion of PBC, reported in the ongoing DESKTOP III trial [19]. Szczesny et al. also suggested that the secondary cytoreductive surgery improves survival outcomes in platinum-sensitive recurrent (PSR) OC patients with no residual tumors after primary surgery [20]. In this study, both PFS (HR=0.45; 95% CI=0.32–0.62; $p<0.001$) and OS (HR=0.50; 95% CI=0.32–0.70; $p<0.001$) were improved in the group who underwent secondary cytoreductive surgery plus PBC compared with the group who received PBC alone. However, Coleman et al. [21] presented that secondary cytoreductive surgery did not improve survival outcomes in women with PSR OC in the 2018 American Society of Clinical Oncology (ASCO) Annual Meeting (GOG-0213, NCT00565851). A total of 485 women were randomized 1:1 to undergo secondary cytoreductive surgery followed by PBC ($n=240$) or PBC alone ($n=245$). Secondary cytoreductive surgery did not improve PFS (18.2 vs. 16.5 months; HR=0.88; 95% CI=0.70–1.11) and OS (53.6 vs. 65.7 month; HR=1.28; 95% CI=0.92–1.79). Thus, secondary cytoreductive surgery can be safely performed in patients with PSR OC, but its survival benefit remains controversial.

4. Surgical treatment update: hyperthermic intraperitoneal chemotherapy

van Driel et al. [22] reported that interval cytoreductive surgery followed by hyperthermic intraperitoneal chemotherapy (HIPEC) improved the survival outcomes in patients with stage III OC in *The New England Journal of Medicine*. All eligible patients received neoadjuvant chemotherapy (NAC) with 3 cycles of carboplatin-paclitaxel followed by interval debulking surgery. At the time of surgery, patients were randomly assigned (1:1) to surgery plus HIPEC group ($n=123$) or surgery alone group ($n=122$). The surgery plus HIPEC group had lesser number of patients who experienced recurrence or death than the surgery alone group (81% vs. 89%; HR=0.66; 95% CI=0.50–0.87; $p=0.003$). Median PFS (14.2 vs. 10.7 months) and OS (45.7 vs. 33.9 months) were longer in surgery with HIPEC group than in the surgery without HIPEC group. In addition, grade 3–4 adverse events occurred with similar percentage in both groups (27% vs. 25%; $p=0.76$).

5. PARP inhibitor: update of clinical outcomes

PARP inhibitors have shown promising results and have the potential of changing the course of OC. The US Food and Drug Administration and European Medicines Agency recently approved niraparib and olaparib as maintenance therapy for patients with recurrent OC and in complete response (CR) or partial response (PR) after PBC [23–25].

In October 2018, Moore et al. [2] published their promising results from the SOLO1 trial in *The New England Journal of Medicine*. They documented an unprecedented benefit of maintenance treatment with PARP inhibitor, olaparib, in patients with newly diagnosed advanced OC who were in CR or PR after the first PBC. The study included International Federation of Gynecology and Obstetrics (FIGO) stages III–IV ovarian, fallopian tube, or primary peritoneal cancer with either *BRCA1*, *BRCA2*, or *BRCA1* and *BRCA2* mutations. Approximately 391 patients were randomized in a 2:1 ratio to receive either olaparib (300 mg twice daily) or placebo for 24 months. Patients treated with olaparib had a lower risk of disease progression (or death)

(70%) than those treated with placebo (HR=0.30; $p<0.001$). The olaparib arm did not reach the median PFS at the time of data cutoff. The results confirmed the substantial potential of PARP inhibitors in the treatment of OC.

Outcomes regarding dose modifications (and predictors of) as well as long-term safety of niraparib was published in 2018, based on data from the ENGOT-OV16/NOVA phase III trial [26]. About 553 patients were randomized in a 2:1 ratio to either the niraparib or placebo group. Hematological, gastrointestinal, fatigue, and cardiovascular adverse effects were commonly observed among these patients. Phase I testing had established a maximum tolerated dose of 300 mg once daily. The hematological adverse effects were thrombocytopenia, anemia, and neutropenia. In the trial, grade ≥ 3 thrombocytopenia (29%) led to most dose reductions but very few dose discontinuations (3.3%) due to active mitigation strategy. The doses of medication administered in majority of patients (73%) were reduced within 3 months to 200 or 100 mg daily. In a post hoc analysis, the efficacy of niraparib seemed unaffected by dose reductions. Most predictive factors for dose reduction were baseline body weight and baseline platelet counts, and patients with a baseline body weight of <77 kg and/or baseline platelets of $<150,000/\mu\text{L}$ could benefit from a starting dose of 200 mg/day. This recommendation was prospectively analyzed and confirmed in a phase III randomized trial (PRIMA) [27]. Moore et al. [28] presented the data from a post hoc analysis of the phase II QUADRA (NCT02354586) trial, which reported the use of niraparib in patients with PSR OC who have homologous recombination deficiency (HRD). In the fourth or later lines of therapy, patients treated with 300 mg/day of niraparib showed an overall response rate (ORR) of 27.5% (95% CI=15.9–41.7). In patients who are considered platinum sensitive and diagnosed with positive HRD, fourth-line therapy with niraparib treatment can be an option. Toxicities were manageable with dose reduction consistent with the results of previous niraparib studies.

