Review Article

A narrative review of neoadjuvant, HIPEC and maintenance treatment in ovarian and peritoneal serous cancer: current status

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Background and Objective: High-grade serous epithelial ovarian cancer (EOC) is the most lethal gynecological disease due to lack of screening test sensitivity. Currently, there is no clear consensus over the regime these patients should receive.

Methods: The PubMed database was searched using the terms "neoadjuvant chemotherapy", "heated intraperitoneal chemotherapy (HIPEC)", "maintenance treatment", "ovarian cancer", and "peritoneal serous cancer". Publications in the English language between September 1998 and February 2020 were eligible for inclusion. Case series of patients with ovarian and peritoneal serous cancer describing therapeutic considerations were included in this study. The screening of the articles was performed manually, based on the publication titles and abstracts. Of the articles retrieved, the reference lists of the relevant papers were checked to detect other articles that may be of interest to our narrative review.

Key Content and Findings: The main two options for the management of patients with advanced EOC are upfront debulking surgery (UDS) with adjuvant chemotherapy (ACT) or neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS). Optimizing patients' selection for UDS might offer higher progression-free survival (PFS) and overall survival (OS) rates. New imaging methodologies and biomarkers can guide this process. Peritoneal metastasis from EOC is a major challenge in the clinical management. The results for the role of heated intraperitoneal chemotherapy (HIPEC) combined with aggressive cytoreductive surgery (CRS) are controversial and prospective randomized trials are warranted. The addition of bevacizumab or poly (ADP-ribose) polymerase (PARP) inhibitors as concomitant and/or maintenance therapy has shown to improve PFS in patients with platinum-sensitive recurrent EOC. Serous peritoneal papillary carcinoma (SPPC) arises in the peritoneal surface lining the abdomen and pelvis without a discriminative primary tumor site. Clinical, pathological and biological differences hint towards SPPC and primary EOC being as a spectrum of disease. Patients with SPPC are traditionally managed similarly to stage III–IV EOC.

Conclusions: The recommended approach integrates aggressive CRS, and systemic chemotherapy to remove the macroscopic tumor, eradicate the microscopic residual disease, and control the microscopic metastasis.

Keywords: Upfront debulking surgery (UDS); interval debulking surgery (IDS); heated intraperitoneal chemotherapy (HIPEC); poly (ADP-ribose) polymerase inhibitors (PARP inhibitors); serous peritoneal papillary carcinoma (SPPC)

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Introduction

Epithelial ovarian cancer (EOC) is the fifth leading cause of cancer mortality among women. Patients are mostly presented with advanced disease at diagnosis, and approximately 80% relapse, with an estimated median progression-free survival (PFS) of around 12–18 months (1). Traditionally, high grade serous EOC is managed with radical surgery, followed by adjuvant chemotherapy (ACT). When upfront surgery is medically contraindicated, or complete cytoreduction not feasible, neoadjuvant chemotherapy (NACT) prior to interval debulking surgery (IDS) could be an alternative therapeutic maneuver in advanced EOC (2,3). Identification of predictive factors for optimal selection of patients for upfront debulking surgery (UDS) may improve PFS and overall survival (OS) rates. There is no consensus on the efficacy of heated intraperitoneal chemotherapy (HIPEC) combined with aggressive cytoreductive surgery (CRS). In the era of novel targeted therapies, HIPEC demands strict criteria for application. The treatment of platinum-sensitive recurrent EOC has improved by the addition to the platinum-based regimen of the anti-vascular endothelial growth factor (VEGF) antibody bevacizumab or the poly (ADP-ribose) polymerase (PARP) inhibitors. In 2016 Food and Drug Administration (FDA) approved bevacizumab for the treatment of platinum-sensitive recurrent EOC in combination with platinum-based chemotherapy (4). Phase II–III placebo-controlled trials have evaluated PARP inhibitors as maintenance therapy following platinum-based treatment. They did demonstrate a benefit in PFS over placebo in the overall population of recurrent EOC patients, which was more significant in those with a germline or somatic mutation in the breast cancer genes 1 and 2 (*BRCA1/2*) (5-9). Beyond *BRCA1/2* mutant cells that are highly susceptible to PARP inhibitors, deficiencies in Fanconi anemia genes (*BRIP1*, *PALB2*), the core RAD genes (*RAD51C*, *RAD51D*), and genes involved in HR pathway either directly (*CHEK2*, *BARD1*, *NBN*, *ATM*) or indirectly [*cyclin-dependent kinase 12* (*CDK 12*)], were also displayed to confer sensitivity to these drugs (10). Identification of the optimal treatment after the first platinum-sensitive recurrence, is still an unmet need. Within this context, it is required design of trials that will directly compare the two available maintenance strategies. Patients with serous peritoneal papillary carcinoma (SPPC) have a similar clinical presentation, histological features, and pattern of spread to those with primary EOC (11). These clinical entities are commonly approached as a single disease and arriving at the correct diagnosis can be challenging. Among patients considered to have primary EOC, 15% suffer instead of SPPC (11). Much effort has been made into researching differences of the molecular mechanisms of EOC and SPPC, but far share the same therapeutic approach.

