Review Article

Landscape of Systemic Therapy for Ovarian Cancer in 2019: Primary Therapy

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According to the statement from the 5th Ovarian Cancer Consensus Conference in 2015, the primary systemic chemotherapy for advanced ovarian cancer is a combination of paclitaxel plus carboplatin administered every 3 weeks (PCq3w). Optional alternatives include weekly dose-dense paclitaxel, in combination and maintenance therapy with bevacizumab, and intraperitoneal chemotherapy. Since then, in addition to the PCq3w strategy, there has been emerging new evidence, especially for poly(adenosine diphosphate-ribose) polymerase inhibitors. Moreover, there are multiple randomized, phase 3 trials testing the addition of antiangiogenic and/or immune checkpoint inhibitors in this patient population. In this article, current and future perspectives of systemic chemotherapy for advanced ovarian cancer are discussed. ***Cancer* 2019;125:4582-4586**. © *2019 American Cancer Society*.

KEYWORDS: antiangiogenic, carboplatin, intraperitoneal chemotherapy, ovarian cancer, paclitaxel, poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitor, primary chemotherapy.

INTRODUCTION

According to the 5th Ovarian Cancer Consensus Conference statement in 2015, intravenous (iv) carboplatin every 3 weeks and paclitaxel remain the standard chemotherapy drugs for first-line therapy in advanced-stage ovarian cancer in combination with primary or interval debulking surgery. Acceptable alternative schedules and routes of delivery include 1) weekly iv paclitaxel in combination with iv carboplatin every 3 weeks, 2) the addition of bevacizumab to the standard chemotherapy drugs after primary surgery, and 3) intraperitoneal (ip) platinum–based chemotherapy after primary surgery with <1-cm residual disease.[1]

Much evidence has been published since then, and the landscape of systemic chemotherapy is now changing dramatically. In this article, we discuss current standard systemic therapy and future possibilities.

WEEKLY PACLITAXEL

The role of the weekly administration of paclitaxel is now very controversial. Although the Japanese Gynecologic Oncology Group (JGOG) 3016 study showed clear progression-free survival (PFS) and overall survival (OS) benefits from changing the administration schedule of paclitaxel from every 3 weeks to a weekly dose-dense schedule (80 mg/m^2/wk),[2] the multicenter Italian trials in ovarian cancer (MITO) 7,[3] Gynecologic Oncology Group (GOG) 262,[4] and International Collaborative Ovarian Neoplasm (ICON) 8 studies[5] failed to reproduce the results.

The MITO 7 trial used a weekly administration schedule for both paclitaxel and carboplatin, and the dose of paclitaxel was 60 mg/m^2; this cannot be considered a dose-dense schedule. Therefore, it was not completely clear what caused the negative outcome of the trial: was it not applying a dose-dense regimen of paclitaxel, or could it be due to the use of a weekly low dose of carboplatin?[3]

The GOG 262 trial used exactly the same dosing schedule as the JGOG 3016 trial except for allowing the optional combination of bevacizumab with chemotherapy plus maintenance for 1 year.[4] In the overall results, there were no differences in PFS or OS between the 3-week schedule and the weekly dose-dense schedule of paclitaxel. On the other hand, in the patient population that did not receive bevacizumab, there was a tendency for the PFS of the weekly dose-dense paclitaxel regimen arm to be better than the PFS of the arm on the regimen of paclitaxel every 3 weeks. Therefore, it was

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concluded at that time that the combination with bevacizumab masked the efficacy of the dose-dense schedule of paclitaxel.

At the European Society of Medical Oncology meeting in 2018, the ICON 8 trial results were presented. ICON 8 was a 3-arm trial designed to test the efficacy and safety of the JGOG 3016 dose-dense regimen and a modified MITO 7 regimen by using now weekly dose-dense paclitaxel (80 mg/m^2) in combination with weekly carboplatin (area under the curve [AUC], 2 mg/mL/min) versus the conventional regimen of paclitaxel every 3 weeks plus carboplatin.[5] The results clearly showed that the use of a weekly dose-dense administration of paclitaxel, whether used in combination with the traditional carboplatin given at AUC 5 or 6 every 3 weeks or used in combination with weekly carboplatin given at AUC 2, did not improve the PFS or OS in the white patient population.