Anti-programmed cell death (PD)-1 single treatment has shown low activity in recurrent OC and beyond *BRCAm*; however, a preclinical data demonstrated the synergy of PARP inhibitors with anti-PD-1 combination therapy. In 2018 ASCO Annual Meeting, Panagiotis et al. presented the results of phase I/II TOPACIO/Keynote-162 (NCT02657889) trial for niraparib with pembrolizumab combination treatment in patients with recurrent OC [29]. Patients who were platinum sensitive and had no more than 5 prior treatment lines were eligible. About 200 mg of niraparib was administered orally once daily and 200 mg of pembrolizumab administered intravenously every 21 days. With ORR of 25% in all PSR OC and ORR of 45% in somatic *BRCAm* patients, niraparib with pembrolizumab combination treatment appeared to be a promising treatment for patients with PSR OC. No unexpected safety events were observed. Another study evaluated the effectiveness of PARP inhibitor combined with anti-PD ligand 1 (PD-L1) agent in patients with PSR OC. MEDIOLA, an open-label, phase II basket study of olaparib and durvalumab, was presented at the SGO Annual Meeting in New Orleans (NCT02734004) [30]. A total of 32 women with *gBRCAm* PSR OC who received one or more prior platinum therapies were enrolled and received olaparib 300 mg tablet po bid for 4 weeks followed by a combination of olaparib 300 mg po bid and durvalumab 1.5 g intravenous every 4 weeks until disease progression. Primary endpoints were disease control rate (DCR) at 12 weeks, safety, and tolerability. Among 32 patients, 22 had *gBRCA1* mutation and 10 had *gBRCA2* mutation. The DCR at 12 weeks was 81%; six (19%) achieved CR and 14 (44%) achieved PR, resulting in an ORR of 68%. Given the reported median PFS of 11 months in an olaparib-based single maintenance therapy setting, the DCRs after addition of durvalumab were calculated based on the expected efficacy. No special safety concerns were

noted. Based on these promising results from the initial analysis, three new PSR OC cohorts including non-*gBRCAm* patients have been added: expansion cohort with *gBRCAm* (n=80, olaparib+durvalumab), doublet cohort with non-*gBRCAm* (n=30, olaparib+durvalumab), and triplet cohort with non-*gBRCAm* (n=30, olaparib+durvalumab+bevacizumab [BEV]) [31].

6. Resistance to PARP inhibitor: methylation of *BRCA1* copies and *PARP1* mutation

PARP inhibitor is now in the best interests with the release of SOLO-1 trial results [2]. Notable, patients with advanced OC with a *BRCA1/2* mutation exhibited a 70% reduction in the risk of disease progression after treatment with olaparib PARP inhibitor. Hence, it is important to identify which patients will appropriately respond to PARP inhibitor. Two studies in *Nature Communications* proposed several strategies to identify the appropriate candidates for PARP inhibitor therapy and prepare for PARP inhibitor resistance.

Kondrashova et al. [32] showed that methylation zygosity (homozygous vs. heterozygous) of *BRCA1* copies is associated with respond to rucaparib. They investigated the methylation zygosity of *BRCA1* in patient-derived xenografts (PDX) from 12 high-grade serous OC patients. About 150, 300, and 450 mg/kg of rucaparib was administered orally to PDX models for 5 days a week for 3 weeks to assess sensitivity to PARP inhibitor. After rucaparib therapy, tumor regression was observed in PDX models with homozygous *BRCA1* methylation but not in PDX models with heterozygous *BRCA1* methylation. *BRCA1* methylation zygosity was also evaluated in human tumor cells from *BRCA1*-methylated platinum-sensitive high-grade serous OC patients in ARIEL2 trial before PARP inhibitor therapy [33]. The PFS was longer in homozygous *BRCA1*-methylated patients (n=6) than in *BRCA1/2* wild-type non-*BRCA1*-methylated patients (n=143) (14.5 vs. 5.5 months; p=0.062), although the results were not considered significant. Hence, it was suggested that quantitative analysis for *BRCA1* methylation before PARP inhibitor therapy may be helpful to predict the patient's response to PARP inhibitor.