Methods

Medline/PubMed was searched from inception until April 2020 for publications in the English language reporting on ovarian and peritoneal serous cancer. The search was carried out using mainly {"ovarian" [Mesh] AND "peritoneal serous cancer" [Mesh]} in Medline or the following keywords such as "upfront debulking surgery (UDS)", "interval debulking surgery (IDS)", "cytoreductive surgery (CRS)", and "heated intraperitoneal chemotherapy (HIPEC)". The screening of the articles was performed manually by SB and MS based on the publication titles and abstracts. Of the articles retrieved, the reference lists of the relevant papers were checked to detect other articles that may be of interest to our review. Descriptive statistics were used for patient and disease characteristics using IBM© SPSS© Statistics version 20.

Neoadjuvant treatment *vs.* UDS

The majority of newly diagnosed EOC patients are treated with radical surgery, followed by adjuvant platinum-based chemotherapy (12). However, surgical treatment options are debated. In advanced EOC, the choice of upfront debulking in cases of high grade-serous EOC versus NACT followed by IDS is not always clear. Precise patient selection criteria to guide therapeutic decisions in this setting is warranted.

Complete cytoreduction represents the most important clinical endpoint, associated with improved survival in patients undergoing debulking surgery (13). Initially, the EORTC 55971 trial randomized patients with advanced/metastatic EOC to primary debulking surgery followed by ACT or to NACT, followed by IDS and ACT (NCT00003636) (2). Five years later was published the similarly designed CHORUS trial (ISRCTN74802813) (3). Both were non-inferiority studies and demonstrated equivalent OS in both treatment arms. Based on these two studies, NACT followed by IDS has been established in advanced EOC as therapeutic choice of equal efficacy, as compared to upfront debulking. Randomized phase III clinical trials comparing upfront versus IDS in advanced

Table 1 Phase III clinical trials on UDS followed by ACT versus IDS after NACT in stage III–IV EOC, peritoneal, or fallopian tube cancer (https://www.clinicaltrials.gov/)

Study/clinicaltrials.gov identifier	Patients (n)		OS (months)		PFS (months)		Complete cytoreduction		Optimal cytoreduction	
	UDS-ACT	NACT-IDS	UDS-ACT	NACT-IDS	UDS-ACT	NACT-IDS	UDS-ACT	NACT-IDS	UDS-ACT	NACT-IDS
EORTC 55971/NCT00003636	336	334	29	30		12	19%	51%		NA
CHORUS/ISRCTN74802813	276	274	22.8	24.5	10.2	11.7	17%	43%		NA
JCOG0602	149	152	49	44.3	15.1	16.4	12%	64%	37%	82%
SCORPION/NCT01461850	55	55			NA		46%	58%	92%	100%
TRUST/NCT02828618	797				Active, not recruiting; estimated study completion date: April 2023					

UDS, upfront debulking surgery; ACT, adjuvant chemotherapy; IDS, interval debulking surgery; NACT, neoadjuvant chemotherapy; EOC, epithelial ovarian cancer; OS, overall survival; PFS, progression-free survival.

EOC are summarized in *Table 1*.

Several prognostic factors should be taken into account prior to surgical decision (14,15). Mesothelin, FLT4, α-1 acid glycoprotein (AGP) and cancer antigen 125 (Ca-125) are proposed as predictive biomarkers for the incorporation of anti-angiogenic agents (bevacizumab) to the first line treatment (16). Angiogenesis and vascular remodeling are complex processes that involve regulation by the cytokines angiopoietin-1 (Ang1) and Ang2. Ang1 is a potent angiogenic growth factor signaling through Tie2, whereas Ang2 was initially identified as a vascular disruptive agent with distinct functions from VEGF and antagonistic activity through Tie2.

