Therapy for Recurrent High-Grade Epithelial Ovarian Cancer—The Current Status and Future Trends

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Abstract

Ovarian malignancy is the seventh most frequently diagnosed cancer among women. The most common type is epithelial ovarian cancer. Several subtypes with distinct biological and molecular properties exist, and there is inconsistency in availability of and access to different modalities of treatment. The standard first-line management is combining surgery and platinum-based chemotherapy. Most of them are diagnosed at an advanced stage due to which they have poor outcomes. The existing screening tests have a low predictive value. Even with the best available upfront treatment, high rates of recurrences are observed. As a result, there have been major advances in the treatment of recurrences with the development of anti-angiogenic agents and PARP inhibitors. It has led to the improvement in survival and quality of life among the relapsed epithelial ovarian cancers. This review is focused on the management of recurrent epithelial ovarian cancers and future directions based on current evidence. The application of a personalized and structured approach will meaningfully bring changes in the paradigm of care in these groups of patients.

Keywords

- epithelial ovarian cancer
- recurrent
- chemotherapy
- targeted therapy

Introduction

The newly diagnosed advanced epithelial ovarian cancer (EOC) is typically treated in the frontline setting by combining cytoreductive surgery and doublet chemotherapy, which is routinely paclitaxel and carboplatin.[1] Most of the women experience good responses, which includes complete responses to neoadjuvant chemotherapy, but disease recurrences are not uncommon.[2]

The indicators which influence prognosis of recurrent EOCs include Eastern Cooperative Oncology Group (ECOG) performance status, tumor volume, histology, and platinum-free interval (PFI).

PFI is defined as the time from last platinum treatment to recurrence and is the basis for rechallenge of platinum-based chemotherapy.[3] The classification was specified at the fourth Vancouver Ovarian Cancer Consensus Conference in 2010 which divided recurrent EOCs into four categories[4]:

a. PFI <1 month—platinum refractory.
b. PFI 1 month to 6 months—platinum resistant.
c. PFI 6 months to 12 months—partially platinum sensitive.
d. PFI >12 months—Platinum sensitive.

This review focuses on the current standards and choices of therapy available in recurrent ovarian cancers (ROCs) and a discussion on future trends.

Methods

We identified articles on PubMed in the past 10 years with keywords "recurrent," "epithelial ovarian cancer," "chemotherapy," "targeted therapy" published in English language as

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randomized controlled trials or systematic review. The articles related to management of recurrent high-grade serous and epithelial carcinomas were included and rest were excluded. The most recent articles were given more value to keep the review as up to date as possible. Of the results, 100 relevant articles were taken for preparation for this review after excluding the irrelevant articles, duplicated articles, and articles which were published only as an abstract. We also identified some relevant articles within the articles that were picked from the above search which were pertinent to the topic.

Mechanisms of Resistance to Platinum Compounds

There are several mechanisms of cellular resistance to platinum compounds that have been described in various in vivo and in vitro studies. These mechanisms can be classified in two groups:[5,6]

1. Those that limit the generation of cytotoxic platinum-deoxyribonucleotide (DNA) adducts.
2. Those that avert cell death that occurs following platinum-DNA adduct formation.

Six DNA repair pathways are involved in maintenance of cellular machinery. These are mismatch repair (MMR), base excision repair (BER), nucleotide excision repair (NER), homologous recombination (HR), non-homologous end joining, and Fanconi Anemia (FA).[6]

NER defects are associated with an exceptional sensitivity to platinum compounds whereas defects of MMR correlate with resistance to the latter.[7] BER has little evidence linked to the repair system of platinum containing drugs. Cells deficient in HR and FA have been shown to be extremely sensitive to platinum agents as these pathways are linked to the cellular response to platinum agents.[8] Other proteins and pathways participating in the DNA damage response that have been involved with the activity of platinum agents are ATR and ATM proteins and checkpoint proteins, CHK1 and CHK2.[9] The DNA repair gene, CDK12 (also known as the master regulator) modulates sensitivity to PARP inhibitors and platinum agents.[10]

The molecular characterization of EOC has unveiled that more than 50% of high-grade serous ovarian cancers have HR repair deficiency due to either germline or somatic mutations, promoter hypermethylation in BRCA1, BRCA2, and RAD51C, and mutations in FA and RAD genes which may determine the extreme sensitivity to platinum agents.[6]