A bacterial clustered regularly interspaced short palindromic repeat (CRISPR)-associated protein-9 nuclease (Cas9) from *Streptococcus pyogenes* was recently regarded as a promising tool for simultaneous editing genes within organisms [34]. Using this CRISPR-Cas9 system, Pettitt et al. found that *PARP1* mutations can lead to PARP inhibitor resistance in *BRCA1* mutant cells [35]. Firstly, they found that loss of *Parp1* DNA binding and activity in ZnF domain by mutation is associated with PARP inhibitor resistance in mouse embryonic stem cells. They also identified a *PARP1* p.R591C mutation in an OC patient who had *de novo* resistance to olaparib. They performed a genome-wide PARP inhibitor resistance CRISPR-Cas9 screening in patients with *BRCA1*-mutated breast cancer cells considered as PARP inhibitor sensitive and, interestingly, found that *PARP1* mutations were tolerated in these cells. PARP inhibitor resistance in some cases might present some level of heterogeneity because there are various PARP inhibitor subclones that can lead to resistance via other mechanisms.

7. Anti-angiogenic treatment in combination with chemotherapy

Bevacizumab

Anti-angiogenic agent BEV given concomitant to combination chemotherapy followed by maintenance therapy is considered the standard of care in patients with advanced OC as first-line therapy [36-38] and in those with PSR OC [39,40]. In platinum-resistant recurrent (PRR) OC, BEV is the standard of care in combination with mono-chemotherapy [41]. However, several questions were left unanswered: can BEV be combined with other platinum doublets

than those studied in the trials? Will re-challenge of BEV be an effective treatment? There were outstanding studies that have answered the two important clinical questions.

Results of a randomized phase III ENGOT/GCIG-Intergroup trial were presented at the European Society of Medical Oncology (ESMO) 2018 Congress [42]. Combination of BEV with carboplatin-pegylated liposomal doxorubicin (CD-BEV) was compared against standard of care carboplatin-gemcitabine-BEV (CG-BEV) in 682 patients with PSR OC. The trial was designed as a non-inferiority study to demonstrate that both regimens are equally effective. PFS was shown to be superior in the experimental CD-BEV arm over the standard CG-BEV arm (HR=0.81; $p=0.01$). Toxicities in the 2 groups were comparable, and no new safety issues were observed.

Pignata et al. [43] reported the results of MITO16B/ENGOT-OV17 at the ASCO Annual Meeting [43]. This randomized phase III trial evaluated the efficacy of adding BEV to PBC regimens (carboplatin+paclitaxel/gemcitabine/pegylated liposomal doxorubicin) in platinum-sensitive patients who relapsed after receiving BEV as first-line treatment. The study included a total of 405 patients with FIGO stages IIIB–IV ovarian, fallopian tube, or primary peritoneal cancer, randomized in a 1:1 ratio to either the experimental arm (+BEV) or the standard arm (–BEV). PFS was significantly prolonged in patients who were re-treated with BEV (median PFS: 11.8 months vs. 8.8 months; HR=0.51; $p<0.001$). Toxicities in the two groups were comparable and no unexpected events were observed.

8. Other anti-angiogenic agents

TRIAS trial, a multicenter, double-blind, placebo-controlled, randomized phase II trial, showed that women with PRR OC who received sorafenib, a multi-kinase inhibitor, combined with 6 cycles of topotecan followed by sorafenib maintenance showed a significant improvement in PFS compared with those treated with placebo (HR=0.60; 95% CI=0.43–0.83; $p=0.0018$) [44]. A total of 174 women with PRR OC with ≤ 2 prior chemotherapy lines were randomized into topotecan plus either oral sorafenib 400 mg or placebo bid from D6 to D15 every 3 weeks for 6 cycles, followed by daily maintenance therapy with sorafenib or placebo for up to 1 year in patients without progression. The median PFS was 6.7 months (95% CI, 5.8–7.6) with sorafenib versus 4.4 months (95% CI=3.7–5.0) with placebo. Although sorafenib was associated with more frequent grade 3 hand-foot syndrome (13% vs. 0) and grade 2 alopecia (29% vs. 13%), the incidence of adverse events was not different between the 2 groups (59% vs. 51%).