Genomic factors, such as cyclin E1 amplifications and loss of *BRCA1/2* mutations, have also been predictive value for the decision of IDS versus upfront surgery, taken that they distinguish chemo-resistant from chemo-sensitive high grade-serous EOC (17). Gorodnova *et al.*, reported that EOC patients with *BRCA1/2* germ-line mutation show high sensitivity to platinum-based NACT (18). Equally, expression of the homologous recombination (HR) genes *BRCA2*, *p53*, and *FANCB* is associated with prolonged OS in EOC patients receiving NACT followed by IDS, and represents a positive predictive factor for platinum-based NACT (19).

Tumor-infiltrating lymphocytes (TILs) and tumor cell-free DNA (cfDNA) have also been proposed as predictive biomarkers; nevertheless, their use is limited and there is lack of standard methods for their isolation (20). It seems that, high levels of TILs are correlated with better response to NACT, suggesting that host immune response influences the tumor chemo-sensitivity (21-23). In a retrospective analysis of tumor tissue from 130 patients with EOC, those with higher CD3 (P=0.03), PD-L1 (P=0.007), and PD-1 (P=0.02) expression had prolonged OS (24). Analysis of cfDNA identify genomic alterations and captures the heterogeneity of the primary and metastatic tumors. cfDNA analysis can provide insight into molecular characterization, early diagnosis, monitoring of treatment response, and/or resistance, and optimal selection of patients for treatment in adjuvant setting (25).

A scoring system evaluating body mass index (BMI) of the patients, Ca-125 levels and imaging staging was conducted to predict those with potential benefit from UDS. Patients with BMI <30 kg/m^2, Ca-125 <100 IU/L and absence of positron emission tomography/computed tomography (PET/CT) findings suggestive of either diaphragmatic and omental carcinomatosis, or parenchymal metastases, have better chance of complete cytoreduction,

following UDS (26). Furthermore, patients older than 65 years of age, with albumin levels <25 g/L and ascites >1 L do not experience benefit from UDS.

Definitely, unresectable disease due to generalized carcinomatosis should be treated with NACT (21). From the surgical perspective, deep infiltration or diffuse metastasis within small and large bowel are correlated with high morbidity rates (16). Similarly, celiac lymph node involvement is associated with increased chance of both large bowel resection and metastasis to small bowel mesentery (27). It seems that lymph node involvement does not promote upfront CRS, whereas peritoneal carcinomatosis leads to surgical complications, within the context of upfront debulking (16,28,29). Laparoscopic index of Fagotti is a 100-point score based on objective parameters determined at pre-cytoreduction laparoscopy. Predictive parameters include elements of extraperitoneal and metastatic disease, such as peritoneal carcinomatosis, diaphragmatic and mesenteric disease, omental metastasis, bowel and stomach infiltration and liver metastases (30). Each parameter was assigned 2 points if present and 0 points otherwise. Patients are classified into three risk groups of incomplete cytoreduction. Those at high risk would be treated with NACT. For the subset of intermediate-risk patients, laparoscopy for the assessment of disease resectability is reasonable, whereas low-risk patients may undergo upfront surgery.

As far as concerned imaging techniques in high-grade serous EOC, PET/CT scan is recommended for the assessment of the extent of the disease and consequently, the decision about IDS versus upfront surgery in advanced EOC (21). Malignant pleural effusion and metastasis over diaphragm are related to lower chances of complete cytoreduction. However, further studies are required for the clarification of the predictive value of these radiological features. Additionally, PET with 2-deoxy-2-(fluorine-18) fluoro-D-glucose (18F-FDG) is proven to be adequate for estimating NACT response (21). Video-assisted thoracoscopy is recommended in patients with pleural involvement, for staging purposes, whereas real-time ultrasound elastography is limited nowadays (21). The predictive value of diffusion-weighted magnetic resonance imaging (DW-MRI) is based on the providing information about serosal intestinal, mesenteric vascular and distant site involvement (21,29).