Higher levels of ERCC1/XPF complex have been ascertained in ovarian cancer patient xenografts that have been made resistant in vivo to cisplatin. However, these data need to be authenticated in a larger cohort of patients with platinum-resistant tumors to draw stronger conclusions.[7]

An enhanced awareness of the molecular basis of platinum resistance may lead to the development of novel antitumor approaches that will sensitize unresponsive ovarian cancers to platinum-based chemotherapy. Various two-dimensional human and murine ovarian cancer cell lines, and patient-derived xenografts (PDXs), have been developed in this regard.[6] The use of organoids derived from distinct tumor types has been suggested as an intermediary tool between 2D cultures and PDXs. They maintain important characteristics of the tumors they arise from along with infiltrating cells.[11]

Primary Therapy

Platinum-Resistant Recurrence

Chemotherapeutic Agents

Platinum-resistant recurrences confer a poor prognosis. They have a chemotherapy response rate of approximately 10 to 15%, with a progression-free survival (PFS) less than 4 months and an overall survival (OS) time of approximately 1 year.[12] Therefore, chemotherapy for platinum-resistant ROC is considered as palliative and currently monotherapy is recommended over multidrug chemotherapy. The agents that are commonly used include liposomal doxorubicin (PLD), paclitaxel, topotecan, or gemcitabine.[13] The choice of drug is mainly dependent on the toxicity profile, the deleterious effects of previous therapy, and the patient's desire.

Two phase 3 trials have compared gemcitabine and PLD.[14,15] A systematic review of these trials revealed no difference in survival but different and comparable adverse events.[16] Six studies comparing topotecan with various agents like PLD and paclitaxel also revealed similar results but with increased rates of toxicity.[17] Several non-platinum agents have been tried as doublets, but none have revealed a significant improvement in survival and yielded increased rates of toxicities. Oral metronomic therapy with cyclophosphamide, etoposide, hormonal agents, and tyrosine kinase inhibitors like pazopanib have been evaluated in various retrospective studies with encouraging results.[18–20]

Targeted Agents

Anti-vascular endothelial growth factor (VEGF) agents redistribute the circulation in tumoral tissue, and increase the overall delivery of chemotherapy and oxygen in tumor tissue. This explains its greater efficacy when combined with chemotherapy. The PLD or taxanes combinations with bevacizumab are the most active and commonly used agents.[21]

The AURELIA trial, which investigated the addition of bevacizumab to single-agent chemotherapy in platinum-resistant ROCs, indicated that the median PFS and overall response rate (ORR) were significantly longer in patients receiving the combination (PFS-6.7 months vs. PFS-3.4 months, $p = 0.001$).[22] A recent update of this study reported a more pronounced effect on OS in the taxane cohort (HR 0.65, 95% CI 0.42–1.02), presumably due to the synergistic antiangiogenic activity of the two agents.[23]

Platinum Sensitive Recurrence

In the platinum sensitive recurrences, a complete response to chemotherapy ranges between 15 to 30% with an overall

response between 30 to 70%. This benefit has a positive correlation with the length PFI.[24]

The frequently used platinum agent is carboplatin and is used in combination with PLD, paclitaxel, or gemcitabine. A pooled analysis of three phase 3 trials of Arbeitsgemeinschaft Gyna kologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and International Collaborative Ovarian Neoplasm collaborators showed a significant improvement in PFS (HR, 0.76; 95% CI, 0.66–0.89; $p = 0.0004$) and OS (HR, 0.82; 95% CI, 0.69–0.97; $p = 0.02$) in platinum-sensitive ROC treated with platinum–paclitaxel combination versus single-agent platinum.[25] A phase 3 trial showed that the combination of gemcitabine and carboplatin had a significantly improved PFS versus single agent carboplatin (HR, 0.72; 95% CI, 0.58–0.90; $p = 0.0031$).[26] The CALYPSO trial showed that the carboplatin and PLD combination had a statistically significant improvement in PFS over paclitaxel and carboplatin (HR, 0.82; $p = 0.005$) with lowering of toxicities including carboplatin hypersensitivity reactions.[2]

In case of further recurrences in more than 6 months, platinum-based combined chemotherapy regimen can be utilized, based on PFI. But at subsequent recurrences the platinum sensitivity abbreviates.[27]

Toxicities to Chemotherapy

A detailed history of previous chemotherapy and toxicities is essential for a decision on the choice of chemotherapy. Residual neuropathy is important before rechallenging a taxane. The possibility of hypersensitivity to carboplatin is always present when used in the recurrent setting. This risk increases with subsequent cycles with inclusion of a carboplatin. The exact mechanism of this toxicity is unknown. Common hematological toxicities include thrombocytopenia and anemia which can occur with any of the agents. Other non-hematological toxicities include chemotherapy induced nausea and vomiting, myalgias, fatigue, etc.