Another study showed the promising efficacy of anti-angiogenic therapy combined with chemotherapy in patients with PRR OC. In a phase II, single-arm prospective study of apatinib, an oral tyrosine kinase inhibitor that selectively inhibits vascular endothelial growth factor receptor 2, and oral etoposide, 35 women with PRR OC was enrolled and received apatinib 500 mg per os once a day and etoposide 50 mg per os once a day from D1 to D14 every 3 weeks until disease progression, withdrawal, or unacceptable toxicity [45]. The primary endpoint was the proportion of patients achieving an objective response (CR or PR). At the data cutoff, wherein 20 (57%) patients discontinued the use of study medications and 15 (43%) remained on treatment, objective responses were observed in 19 (54%; 95% CI=36.6–71.2) of 35 patients in intention-to-treat population and in 19 (61%; 95% CI=42.2–78.2) of 31 patients in the per-protocol population. Most common serious adverse effects included neutropenia (50%), fatigue (32%), anemia (29%), and mucositis (24%). No treatment-related deaths were reported. This was the first study to report the favorable

efficacy results with tolerable toxicity profiles of oral combination therapy of apatinib and etoposide in patients with PRR OC.

CORPUS CANCER

1. Update of clinical outcomes using sentinel lymph node mapping

Sentinel lymph node (SLN) mapping has been globally used as an alternative staging technique in endometrial cancer. In the FIRES trial, a sensitivity to detect node-positive disease of 97.2% (95% CI=85.0–100) and a negative predictive value of 99.6% (95% CI=97.9–100) of SLN mapping using near-infrared fluorescence imaging with indocyanine green (ICG) tracer were reported [46]. This trial provided acceptable sensitivity and negative predictive value of SLN mapping using ICG in a particular robotic system. In 2018, Frumovitz et al. [47] showed that ICG visualized by near-infrared fluorescence imaging identified more SLN than isosulfan blue dye visualized by white light in laparoscopic surgery. This FILM trial was designed to evaluate the safety and efficacy of ICG (“green dye”) and PINPOINT near-infrared fluorescence imaging (Stryker, Kalamazoo, MI, USA) in identifying SLN in women with cervical and uterine cancer. All enrolled patients underwent laparoscopic surgery for clinical stage I cervical and uterine cancer, and were randomly assigned (1:1) into 2 groups: blue dye followed by green dye group or green dye followed by blue dye group. Of the 478 pathologically confirmed nodes, 219 (92%) of 238 nodes were blue and green, 7 were blue, and 252 (95%) of 265 nodes were green. Of 485 retrieval nodes, 471 (97%) were identified by green dye and 226 (47%) by blue dye (difference, 50%; 95% CI=39–62; $p<0.0001$). The FILM protocol did not complete lymphadenectomy after SLN mapping; thus, sensitivity and negative predictive values for the PINPOINT system cannot be compared with those reported in FIRES study. However, they were able to conclude that ICG is not inferior to isosulfan blue dye when used in SLN mapping regardless of the surgical approach.

2. Adjuvant therapy in high-risk endometrial cancer: PORTEC-3 vs. GOG-258

In endometrial cancer, high-risk disease is described as presence of endometrioid type stage I grade 3 with deep invasion or with LVSI, stages II–III endometrioid type, or stages I–III serous/clear cell type. Pelvic external beam radiotherapy (EBRT) has been considered as the standard adjuvant treatment for high-risk endometrial cancer until now. The PORTEC-3 trial showed that adjuvant chemotherapy after radiotherapy (chemoradiotherapy [CRT], 4 cycles of carboplatin and paclitaxel followed by EBRT) improved the PFS in women with stage III endometrial cancer [48]. Although the 5-year OS was not significantly different between the CRT and radiotherapy groups (81.8% vs. 76.7%; HR=0.76; 95% CI=0.54–1.06; $p=0.11$), the 5-year PFS was better in the CRT group than in the radiotherapy (RT) group (75.5% vs. 68.6%; HR, 0.71; 95% CI, 0.53–0.95; $p=0.022$). However, CRT was not recommended in stages I–II disease in this trial as this treatment had no PFS benefit (80.0% vs. 76.6%; HR=0.85; 95% CI=0.54–1.33; $p=0.47$). Earlier, the GOG-258 trial randomly assigned (1:1) patients to receive CRT or six cycles of carboplatin and paclitaxel to compare the efficacy of CRT and chemotherapy alone in patients with stage III–IV endometrial cancer [49]. In the 2017 ASCO Annual Meeting, Matei et al. [49] reported that there was no difference in PFS between the CRT and chemotherapy groups in this trial (HR, 0.9; 95% CI, 0.74–1.10). Although CRT reduced vaginal (3% vs. 7%; HR, 0.36; 95% CI, 0.16–0.82), pelvic, and para-aortic recurrences (10% vs. 21%; HR=0.43; 95% CI=0.28–0.66), distant recurrences were more common in the CRT group (28% vs. 21%; HR=1.36; 95% CI=1–1.86) than in the chemotherapy group. Final OS result is waiting for maturation.