HIPEC

Regardless that CRS and systemic chemotherapy remain the standard treatment of EOC, HIPEC becomes nowadays an option for candidate patients (31). HIPEC is the delivery of intraperitoneal chemotherapy in heated perfusate, following aggressive CRS. Intraperitoneal chemotherapy could reduce plasma toxicity compared with intravenous administration and increase the effect upon heating (32).

Several randomized phase II/III trials in different settings are summarized in *Table 2*. Among them, 4 enrolled patients during upfront treatment, 1 at the time of primary debulking surgery, whereas 2 at the time of interval debulking, after 3 cycles of NACT. The latest National Comprehensive Cancer Network (NCCN) guidelines support the policy of HIPEC at interval cytoreduction (33). Furthermore, 4 clinical trials recruited patients with recurrent disease, eligible for secondary CRS. It seems that the use of HIPEC in this setting has been more extensively investigated. An analysis of 16 studies, concluded that HIPEC in recurrent EOC, resulted in improved survival (34). Morbidity consistently ranged between 12% and 30%. Treatment related side effects usually were related to myelosuppression and nephrotoxicity (35). However, differentiation between surgical complications and HIPEC is challenging (35). The OS and PFS rates were compatible with those reported in the OCEANS, DESKTOP, and CALYPSO trials; nevertheless, due to the separate designs of these trials, direct head to head comparison is not feasible (34,36-38).

Furthermore, the tasks of optimal drug choice, dosing, time and temperature should also be resolved. Currently, the rationale for HIPEC incorporated in a multi-model treatment in patients with advanced EOC is strong. The main concern is related to the tolerance, which maintain skepticism about the implementation of this therapeutic intervention (39). The evidence of the mortality and morbidity of HIPEC compared to CRS alone is rather inconclusive, and inconsistent (40,41). In any case, HIPEC should be offered at well-organized centers after precise patients' selection (42). Obviously, further well-designed prospective randomized trials are warranted to clarify the role of HIPEC application in the management of primary EOC.

Maintenance treatment

Despite recent achievements in the upfront treatment, approximately 80% of EOC patients experience disease relapse within 5 years following initial diagnosis. The median OS of recurrent EOC ranges from 12 to 24 months (43).

Table 2 Phase II/III randomized controlled HIPEC trials (https://www.clinicaltrials.gov/)

Clinicaltrials.gov identifier	Condition	Intervention	HIPEC regimen	Status
NCT02681432	Primary or recurrent EOC	CRS followed by HIPEC, ACT	Paclitaxel 175 mg/m^2 for 60 min at 42–43 ℃	Recruiting
NCT01539785	Recurrent, platinum-sensitive EOC	Secondary CRS followed by HIPEC, ACT	Cisplatin 75 mg/m^2 for 60 min at 41–42.5 ℃	Unknown
NCT01091636	Primary EOC, tubal, and peritoneal cancers	CRS followed by HIPEC, ACT	Cisplatin 75 mg/m^2 for 90 min at 41.5 ℃	Completed
NCT02124421	Stage IIIC unresectable EOC/tubal, with PR or CR after 3 cycles of 1st-line chemotherapy	Interval CRS followed by HIPEC	Cisplatin 100 mg/m^2 and paclitaxel 175 mg/m^2 for 90 min at 42 ℃	Recruiting
NCT00426257	Stage III EOC, tubal, and peritoneal cancer patients eligible for IDS either following NACT or following incomplete UDS and chemotherapy	Interval CRS followed by HIPEC	Cisplatin 100 mg/m^2	Completed
NCT01588964	Recurrent, platinum-sensitive EOC	Secondary CRS followed by HIPEC, ACT	Oxaliplatin 460 mg/m^2 at 42 ℃	Completed
NCT01376752	Recurrent, platinum-sensitive EOC with peritoneal disease only after platinum-based second-line chemotherapy	CRS followed by HIPEC	Cisplatin 75 mg/m^2 for 60 min	Suspended (due to COVID-19 pandemic)
NCT01767675	Recurrent platinum-sensitive EOC, tubal, and peritoneal cancer	Secondary CRS followed by HIPEC, ACT	Carboplatin 800 mg/m^2 for 90 min at 41–43 ℃	Active, not recruiting
NCT02567253	Primary or recurrent platinum-sensitive serous EOC, or peritoneal cancer	CRS followed by normothermic or hyperthermic IP chemotherapy	Cisplatin 75 or 120 mg/m^2 for 90 min at 37 or 41 ℃	Recruiting
NCT02328716	Peritoneal carcinomatosis arising from primary or platinum-sensitive recurrent EOC, peritoneal, or tubal carcinoma (stage III/IV)	CRS followed by HIPEC	Cisplatin	Unknown

HIPEC, heated intraperitoneal chemotherapy; EOC, epithelial ovarian cancer; ACT, adjuvant chemotherapy; CRS, cytoreductive surgery; PR, partial response; CR, complete response; IDS, interval debulking surgery; NACT, neoadjuvant chemotherapy; UDS, upfront debulking surgery.