Although there is no clear evidence, it is most likely that there are pharmacogenomic differences between Japanese and white patients. Thus, weekly dose-dense paclitaxel with the administration of carboplatin every 3 weeks may be a standard (or optional) regimen for Japanese patients, whereas the regimen of paclitaxel at 175 mg/m^2 and carboplatin at AUC 6 every 3 weeks still remains the standard iv chemotherapy regimen in the rest of the world.

BEVACIZUMAB

Bevacizumab is a monoclonal antibody for vascular endothelial growth factor (VEGF). Since the GOG 218[6] and ICON 7 trials[7] showed a PFS benefit, the addition of bevacizumab to carboplatin and paclitaxel, followed by 1-year maintenance therapy with bevacizumab, has become one of the standard treatments for patients with advanced ovarian cancer. However, it is still controversial because none of the studies demonstrated an OS benefit. However, in an exploratory analysis of ICON 7, a significant difference in OS was noted in the patient cohort at high risk of progression in favor of those receiving bevacizumab versus those who did not. The restricted mean survival time was 34.5 months (95% confidence interval [CI], 32.0-37.0 months) for those receiving standard chemotherapy alone and 39.3 months (95% CI, 37.0-41.7 months) for those receiving bevacizumab in addition (log-rank $P = .03$).[8]

Another weakness in the use of bevacizumab in the first-line treatment setting is the fact that there are no useful biomarkers that clearly identify patients who might benefit from those who will not benefit from the additional use of bevacizumab. In that sense, the results in the recurrent disease setting are somewhat more promising because an OS benefit has been observed with the use of bevacizumab (in addition to paclitaxel/carboplatin) in platinum-sensitive recurrent ovarian cancer in GOG 213.[9]

POLY(ADENOSINE DIPHOSPHATE-RIBOSE) POLYMERASE INHIBITORS

The most important recent paradigm change in the treatment for ovarian cancer is the incorporation of a poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitor. Since 2017, 3 PARP inhibitors—olaparib, niraparib, and rucaparib—have been approved as maintenance therapy for platinum-sensitive recurrent ovarian cancer.[10-13] The results of the SOLO-1 trial, which concerned patients with ovarian cancer in the primary disease setting, were published in 2018.[14] SOLO-1 was an international, randomized, double-blind, phase 3 trial designed to evaluate the efficacy of one of the PARP inhibitors as maintenance therapy in patients with newly diagnosed stage III or IV high-grade serous or endometrioid ovarian cancer, primary peritoneal cancer, or fallopian tube cancer (or a combination thereof) with a mutation in BRCA1, BRCA2, or both (BRCA1/2) who had a complete or partial clinical response after platinum-based chemotherapy. The patients were randomly assigned in a 2:1 ratio to receive olaparib tablets (300 mg twice daily) or a placebo. The primary efficacy outcome was investigator-assessed PFS evaluated according to the Response Evaluation Criteria in Solid Tumors (version 1.1). The trial demonstrated a statistically significant improvement in investigator-assessed PFS with olaparib versus the placebo. The estimated median PFS was not reached in the olaparib arm and was 13.8 months in the placebo arm (hazard ratio, 0.30; 95% CI, 0.23-0.41; $P < .0001$). At the time of the analysis of PFS, OS data were not mature. The most common (≥10%) adverse reactions of any grade occurring in patients who received olaparib in SOLO-1 were nausea, fatigue, abdominal pain, vomiting, anemia, diarrhea, upper respiratory tract infections/influenza/nasopharyngitis/bronchitis, constipation, dysgeusia, decreased appetite, dizziness, neutropenia, dyspepsia, dyspnea, urinary tract infections, leukopenia, thrombocytopenia, and stomatitis.