3. Targeted therapy in recurrent endometrial cancer

Although uterine serous carcinoma (USC) only occurs in 3%–10% of patients with cancer, it accounts for 39% of endometrial cancer-specific deaths [50]. In up to 70% of cases, women with this histologic type usually develop extrauterine spread at diagnosis; therefore, patients with USC have poorer outcomes than those with endometrioid type. Fader et al. [51] showed that addition of trastuzumab, a humanized monoclonal antibody against human epidermal growth factor receptor (HER2)/neu, to carboplatin-paclitaxel increased PFS in patients with stages III–IV or recurrent HER2/neu-positive USC. In this study, trastuzumab was initially administered at a dose of 8 mg/kg and then 6 mg/kg in subsequent cycles until disease progression or drug toxicity. Median PFS was longer in the experimental arm (those treated with trastuzumab plus carboplatin-paclitaxel) than in the control arm (those treated with carboplatin-paclitaxel only) (12.6 vs. 8.0 months; HR=0.44; 95% CI=0.26–0.76; $p=0.005$); objective response rates were 75% in the experimental arm and 44% in the control arm ($p=0.33$). The drug toxicity was not different between the 2 arms.

TSR-042 is another humanized monoclonal antibody to PD-1, which blocks its interaction with its ligands PD-L1 and PD-L2. Moreno et al. [52] presented the efficacy and safety of TSR-042 in microsatellite instability-high (MSI-H) endometrial cancer and non-small cell lung cancer (NSCLC) cohorts in the 2018 AACR Annual Meeting. In this ongoing phase I GARNET trial (NCT02715284), recurrent or advanced 19 MSI-H endometrial cancer and 30 NSCLC patients were enrolled. In MSI-H endometrial cancer patients, 4/11 (36.4%) had PR and 2/11 (18.2%) had stable disease. In NSCLC patients, 7/21 (33.3%) had PR and 6/21 (28.6%) had stable disease. The safety profile of TSR-042 was similar to that of other PD-1 inhibitors in this study.

In recurrent disease setting of endometrial cancer, BEV [53], temsirolimus [54], and ixabepilone [55] had already shown single-agent activity in previous studies. Aghajanian et al. [56] evaluated the efficacy and safety of incorporating three novel agents into chemotherapy as treatment for patients with advanced or recurrent endometrial cancer. Chemo-naïve patients were randomly assigned to three arms: carboplatin-paclitaxel plus BEV (Arm 1, $n=116$), carboplatin-paclitaxel plus temsirolimus (Arm 2, $n=115$), and ixabepilone and carboplatin plus BEV (Arm 3, $n=118$). During the study period of 2.3 years, the ORRs were 59%, 55%, and 53% in Arms 1, 2, and 3, respectively (51% in the carboplatin-paclitaxel arm for reference). Although PFS was not significantly increased in any arm, OS was significantly increased in the carboplatin-paclitaxel plus BEV arm than in the carboplatin-paclitaxel arm (HR=0.71; 92.2% CI=0.55–0.91) (Table 2). In contrast to this study, END-2 trial showed increased response rate with carboplatin-paclitaxel plus BEV (54% vs 73%) and improved PFS (8.7 vs 13 months; HR=0.57; 95% CI=0.34–0.96; $p=0.036$) [57]. The discordance between the two trials was probably due to the different chemotherapy settings (first-line vs. second-line chemotherapy) or heterogeneous patient populations.

RADIATION ONCOLOGY

1. Role of pelvic RT vs. chemotherapy in metastatic cervical cancer

Definitive pelvic CRT is the standard of care for locally advanced cervical cancer. However, the role of pelvic RT for metastatic cervical cancer has not been established. Recently, there was growing evidence that local therapies may be associated with an increase in survival in patients with certain types of metastatic cancers. In this context, a study using National Cancer Database data reported in *JAMA Oncology* highlighted that definitive pelvic RT was