Until recently, patients with platinum-sensitive recurrent EOC were treated with re-challenging platinum-based regimens. The therapeutic outcome of this subset of patients has been improved by the addition to the platinum-based regimen of the anti-VEGF antibody bevacizumab or PARP inhibitors.

Indeed, results from three phase III trials demonstrated prolongation of the PFS with the incorporation of bevacizumab to the platinum-based chemotherapy, followed by maintenance bevacizumab, when compared to chemotherapy alone (4,38,44). This therapeutic strategy should be specifically indicated in the subset of patients with high disease burden at relapse, where a prompt tumor shrinkage could lead to better control of disease related symptoms. The FDA and the European Medicine Agency (EMA) approved bevacizumab for the treatment of platinum-sensitive recurrent EOC in combination with carboplatin and either gemcitabine or paclitaxel in 2016 and 2017, respectively. Approval was granted based on findings from OCEANS trial, which demonstrated increased objective response rate (ORR) of about 20% for the combination arm, as compared to chemotherapy alone (38). Despite this, recent evidence from the ENGOT-ov18/AGO-OVAR 2.21 trial demonstrated better efficacy of carboplatin plus pegylated liposomal doxorubicin as compared to carboplatin plus gemcitabine, either combined with bevacizumab [median PFS 13.3 *vs.* 11.7 months, hazard ratio (HR): 0.80; 95% confidence interval (CI): 0.68–0.96, P=0.0128] (45).

PARP inhibitors have changed management standards of patients with platinum-sensitive recurrent EOC. Olaparib, rucaparib, and niraparib have all obtained FDA and/or EMA approval in EOC in different settings. Veliparib and talazoparib are in earlier clinical development (46,47). Approved PARP inhibitors have been evaluated as maintenance therapy of recurrent EOC patients. Phase II–III placebo-controlled trials demonstrated a benefit in PFS in the overall population, specifically in those with either germline or somatic BRCA1/2 mutations (5-9). Both BRCA and HR deficiency status represent novel predictive biomarkers of response to chemotherapy and PARP inhibitors. Germline *BRCA1/2* mutations enhance EOC risk and account for approximately 14% of EOC. These genes encode proteins with a crucial role in the repair of double-strand DNA breaks (DSBs) through HR deficiency. Furthermore, somatic mutations and epigenetic inactivation of *BRCA1/2* have been implicated in sporadic EOC. Beyond germline pathogenic variants in *BRCA1/2* genes, alterations in *BRIP1*, *RAD51C*, *RAD51D*, and mismatch repair genes also increase the risk of EOC (10). Furthermore, the option of PARP inhibitors combined with drugs that inhibit HR deficiency represent a novel treatment that may sensitize EOC with *de novo* or acquired HR proficiency to PARP inhibitors. Further research should aid identification of patients' most likely to benefit from combined treatment (48).

Side effects represent a crucial factor for the choice of the optimal agent for the maintenance treatment. Bevacizumab has overall manageable side effects, and the specific toxicity profile is related to its mechanism of action. The most frequent adverse events include hypertension, proteinuria, hemorrhages and thromboembolic events, poor wound healing and gastrointestinal perforation. As a consequence, patients at higher risk to experience bevacizumab induced side effects should be treated with a PARP inhibitor if indicated (49). Maintenance therapy with PARP inhibitors is generally well tolerated, which affects patients' compliance and quality of life, hugely important parameters in the maintenance setting. The most common severe toxicities attributed to these drugs include anemia and fatigue (50). Although PARP inhibitors oppose the catalytic activity of PARP in general, there are remarkable differences in their abilities to trap PARP, based on the size and structure of each separate molecule. This explains the different magnitude of cytotoxicity and their distinct safety profile (51).