Targeted Agents

The trials that investigated the role of bevacizumab in platinum-sensitive ROC were the OCEANS and GOG-213.

The OCEANS trial was conducted among 484 patients who were randomized to the standard chemotherapy with placebo or to standard chemotherapy and 3-weekly bevacizumab (15 mg/kg) followed by maintenance until progression of disease or intolerable toxicity. Median PFS (12.4 vs. 8.4 months) and ORR (78.5 vs. 57%) was significantly higher among the bevacizumab group with acceptable toxicity profile.[28] However, this trial failed to prove an OS advantage in the recently updated report (33.6 vs. 32.9 months; $p = 0.65$).[29]

The GOG 213 trial randomized 674 patients of platinum sensitive ROC to a combination of carboplatin with paclitaxel with or without bevacizumab and maintenance bevacizumab which was continued until disease progression or impermissible toxicity. The results showed an improvement in the PFS and median OS in the bevacizumab group with acceptable toxicity profile.[30]

In the ICON 6 trial, platinum sensitive ROC patients were randomized to three cohorts: platinum-based chemotherapy alone, platinum-based chemotherapy with cediranib followed by maintenance placebo, or platinum-based chemotherapy plus cediranib followed by cediranib maintenance. The cediranib maintenance arm showed a significant enhancement in PFS when compared with chemotherapy alone but with added toxicities. The OS data are still immature.[31]

The MITO16/MaNGO-OV2B study evaluated the use of bevacizumab beyond progression in platinum sensitive ROC. Four hundred and five subjects, previously treated with bevacizumab, were incorporated into the study. The analysis was done at a median follow-up period of 20.3 months; the median PFS was 8.8 months in the chemotherapy set and 11.8 months in the bevacizumab plus chemotherapy group and the results reached statistical significance. The OS data are immature. The adverse effects were manageable and included thrombocytopenia, hypertension, and proteinuria.[32]

Partially Platinum Sensitive Recurrence

Most of the trials of platinum sensitive recurrence included patient groups recurring at more than 6 months interval. But the group recurring at 6 to 12 months represents a special group with characteristics linking platinum sensitive and platinum resistant recurrences. This cohort demonstrates discouraging response rates and survival to rechallenge of platinum-based therapy as compared with those recurring >12 months from previous platinum therapy. They are mostly treated in lines of platinum sensitive recurrences with addition of anti-angiogenic agents.

There have been attempts to extend PFI to more than 12 months. The MITO-8 trial randomized subjects of partially platinum sensitive ROC to either non-platinum chemotherapy followed by platinum chemotherapy at subsequent recurrence (experimental arm) or platinum-based chemotherapy followed by non-platinum chemotherapy at subsequent recurrence. No OS benefit was noted, and both PFS and quality of life worsened in the set of patients receiving non-platinum therapy at the first instance.[3]

Maintenance Therapy

Multiple trials and reviews have analyzed the utilization of maintenance therapy in ROCs after the primary treatment in the recurrent setting for improvement of durability in the second remission. The main goals of maintenance treatment are to lengthen survival meaningfully and extend the period between subsequent treatment lines, thus allowing patients to avoid the unwanted chemo toxicities that can adversely affect their quality of life.[33] Maintenance therapy may be distinguished into two types:

1. Introduction of a new therapy after a patient achieves a response to primary chemotherapy (switch maintenance).
2. Continual administration of a drug that was used in combination with chemotherapy (continuation maintenance).[34]

As detailed earlier, the OCEANS and GOG 0213 trial (platinum sensitive), AURELIA (platinum resistant) which

evaluated maintenance bevacizumab and ICON 6 (platinum sensitive) with maintenance cediranib in platinum sensitive ovarian cancers showed PFS benefit.[28–31] ►**Table 1** recapitulates the role of antiangiogenic maintenance in ROCs.