Table 2. New regimens with targeted therapy in recurrent endometrial cancer

Drug	Indications	Regimen setting	Efficacy	Safety	Reference
Trastuzumab	Primary stage III-IV or recurrent HER2/neu-positive uterine serous carcinoma	IV carboplatin AUC 5 IV paclitaxel 175 mg/m ² IV trastuzumab at 8 mg/kg for the first dose and 6 mg/kg in subsequent cycles until disease progression or prohibitive toxicity	PFS improvement	No unexpected safety	[51]
TSR-042	Recurrent or advanced MSI-H endometrial cancer	TSR-042 500 mg every 3 weeks for the first 4 cycles and 1,000 mg every 6 weeks thereafter	-	Similar safety profile to other PD-1 inhibitors	[52]
BEV	Chemo-naïve recurrent or advanced endometrial cancer	IV carboplatin AUC 6 IV paclitaxel 175 mg/m ² IV BEV 15 mg/kg	OS improvement	No unexpected safety	[56]
Temsirolimus	Chemo-naïve recurrent or advanced endometrial cancer	IV carboplatin AUC 6 IV paclitaxel 175 mg/m ² IV temsirolimus at 25 mg IV on days 1 and 8 (concurrent with chemotherapy) and days 1, 8, and 15 (during maintenance)	No PFS/OS improvement	No unexpected safety	[56]
Ixabepilone	Chemo-naïve recurrent or advanced endometrial cancer	IV ixabepilone 30 mg/m ² IV carboplatin AUC 6 IV bevacizumab 15 mg/kg	No PFS/OS improvement	No unexpected safety	[56]

AUC, area under curve; HER2; human epidermal growth factor receptor; IV, intravenous; MSI-H, microsatellite instability-high; OS, overall survival; PD, programmed cell death; PFS, progression-free survival.

associated with improved survival vs. chemotherapy alone in patients with newly diagnosed metastatic cervical cancer [58]. The study conducted by Wang et al. [58] included the data from 3,169 patients treated between 2004 and 2014. Among these, 808 received chemotherapy alone and 2,361 received pelvic CRT. Multivariate and propensity score-matched analyses were performed taking into account RT, age, year of diagnosis, race, comorbidity score, tumor grade, clinical stage, nodal stage, facility type, insurance, and metastatic site. After a median follow-up time of 13.3 months (range, 0.1–151), the median OS rates were 15.6 months in the pelvic CRT group vs. 10.1 months in the chemotherapy group (HR=0.72; 95% CI=0.66–0.79; $p<0.001$) and the 2-year OS rates were 36% in the pelvic CRT group vs. 23% in the chemotherapy group. In a propensity score-matched analysis, median survival was 14.4 (95% CI=12.8–15.7) vs. 10.6 months (95% CI=9.7–11.3; $p<0.001$). CRT was associated with improved OS among all examined subgroups, including patients with distant node-only metastasis (HR=0.64; $p<0.001$), organ-only metastasis (HR=0.71; $p<0.001$), and both nodal and organ metastasis (HR=0.83; $p=0.02$). Median survival was longer among patients who received therapeutic RT with a dose ≥ 45 Gy vs. those who received a dose of <45 Gy (18.5 vs. 10.2 months) and those who received EBRT plus brachytherapy vs. those who received EBRT alone (27.5 vs. 12.9 months; $p<0.001$).

2. Role of NAC in locally advanced cervical cancer

Whether NAC improves treatment outcomes in patients with locally advanced cervical cancer remains debatable. Overall, two strategies using NAC were applied in these patients: NAC followed by surgery and NAC followed by CRT. In this context, the following two studies discussed this issue.

Gupta et al. [59] reported a study in *Journal of Clinical Oncology* that compared the efficacy and toxicity of NAC followed by radical surgery vs. standard cisplatin-based CRT in patients with locally advanced squamous cell carcinoma in the uterine cervix. The study was a single-center, phase III, randomized controlled trial (NCT00193739). Six hundred thirty-five patients aged between 18 and 65 years with clinical stage IB2, IIA, or IIB squamous cell carcinoma were randomized as follows: those treated with three cycles of paclitaxel (175 mg/m²) and carboplatin (dosed to an area under curve of 5–6) once every 3 weeks followed by radical hysterectomy ($n=316$) or those treated with CRT plus cisplatin administered weekly for 5

weeks (n=317). Patients in the NAC group received postoperative RT or CRT, as indicated. The primary end point was DFS. After a median follow-up time of 58.5 months, the 5-year DFS was 69.3% in the NAC group vs. 76.7% in the CRT group (HR=1.38; 95% CI=1.02–1.87; p=0.038), whereas the corresponding 5-year OS rates were 75.4% vs. 74.7% (HR=1.03; 95% CI=0.75–1.40; p=0.870), respectively. The following late-onset toxicities occurred at 24 months or later: rectal (2.2% vs. 3.5%), bladder (1.6% vs. 3.5%), and vaginal (12.0% vs. 25.6%). Authors concluded that cisplatin-based concomitant CRT resulted in superior DFS compared with NAC followed by radical surgery in locally advanced cervical cancer.