The therapeutic approach of recurrent EOC is further influenced by the changing landscape of the first line treatment. The SOLO-1 trial has established a new standard of care in patients with BRCA1/2 mutations; olaparib arm achieved approximately 70% reduction in risk of disease progression compared to placebo (1). Niraparib has also been effective in the up-front setting with prolongation of PFS over placebo in a population at high-risk of recurrence. The benefit was reached in patients with *BRCA1/2* mutations and in BRCA wild-type patients with a positive HR deficiency score, assessed by "myChoice HRD" commercial genomic scar assay by Myriad (9,52). Similar results have been reported by PAOLA1 GINECO/ENgOT-ov25 trial, assessed the combination of olaparib with bevacizumab (53). As more patients access to PARP inhibitors first line therapy, clinical trials for the establishment of the optimal therapeutic sequence are warranted.

Table 3 summarizes maintenance clinical trial data, following the first platinum-sensitive recurrence. It is difficult to directly compare the activity of different PARP

Table 3 Randomized studies of maintenance treatment in platinum sensitive (PFI ≥6 m) recurrent EOC

Authors/study/ref	Phase	Population	Primary endpoint	Randomized patients	Treatment arms	HR for PFS	CI (95%)	P value
Coleman *et al.*/ GOG 0213/(4)	III	Prior anti-VEGF allowed	OS	A: 337; B: 337	A: Carbo AUC5 + Pac 175 mg/m^2 q21d ×6 cycles; B: Carbo AUC5 + Pac 175 mg/m^2 + Bev 15 mg/kg q21d ×6 cycles, followed by Bev 15 mg/kg, q21d (maintenance)	0.628 for B	0.534–0.739	0.0001
Aghajanian *et al.*/ OCEANS/(38)	III	Prior anti-VEGF not allowed	PFS	A: 242; B: 242	A: Carbo AUC4 d1 + Gem 1,000 mg/m^2 d1–8 q21d ×6 cycles; B: Carbo AUC4 d1 + Gem 1,000 mg/m^2 d1–8 + Bev 15 mg/kg d1 q21d ×6 cycles, followed by Bev 15 mg/kg, q21d (maintenance)	0.484 for B	0.388–0.605	0.0001
Pignata *et al.*/ MITO-16/(44)	III	Anti-VEGF in first line	PFS	A: 203; B: 202	A: Carbo + Pac/Gem/PLD q21d ×6 cycles; B: Carbo + Pac/Gem/PLD + Bev 15 mg/kg q21d ×6 cycles, followed by Bev 15 mg/kg, q21d (maintenance)	0.51 for B	0.41–0.64	0.001
Ledermann *et al.*/ STUDY-19/(5)	II	HGSOC, treated with a median of 2 platinum-based regimens	PFS	A: 129; B: 136	A: Placebo; B: Olaparib 400 mg BID	0.35 for B (overall) 0.18 for B (BRCAm) 0.54 for B (BRCA wt)	0.25–0.49 (overall) 0.10–0.31 (BRCAm) 0.34–0.85 0.54 for B (BRCA wt)	0.001 (overall) 0.0001 (BRCAm) 0.0075 0.54 for B (BRCA wt)
Coleman *et al.*/ ARIEL-3/(6)	III	HGSOC or endometrioid ovarian cancer, ≥2 platinum-based regimens	PFS	A: 189; B: 375	A: Placebo; B: Rucaparib 600 mg BID	0.36	0.30–0.45	0.0001
Pujade-Lauraine *et al.*/SOLO-2/(7)	III	HGSOC or endometrioid ovarian cancer with g/sBRCAm ≥2 platinum-based regimens	PFS	A: 99; B: 196	A: Placebo; B: Olaparib 300 mg BID	0.30 for B	0.22–0.41	0.0001
Oza *et al.*/ NCT01081951/(8)	II	HGSOC <3 platinum-based regimens	PFS	A: 81; B: 81	A: Carbo AUC5 + Pac 175 mg/m^2 q21 ×6 cycles; B: Carbo AUC5 + Pac 175mg/m^2 q21 + Olaparib 200 mg d1–10 q21 ×6 cycles, followed by Olaparib 400 mg BID (maintenance)	0.51 for B (overall) 0.21 for B (BRCAm)	0.34–0.77 (overall) 0.08–0.55 (BRCAm)	0.0012 (overall) 0.0015 (BRCAm)
Mirza *et al.*/ NOVA/(9)	III	HGSOC ≥2 platinum-based regimens	PFS	A: 181; B: 372	A: Placebo; B: niraparib 300 mg BID	0.27 for B (gBRCAm) 0.45 for B non-(gBRCAm) 0.23 (BRCAm)	0.173–0.410 (gBRCAm) 0.338–0.607 non-(gBRCAm) 0.16–0.34 (BRCAm)	0.0001 (gBRCAm) 0.0001 non-(gBRCAm) 0.0001 (BRCAm)