The dose of bevacizumab used in clinical trials and that has been approved is 15 mg/kg. Only trial to use a different dose is the ICON 7 trial which used 7.5 mg/kg every 3 weeks. Recently an expert panel from India has recommended the use of 7.5 mg/kg in ovarian cancers considering the practicality in clinical use.[35]

PARP Inhibitors

Poly (ADP-ribose) polymerase (PARP) inhibitors (PARPi) represent one of the most promising agents in the treatment of ovarian malignancy. The PARPi act on the principle of synthetic lethality. Synthetic lethality is where disarray of one gene is compatible with cell viability; however, simultaneous loss of both the genes results in cell death. These compounds compete with nicotinamide for the active site of PARP enzyme which is essential for the repair of single strand breaks[36] (mainly the PARP 1 and to a lesser extent PARP 2 and PARP 3). They are efficacious against HR repair deficient tumors. Since BRCA1/2 mutated tumor cells have hampered HR activity, they are used in the treatment of BRCA mutant breast, ovarian, pancreatic, and prostate cancers.[37] Further details on the mechanism of action of PARPi are beyond the scope of this review.

The approximate prevalence of BRCA1/2 mutation in patients with high-grade serous ovarian cancers is 20 to 25% and might be higher in patients with platinum-sensitive, ROC.[38–40] Several PARPi have been used in various clinical settings. The commonly used molecules include olaparib, rucaparib, niraparib and the newer ones are veliparib and talazoparib.

The SOLO2, which was a phase 3 trial of olaparib maintenance therapy in platinum-sensitive ROCs in subjects harboring germline BRCA mutations, showed a statistically significant improvement in PFS for olaparib maintenance versus placebo (19.1 vs. 5.5 months, HR = 0.30; $p < 0.001$).[41]

In the NOVA trial with niraparib in platinum sensitive ROC, the PFS in patients harboring germline BRCA mutations was significantly improved when compared with placebo (21.0 vs. 5.5 m). The more interesting fact of this trial was that there was sustained PFS benefit in the non-germline BRCA subjects and those without HR deficiency (9.3 vs. 3.9 months) indicating a possible utility for patients when used as a maintenance in platinum sensitive settings irrespective of mutational status.[42]

Lastly, in the ARIEL3 trial, rucaparib maintenance therapy significantly ameliorated the median investigator-assessed PFS versus placebo in all cohorts of patients with platinum sensitive ROCs (16.6 vs. 5.4 months; hazard ratio 0·23 [95% CI 0.16–0.34]; $p < 0.0001$).[43]

The adverse event profiles of PARPi as maintenance treatment in the recurrent setting are similar. Most of them are low grade (grade 1 or 2) and manageable with supportive care or dose modification. Hematologic adverse events are considered as a class effect of PARP inhibitors, most common being anemia. The most common non hematologic adverse events associated with PARPi are gastrointestinal side effects. There have been occurrences of myelodysplastic syndrome or acute myeloid leukemia, but the incidence seems to be low.[41–43]

►**Table 2** summarizes the PARPi in platinum sensitive ROC.

Endocrine Therapy

The Ovarian Cancer Tissue Consortium Study established that high-grade and low-grade serous ovarian carcinomas, and endometrioid variants express maximum levels of estrogen receptors.[44] Various trials of endocrine therapy in EOC have shown response rates ranging from 10 to 15% and disease stabilization rates between 30 and 40% as detailed in various systematic reviews and meta-analyses.[45,46] Even though both tamoxifen and aromatase inhibitors have been studied in various retrospective studies, none have yielded encouraging results. Moreover phase 3 studies are lacking introspection on this aspect. As such,

Table 1 Anti angiogenic agents in recurrent ovarian cancers

Trial	Experimental arm	Response rates (%)	Median PFS
OCEANS[28] (platinum sensitive)	Carboplatin AUC 4 plus gemcitabine 1,000 mg/m^2/d on every 21 d plus bevacizumab 15 mg/kg followed by bevacizumab maintenance.	78.5 vs. 57.4 $p < 0.001$	12.4 vs. 8.4 mo HR, 0.484 (95% CI, 0.388–0.605) $p < 0.001$
GOG 213[30] (platinum sensitive)	Carboplatin AUC 5 plus paclitaxel 175 mg/m^2 plus bevacizumab 15 mg/kg every 21 d followed by maintenance of bevacizumab.	78 vs. 59 $p < 0.001$	13.8 vs. 10.4 mo HR, 0.628 (95% CI, 0.534–0.739) $p < 0.001$
ICON 6[31] (platinum sensitive)	Cediranib in combination with platinum-based chemotherapy followed by maintenance of cediranib.	–	11.0 vs. 8.7 mo HR 0·56 (95% CI, 0.44–0.72) $p < 0·0001$
AURELIA[22] (platinum resistant)	Bevacizumab to single-agent chemotherapy.	27.3 vs. 11.8	6.7 vs. 3.4 mo HR 0.48 (95% CI, 0.38–0.60; $p < 0$ 0.001