In the 2018 ASCO Meeting, an abstract investigating whether NAC prior to definitive CRT improves treatment outcomes (NCT01973101) was posted [60]. Silva et al. [60] randomized 107 patients with locally advanced cervical cancer as follows: those treated with three cycles of NAC with cisplatin (50 mg/m²) and gemcitabine (1,000 mg/m²) followed by standard CRT plus cisplatin (40 mg/m²) administered weekly for 6 weeks and those treated with standard CRT. The primary endpoint was 3-year PFS, and the secondary endpoints were response rate, OS, and toxicities. After a median follow-up of 25.5 months, the 3-year PFS rates were 41.1% (95% CI=26.5–55.2) in the NAC group vs. 59.6 (95% CI=42.5–73.1) in the CRT group (HR=1.48; 95% CI=0.862–2.82; p=0.130), while the corresponding 3-year OS rates were 74.2% vs. 81.9% (HR=1.64; 95% CI=0.71–3.77; p=0.230). DFS, OS, and response rate were not different between the 2 groups. However, a trend toward inferior PFS in the NAC group was observed with inferior complete remission rate (54% NAC vs. 82% CRT alone; p=0.002).

BREAST CANCER

1. Talazoparib and germline BRCA mutation

Talazoparib is a PARP inhibitor with both strong catalytic inhibition (half-maximal inhibitory concentration, 4 nM) and a PARP-trapping potential that is approximately 100 times greater than that of other PARP inhibitors currently under investigation.

EMBRACA study [61] was a randomized, open-label, phase III trial conducted in 431 breast cancer patients with a germline *BRCA1/2* mutation treated with either talazoparib (1 mg once daily) or standard single-agent therapy as per the physician's choice (capecitabine, eribulin, gemcitabine, or vinorelbine in continuous 21-day cycles). Median PFS rates were 8.6 vs. 5.6 months for the talazoparib and physician's choice groups, respectively (HR=0.54; 95% CI=0.41–0.71; p<0.001). The objective response rate was also higher in the talazoparib group (62.6% vs. 27.2%; odds ratio=5.0; 95% CI=2.9–8.8; p<0.001). The primary adverse event of talazoparib therapy was hematologic symptoms (mainly anemia), which occurred in 55% of the patients.

Another success story of a PARP inhibitor administered in patients with breast cancer with a germline *BRCA1/2* mutation after olaparib therapy [62] was reported in a last year's review in this journal [63]. Talazoparib has strong PARP-trapping potential, as well as catalytic inhibition of PARP, and shows comparable clinical efficacy in this patient population.

2. Adjuvant endocrine therapy for premenopausal breast cancer

The first results of the Suppression of Ovarian Function Trial (SOFT) and the tamoxifen and exemestane trial were previously reported in this journal [3]. They were phase III trials that investigated the clinical value of suppression of ovarian function in premenopausal women with breast cancer treated with the adjuvant-supplemented tamoxifen or aromatase inhibitor

exemestane therapy. In the combined analysis, disease recurrence was significantly lower in patients who received the aromatase inhibitor exemestane plus ovarian suppression than among those who received tamoxifen plus ovarian suppression. The addition of ovarian suppression to tamoxifen did not result in significantly lower recurrence rates than that in those treated with tamoxifen alone. In 2018, the updated results from the two trials were reported [64].

Premenopausal patients who received ovarian suppression therapy plus tamoxifen showed significantly higher 8-year DFS and OS than those treated with tamoxifen alone, and those who received exemestane plus ovarian suppression therapy showed better results. In the SOFT, the 8-year DFS rate of patients treated with tamoxifen alone was 78.9%, 83.2% in those treated with tamoxifen plus ovarian suppression, and 85.9% those treated with exemestane plus ovarian suppression ($p=0.009$ for tamoxifen alone vs. tamoxifen plus ovarian suppression). The 8-year rate of OS of patients treated with tamoxifen alone was 91.5%, 93.3% in those treated with tamoxifen plus ovarian suppression, and 92.1% in those treated with exemestane plus ovarian suppression ($p=0.01$ for tamoxifen alone vs. tamoxifen plus ovarian suppression); among women who remained premenopausal after chemotherapy, the rates were 85.1%, 89.4%, and 87.2%, respectively. The frequency of adverse events was higher in the two groups that received ovarian suppression than in the tamoxifen alone group (grade 3 or higher adverse events in 24.6% of the tamoxifen alone group, 31.0% of the tamoxifen–ovarian suppression group, and 32.3% of the exemestane-ovarian suppression group).