On the basis of the results, the US Food and Drug Administration approved olaparib for germline BRCA-mutated (gBRCAm) or somatic BRCA-mutated ovarian cancer. The Food and Drug Administration also approved the BRACAnalysis CDx test (Myriad Genetic

Laboratories, Inc) to identify patients with gBRCAm advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are eligible for olaparib. The effectiveness of the BRACAnalysis CDx test was based on the SOLO-1 trial population for which a deleterious or suspected deleterious gBRCAm status was confirmed with either prospective or retrospective testing with the BRACAnalysis CDx test (https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm628876.htm).

It is to be expected that olaparib will be incorporated as standard maintenance therapy for patients with advanced, BRCA1/2-mutated (germline and/or somatic), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who have a response (complete or partial) after completion of first-line platinum-based chemotherapy.

FUTURE DIRECTIONS OF PARP INHIBITORS IN PRIMARY THERAPY FOR OVARIAN CANCER

Combination of PARP Inhibitors With Other Agents

With antiangiogenics

In the PAOLA-1 study, maintenance therapy with olaparib in combination with bevacizumab is compared with bevacizumab maintenance therapy alone in patients with advanced, high-grade serous ovarian cancer. In this study, the tumor BRCA mutation status is a stratification factor, but all the patients who responded to first-line chemotherapy are included. The results will be available in the third quarter of 2019.

With immune checkpoint inhibitors

Currently, multiple studies have just started to evaluate the combined use of PARP inhibitors and immune checkpoint inhibitors in the primary disease setting. The use of PARP inhibitors in that setting is for maintenance, but the use of immune checkpoint inhibitors varies (ie, in combination with chemotherapy and/or maintenance only).

Intraperitoneal Chemotherapy

The use of ip chemotherapy has been one of the most important research questions. Although 3 randomized trials using cisplatin showed a survival benefit from ip chemotherapy for optimally debulked patients with stage III ovarian cancer,[15] it has not been accepted as standard therapy, mainly because it has not been shown that ip administration of carboplatin is more efficacious than iv administration. There have been 3 randomized trials that tried to elucidate the benefit of ip carboplatin administration.[16] The OV21 trial was a 3-arm, phase 3 study designed to compare and evaluate 2 ip regimens against standard iv carboplatin/paclitaxel chemotherapy. Patients with stage IIB to IVA epithelial ovarian cancer who were treated with platinum-based iv neoadjuvant chemotherapy and had reached optimal (<1 cm) debulking at the time of interval debulking surgery were eligible. Patients were then randomized to 1 of the 3 treatment arms: 1) iv carboplatin/paclitaxel, 2) ip cisplatin plus iv/ip paclitaxel, or 3) ip carboplatin plus iv/ip paclitaxel. The primary endpoint was the 9-month progressive disease rate. Two hundred seventy-five patients were randomized; the ip cisplatin–containing arm did not progress beyond the first stage of the study after failing to meet the preset superiority rule. The final analysis compared arm 1 (n = 101) with arm 3 (n = 102). The intention-to-treat 9-month progressive disease rate was lower in the ip carboplatin arm (24.5%; 95% CI, 16.2%-32.9%) than the iv carboplatin arm (38.6%; 95% CI, 29.1%-48.1%; $P = .065$). Unfortunately, the study was underpowered to detect differences in PFS; in fact, the study did not proceed to phase 3 because of funding issues. Nevertheless, in addition to the promising efficacy data, the ip carboplatin–based regimen was well tolerated with no reductions in quality of life or increases in toxicity in comparison with iv administration alone.[17]

Although the OV21 study showed significant improvement in the progression-free rate at 9 months,[17] another large-scale, randomized, phase 3 study (GOG 252) failed to show a survival benefit of ip carboplatin when bevacizumab was integrated into the ip arm.[18]