Abbreviations: AUC, Area under the curve; HR, Hazard ratio; CI, Confidence Interval.

Table 2 PARP inhibitors in recurrent platinum sensitive ovarian cancers

Agent	Trial	Arms	Results
Olaparib	SOLO2[41]	Arm 1: Placebo maintenance Arm 2: Olaparib 300 mg bd maintenance	PFS Arm 2–19.1 m PFS Arm 1–5.5 m Updated OS HR 0.74 in favor of Olaparib (median follow-up: 65 mo)
Niraparib	NOVA[42]	Arm 1: placebo maintenance Arm 2: niraparib 300 mg q d	Arm 1: gBRCA +: 5.5 gBRCA −, HRD +: 3.8 gBRCA −, HRD −: 3.9 Arm 2: gBRCA +: 21.0 gBRCA −, HRD +: 12.9 gBRCA −, HRD −: 9.3
Rucaparib	ARIEL 3[43]	Arm 1: placebo maintenance Arm 2: rucaparib 600 mg bid	Arm 1: gBRCA +: 5.4 HRD +: 5.4 Intention to treat: 5.4 Arm 2: BRCA +: 16.6 HRD +: 13.6 Intention to treat: 10.8

Abbreviations: PARP, Poly (ADP-ribose) Polymerase; PFS, Progression Free Survival; gBRCA, Germline BRCA; HRD, Homologoud recombinant Deficient.

endocrine therapy is not considered a standard of care and its use is not consistent worldwide. But in clinics many clinicians find it as a good alternative in relapsed cases in view of its ease of administration, favorable toxicity profile, and inexpensiveness. Patients with an estrogen receptor histoscore >200 (calculated as the percentage of tumor cells stained and intensity of the stain) and a treatment free interval of 180 days are most likely to derive benefit.[47]

Surgery

The role of secondary cytoreductive surgery (SCS) is a controversial area which still needs further research. Two trials have investigated this aspect of ROC. The GOG 213 trial conducted in platinum sensitive ROC had an arm randomized to SCS and did not show an improvement in median OS with SCS followed by chemotherapy compared with chemotherapy alone (50.6 vs. 64.7 months, respectively).[48] On the other hand, the results of AGO DESKTOP III/ENGOT ov20 trial which was recently presented, demonstrated a significant improvement in median OS of 7.5 months in the SCS followed by chemotherapy arm compared with the chemotherapy-alone group (53.7 vs. 46.2 months, respectively).[49] A positive AGO-score is based on PS ECOG 0, ascites ≤500 mL, and complete resection at initial surgery. One of the main reasons quoted as the reason for this difference were selection criteria or surgical techniques. The most recent SOC 1 trial conducted in China at multiple centers in the platinum sensitive ROCs showed that the median PFS was 17.4 months in the surgery group and 11.9 months in the no surgery group (HR 0·58; 95% CI 0.45–0.74; p <0·0001). The OS data are still immature to draw further conclusions on the trial results.[50]

Hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC) is being increasingly used in the first-line setting along with primary cytoreductive surgery. Trials are ongoing to evaluate its role in secondary and further recurrences, although further evidence is required. Many retrospective studies have pointed toward a role of HIPEC in the recurrent setting.[51,52]

Future Directions

As detailed earlier, most patients with advanced ovarian malignancies eventually progress to develop recurrences that are chemotherapy resistant. Novel methods to the diagnosis and treatment are, therefore, urgently needed to improve the current standards of care.

Recent advances in molecular characterization have revealed that EOC can be classified into two distinct groups termed type I and type II carcinomas.[53,54] This aids in more definitive depiction of disease and prediction of patient prognosis. This provides insight into the mechanisms cardinal to the evolution of EOCs.[55] The classification is provided in ►**Fig. 1**.