PFI, platinum-free interval; EOC, epithelial ovarian cancer; ref, reference; HR, hazard ratio; PFS, progression-free survival; CI, confidence intervals; GOG, Gynecologic Oncology Group; M, months; VEGF, vascular endothelial growth factor; OS, overall survival; Carbo, carboplatin; AUC, area under the curve; Pac, paclitaxel; D, days; Bev, bevacizumab; Gem, gemcitabine; PLD, pegylated liposomal doxorubicin; HGSOC, high-grade serous ovarian cancer; BID, twice a day; BRCAm, BRCA mutated; BRCAwt, BRCA wild-type; gBRCAm, germline BRCA mutated; g/sBRCAm; germline/somatic BRCA mutated.

inhibitors and bevacizumab since head-to-head studies are lacking.

Future directions of immunotherapy in EOC

Despite the fact that early data from preclinical studies imply that EOC has an immunogenic microenvironment, immune checkpoint inhibitors have not yet produced favorable responses in clinical trials. When analyzed according to biomarker status, PD-L1 positivity did not predict objective response in nivolumab trial, while objective response to atezolizumab was observed in 2 out of 8 patients who had ≥5% PD-L1 expression in immune cells (54,55). In a study evaluated efficacy of avelumab, ORR in PD-L1 positive and negative cohorts were 11.8% and 7.9%, respectively, when cut-off for PD-L1 positivity was set at 1% (56). The KEYNOTE-100 trial was the largest study on single immune checkpoints inhibitors in EOC. PD-L1 expression was measured as combined positive score (CPS), defined as the ratio of PD-L1 positive cells to viable tumor cells (57). The ORR to pembrolizumab was reported as 5% for CPS <1, 10.2% for CPS ≥1 and 17.1% for CPS ≥10, respectively. Ipilimumab, a monoclonal antibody against cytotoxic T-lymphocyte associated protein 4 (CTLA-4), was administered to 9 advanced EOC patients after immunization with granulocyte-macrophage colony-stimulating factor and only one patient had a partial response (PR) (58). In a phase II trial of 40 recurrent platinum-sensitive EOC patients, treated with the monoclonal against CTLA-4 antibody ipilimumab, ORR was reached at 10.3% (59). Based on the outcome of these trials, EOC does not seem to respond well to anti PD-1/PD-L1 or anti-CTLA monotherapy. However, it should be taken into consideration that enrolled patients were heavily pretreated with chemotherapy. Furthermore, the samples of these studies were mostly small. As such, conclusions should be drawn carefully.

A reasonable strategy for increasing tumor immunogenicity and enhancing efficacy of immunotherapy is the combination with chemotherapy. The phase III JAVELIN Ovarian 200 trial, enrolled 566 platinum-resistant or platinum-refractory EOC patients who had received up to 3 lines of treatment (60). Addition of avelumab to pegylated liposomal doxorubicin did not significantly prolong PFS and OS. However, patients of PD-L1 positive subgroup (≥1% of tumor cells or ≥5% of immune cells) achieved an improved survival (HR: 0.72; P=0.11 for PFS and HR: 0.59; P=0.005 for OS). Furthermore, combination with VEGF blockade is an additional potential method to increase anti-tumor efficacy of immunotherapy. There are ongoing randomized phase III trials investigating addition of atezolizumab to chemotherapy and/or bevacizumab in different EOC settings (NCT03038100, NCT02891824, and NCT02839707) (61-63). Overall, identification of predictive biomarkers for the optimal selection of candidates for immunotherapy is crucial.

Serous primary peritoneal carcinoma

SPPC share subtle clinical features that differ from those with primary EOC. SPPC affects overweight and older patients, as well as those with high parity and later menarche. It is mostly multifocal, characterized by diffuse micronodular spread, resulting in high tumor burden in upper abdomen and diaphragmatic surfaces. Furthermore, discordant allelic losses have been observed among multiple intrapatient peritoneal deposits. The fact that different genetic events take place at different peritoneal loci, distinguishes SPPC from EOC with the unifocal nature (64,65).