In the GOG 252 trial, eligible patients were randomly assigned to 1 of 3 arms: 1) the iv carboplatin arm (6 cycles of weekly iv paclitaxel at 80 mg/m^2 with iv carboplatin at AUC 6 every 3 weeks), 2) the ip carboplatin arm (weekly iv paclitaxel at 80 mg/m^2 with ip carboplatin at AUC 6), or 3) the ip cisplatin arm (iv paclitaxel at 135 mg/m^2 over 3 hours on day 1 every 3 weeks, ip cisplatin at 75 mg/m^2 on day 2, and ip paclitaxel at 60 mg/m^2 on day 8). All participants received iv bevacizumab at 15 mg/kg every 3 weeks in cycles 2 to 22. A total of 1560 participants were enrolled, and they had a median follow-up of 84.8 months. The median PFS and OS data are summarized in Table 1. The mean patient-reported Functional Assessment of Cancer Therapy neurotoxicity scores (GOG) were similar for all arms, but the mean Trial Outcome Index of

TABLE 1. PFS and OS in the GOG 252 Trial

	Median PFS (mo)			Median OS (mo)		
		Stage II/III			Stage II/III	
Arm	ITT	Residual ≤1 cm	No Residual	ITT	Residual ≤1 cm	No Residual
Intravenous carboplatin	24.9	26.9	35.9	75.5	80	98.8
Intraperitoneal carboplatin	27.4	28.7	38.8	78.9	84.7	104.8
Intraperitoneal cisplatin	26.2	27.8	36.5	72.9	76.3	Not reached

Abbreviations: GOG, Gynecologic Oncology Group; ITT, intention-to-treat; mo, months; OS, overall survival; PFS, progression-free survival.

the Functional Assessment of Cancer Therapy–Ovary scores during chemotherapy were statistically worse in the ip cisplatin arm.

The reasons that this trial had a negative outcome are purely speculative. However, besides the fact that a suboptimal dose of ip cisplatin was given (75 mg/m^2 instead of 100 mg/m^2), the use of bevacizumab might have interfered with the penetration of the cytostatic drugs into the peritoneal linings.

At this time, there is 1 randomized trial (the Intraperitoneal Therapy for Ovarian Cancer With Carboplatin [iPocc] trial) that is waiting for survival data maturation to evaluate the efficacy of ip carboplatin.[19] The iPocc trial is an international, randomized, phase 3 trial by the Gynecologic Cancer Intergroup that is testing the superior role of ip carboplatin therapy over standard iv carboplatin therapy. The trial design is exactly the same as the design for the iv carboplatin arm and ip carboplatin arm of the GOG 252 trial except for the use of bevacizumab. Therefore, iPocc is a pure comparison of ip and iv carboplatin therapy. The trial started in 2010 and completed accrual of 655 patients in 2016. The primary analysis is expected to be conducted in 2020.

If these trial data are positive, there will be further discussion about how to best incorporate ip chemotherapy into the primary treatment of advanced ovarian cancer, particularly in combination with PARP inhibitors. In the retrospective analysis of the GOG 172 trial, a dramatic improvement in OS was observed in patients who had decreased BRCA1 expression and were treated with ip chemotherapy.[20] In that study, the researchers conducted immunohistochemical staining of tumor cells and showed that among patients with normal BRCA1 expression, the median OS was 58 months for the ip group and 50 months for the iv group ($P = .818$). Among patients with tumors with aberrant BRCA1 expression, the median OS was 84 and 47 months in the ip and iv groups, respectively ($P = .0002$). They also demonstrated by multivariate analysis that aberrant BRCA1 expression was an independent prognostic factor for better survival in women randomized to ip therapy (hazard ratio, 0.67; 95% CI, 0.47-0.97; $P = .032$).

Therefore, it is anticipated that patients with BRCA mutations will receive the largest benefit from ip chemotherapy followed by PARP inhibitors.

Another approach to ip chemotherapy is hyperthermic ip chemotherapy.[21] This is discussed in other articles in this supplement.

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AUTHOR CONTRIBUTIONS

Keiichi Fujiwara: Planning of article, data collection from references, writing, review, and final approval. **Kosei Hasegawa:** Data collection from references, writing, review, and final approval. **Shoji Nagao:** Data collection from references, writing, review, and final approval.

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