The Cancer Genome Atlas (TCGA) has identified that around 96% of high-grade serous ovarian cancer is characterized by TP53 mutations; low prevalence but statistically frequent somatic mutations in nine genes including NF1, BRCA1, BRCA2, RB1, and CDK12. The various pathways altered in serous ovarian cancers are RB and PI3K/RAS pathways, NOTCH pathway, genesis in the HR pathway, and FOXM1 transcription pathway network. Four subtypes were identified based on gene content—immunoreactive, differentiated, proliferative, and mesenchymal.[38] The clinical significance of this classification is yet to be utilized in clinical practice.

In yet another classification, the serous ovarian cancers have been divided into four classes in relation to DNA repair,[56] after the introduction of PARP inhibitors:

1. Women having a germline mutation in *BRCA1*/2 or other DNA repair-related genes.
2. Tumors having somatic mutations in the DNA repair genes.
3. Homologous recombinant-deficient tumors.
4. Those without identifiable DNA repair defects.

Various chemosensitivity and resistance assays (chemoresponse assays) have been used to interrogate the complex biology of EOC. Initially, two 2D culture systems, MiCK assay (based on the principle of drug-induced apoptosis) and ChemoFx assays (live cells quantified microscopically using automated cell-counting software) were commercially tested. At present, 3D culturing techniques, in which cells are able to interact with each other and with the ECM to form organoids or spheroids, are being widely adopted in drug screening and toxicity assays. These are rich in cancer stem cells, which in their natural tumor microenvironment can be studied for disease progression, metastasis, and chemotherapy resistance. These assays need to be validated through well-designed prospective and blinded multicenter clinical trials for further use in clinical practice.[57]

Newer Therapies

The combination of PARPi, niraparib, and the anti VEGF agent, bevacizumab has been tried in platinum sensitive ROC in the phase 2 AVANOVA trial. Ninety-seven patients were enrolled and randomly assigned to the treatment. At a median follow-up of 16.9 months, the combination significantly improved the PFS (11.9 months [95% CI 8.5–16.7] vs. 5.5 months [3.8–6.3]).[58] The updated analysis continued to reinforce the preliminary results, with 66% reduction in the risk of progression of disease or death (HR, 0.34; 95% CI, 0.21–0.54). The median PFS in the bevacizumab arm was 12.5 months versus 5.5 months with niraparib alone arm.[59] Further phase 3 trials are required for drawing a definitive conclusion. A phase 3 ICON 9 trial which is evaluating the combination of olaparib and cediranib (both oral agents; hence the convenience of administration) in platinum sensitive ROC is recruiting to answer this question.

The SOLO 3 trial which compared olaparib and PLD in BRCA mutant platinum sensitive ROC after two prior lines of therapy resulted in statistically significant and clinically relevant improvement in ORR and PFS in favor of olaparib (median PFS 13.4 vs. 9.2 months, HR 0.62 [95% CI, 0.43–0.91]).[60]

Mirvetuximab Soravtansine, an antibody–drug conjugate (ADC) comprising a humanized anti-folate receptor α (FRα) monoclonal antibody, has been tried in platinum-resistant ROC. Although the initial phase 2 trials were encouraging, the phase 3 FORWARD 1 trial failed to meet its primary end