These updated data confirmed the effects of ovarian suppression added to tamoxifen or exemestane as an adjuvant endocrine treatment in premenopausal women included in earlier analyses.

3. Adjuvant chemotherapy based on Oncotype DX: TAILORx trial

Risk prediction of relapse after surgery of hormone receptor-positive breast cancer is clinically important, and multi-gene expression panels are being used in the clinical setting. TAILORx trial [65] was a prospective trial that investigated whether the recurrence score based on the 21-gene breast cancer assay (Oncotype DX) predicts the benefit of chemotherapy for most patients who have a midrange score.

The trial involved 10,273 women with hormone receptor-positive, HER2-negative, axillary node-negative breast cancer. Of the 9,719 eligible patients with follow-up information, 6,711 (69%) had a midrange recurrence score of 11–25 and were randomly assigned to receive either chemoendocrine therapy or endocrine therapy alone. Endocrine therapy was non-inferior to chemoendocrine therapy in terms of invasive DFS (HR for endocrine vs. chemoendocrine therapy=1.08; 95% CI=0.94–1.24; $p=0.26$). There was some benefit of chemotherapy found in women 50 years of age or younger with a recurrence score of 16–25.

These results showed that Oncotype DX can be used to determine whether chemotherapy is indicated in hormone receptor-positive early breast cancer patients. However, in younger patients (50 years of age or younger), which is a more common age group in Asian countries, age should be taken into account in the treatment decision using these multi-gene tests.

4. Combination of atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer

There are limited treatment options for triple-negative breast cancer (TNBC), and chemotherapy remains the mainstay for this subtype. Targeted therapies for TNBC have been investigated but

their efficacies have not yet been proven, unlike the other subtypes of breast cancers (hormone receptor-positive or HER2 positive). Expression of PD-L1 is limited in breast cancer, but it is expressed mainly on tumor-infiltrating immune cells in TNBC-inhibiting immune response.

Impassion130 [66] was a phase III trial evaluating the effects of atezolizumab (a PD-L1 antibody) in combination with nab-paclitaxel and nab-paclitaxel monotherapy as first-line treatment in patients with TNBC. Each group included 451 patients. After a median follow-up of 12.9 months, the atezolizumab group showed longer median PFS (7.2 vs. 5.5 months; HR=0.80; 95% CI=0.69–0.92; p=0.002). The difference was more remarkable among patients with PD-L1-positive tumors; the median PFS rates of the atezolizumab group and nab-paclitaxel monotherapy group were 7.5 and 5.0 months, respectively (HR=0.62; 95% CI=0.49–0.78; p<0.001).

Atezolizumab plus nab-paclitaxel is the first successful immunotherapy for breast cancer and the first targeted therapy for TNBC. As the benefit was observed mainly in patients with PD-L1-expressing tumors, the selection of this therapy for optimal patients would be of great importance.

5. OS results of palbociclib and fulvestrant in advanced breast cancer: PALOMA-3 study

PALOMA-3 study [67] demonstrated the efficacy of palbociclib in combination with fulvestrant in advanced breast cancer after disease progression during prior endocrine therapy in terms of PFS, the primary endpoint, and was reported in a previous review in the journal [68]. Prespecified analysis of OS was reported in 2018.

Among 521 patients who underwent randomization, the median OS was numerically longer in palbociclib+fulvestrant group than in fulvestrant group (34.9 vs. 28.0 months; HR=0.81; 95% CI=0.64–1.03; p=0.09), although 16% of patients in the fulvestrant group received CDK4/6 inhibitors after the trial. In 410 patients who developed sensitivity to previous endocrine therapy, the difference was even greater (39.7 vs. 29.7 months; HR=0.72; 95% CI=0.55–0.94). The median time to the receipt of chemotherapy was also delayed (17.6 vs. 8.8 months).

Although the differences in OS in the entire trial group were not significant, these follow-up data confirmed the efficacy of palbociclib in advanced breast cancer patients and suggests greater benefit in patients who had sensitivity to previous endocrine therapy.

CONCLUSION

Medicine is still evolving. The best of today may be the second of tomorrow. Good of today could be harm of tomorrow. Quality studies that can satisfy a lot of unmet needs in this field of gynecologic oncology are warranted.

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