In terms of the molecular biology, SPPC is more commonly characterized by immunohistochemical overexpression of human epidermal growth factor receptor 2 (HER2), and higher proliferation index Ki-67 as compared to EOC (66-68). This provided the rationale of the anaplastic nature of the SPPC, along with the common development of platinum resistance. Expression of estrogen and progesterone receptors is less frequent in SPPC, similarly to the lower incidence of loss of heterozygosity on chromosomes (66,68). Finally, there is no distinction in the protein expression patterns of *p53* and *BCL2*, the microvessel density, and microRNA profiles (66,67,69,70). Based on this molecular evidence, SPPC and primary EOC seem to represent two clinical entities of a spectrum of disease rather than completely separate malignancies.

The recommended diagnostic work-up for patients with SPPC includes basic blood analyses and imaging with scans of chest, abdomen, and pelvis (71). The serum Ca-125 is not pathognomonic but can be monitored if the baseline level is raised (72). Overall, surgical staging remains diagnostically the gold standard, whereas endoscopies of the upper and lower gastrointestinal system and PET-CT scans may provide additional information (73).

Histologically, SPPC exhibits a complex papillary or glandular architecture, similarly to the papillary serous EOC (74). Immunohistochemically, it is typically positive for CK7, CD15, S-100, P53, WT-1, ER, and PAX-8

and negative for calretinin (75-77). SPPC should be differentiated from peritoneal mesotheliomas, which are negative for Ber-EP4 and MOC-31 and positive for calretinin and D2-40 (78).

SPPC typically metastasize to the peritoneal cavity, pelvic and para-aortic lymph nodes, which highlights the importance of aggressive local control (79). The rationale of total peritonectomy is the removal of precursor sites and microscopic residual disease (80). Impressively, residual tumors have been reported in 60% of grossly normal appearing peritoneum (81,82). Lymph nodes are in general equally involved in both clinical entities. The strong recommendation of systematic lymph node dissection in those with SPPC is related to the fact that the more frequently met postoperative adhesions as compared to EOC, limit further surgeries at recurrence (80,83). NACT is effective for achievement of optimal local control (84). Patients with complete response (CR) to NACT may not require surgery. A case series described that among 44 patients with SPPC treated with NACT, only 17 underwent CRS (85). However, the surgical subset experienced lower recurrence rates (65% *vs.* 93%) and significantly longer median PFS (25 *vs.* 9 months; P=0.001) and OS (48 *vs.* 18 months; P=0.0016) (85).

The treatment strategy of CRS-HIPEC in patients with primary or recurrent SPPC is still under investigation. Incorporation of HIPEC to standard multimodality therapy allows local control of peritoneal carcinomatosis (86). In two case series of 32 and 22 patients treated with CRS followed by HIPEC, the reported 5-year OS was 57.4% and 64.9%, respectively (80,87). In terms of systematic chemotherapy, the combination of platinum/taxane yielded an ORR of 53–100% and median OS of 15–42 months (88). Apart from EOC patients, clinical trials of PARP inhibitors and bevacizumab in either upfront or maintenance setting, enroll those with SPPC; nevertheless, studies has not provided outcomes of each disease separately (46,48).

Conclusions

There is a lack of consensus regarding the optimal surgical timing and patients' selection criteria for either upfront debulking surgery, or IDS. Algorithms should be conducted, depending on evidence-based prognostic factors. Complete surgical debulking remains the most reliable clinical endpoint, associated with longer survival. There is as strong rationale for the implementation of HIPEC in EOC treatment and data from randomized clinical trial are pending. The landscape of maintenance therapy for EOC is rapidly changing. Currently, antiangiogenesis (bevacizumab), and PARP inhibitors (olaparib, niraparib and rucaparib) have been incorporated in maintenance treatment and led to prolongation of PFS in patients with platinum-sensitive recurrent EOC. However, question remains regarding the choice of the optimal agent in the absence of head-to-head clinical trials' data. Patients with SPPC are traditionally managed similarly to patients with advanced/metastatic primary EOC. Due to lack of prospective trials, the supportive evidence is limited to single institutions retrospective series.

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Footnote

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