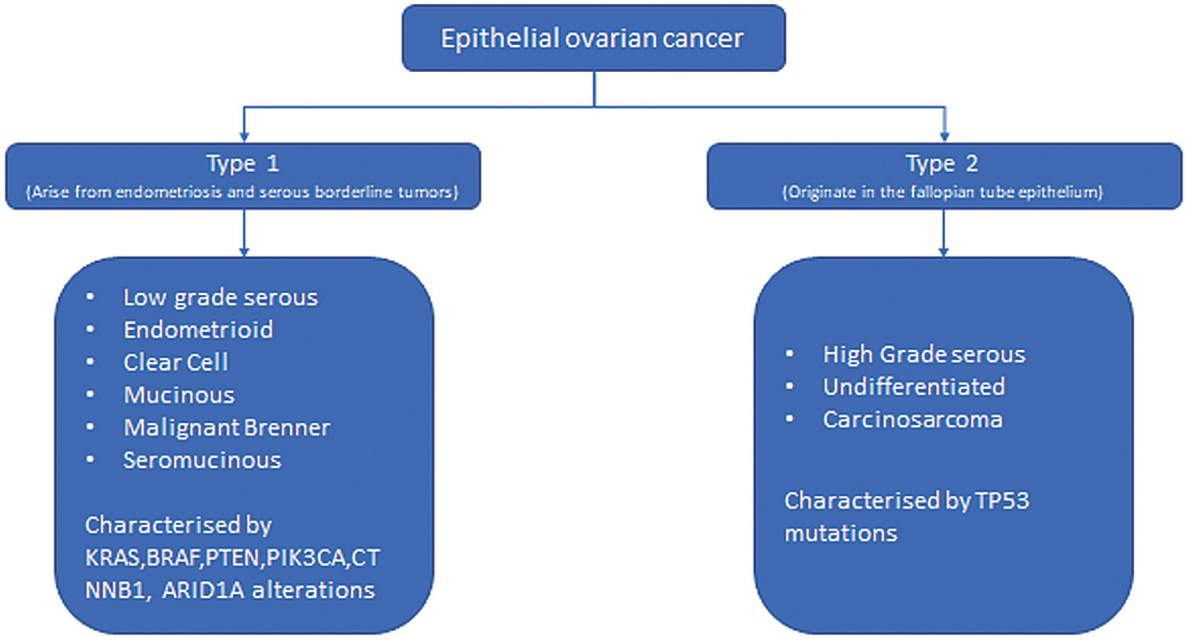

Fig. 1 Dualistic model of ovarian carcinogenesis.

point of PFS.[61] Currently, the combination of this ADC with bevacizumab is being tried in clinical trials. The phase 1b trial has shown good efficacy and tolerability to this combination.[62] Other molecules targeting FRα like vintafolide, farletuzumab had shown initial promise but failed to show significant benefits in phase 3 trials.

In a phase 2 trial, the WEE1 inhibitor, adavosertib, combined with gemcitabine was attempted in platinum resistant and refractory ovarian cancers. The combination yielded improved PFS (median PFS 4.6 months [95% CI 3.6–6.4] with adavosertib plus gemcitabine vs. 3.0 months [1.8–3.8] with placebo plus gemcitabine) which was statistically significant.[63] ATR inhibitor, berzosertib combined with gemcitabine, has been tried in a phase 2 trial and has shown improvement in PFS but warrants further investigation.[64]

Immunotherapeutic agents have also been tried in ovarian cancers but have not shown much value in contrast to other malignancies like lung cancer, bladder cancer, etc. Single agent anti PDL1 therapy has shown limited benefit. The combination of nivolumab and ipilimumab has been tried in patients with ROCs with a PFI <12 months, who have received one to three prior lines of therapy. The combination showed superior response rates and longer PFS.[65] Similarly, a combination of pembrolizumab with bevacizumab and metronomic cyclophosphamide in ROC has been studied in a phase 2 trial. It demonstrated a meaningful clinical response in 95% patients and durable responses in 25% of patients.[66] A phase 3 trial of atezolizumab in combination with bevacizumab and chemotherapy versus bevacizumab and chemotherapy in ROCs is under way, the results of which may throw more light on the role of these agents.[67]

Newer avenues like cancer vaccines, adoptive cell therapy, dendritic cell therapy, and oncolytic virus therapy are also being tried in ROC to improve survival especially in the platinum-resistant setting.[68]

Homologous Recombinant DNA (HRD) Testing in ROCs

HRD is tested using three main strategies[69]:

- Germline mutation screening—Germline mutation screening can be performed using next generation sequencing analysis of DNA from blood.
- Somatic mutation screening—Somatic mutation screening is performed on DNA from tumor samples. This analysis can evaluate any mutation (germline and/or somatic) in HR genes and is thus a broader evaluation. Germline analysis of normal cells is still necessary to determine whether the mutation is germline or somatic. Limitations include the variability of tumor samples available and intratumoral heterogeneity.
- The genomic instability secondary to HRD can be tested to assess the genomic scars based on the loss of heterozygosity, telomeric allelic imbalance, and large-scale transitions. This represents a more functional way and an HRD score can be calculated.

Supportive Care

Patients with ovarian carcinomas have excessive occurrences of malignant bowel obstruction and ascites when compared with patients with other cancer types because of extensive peritoneal disease. They require frequent admissions for the same thus deteriorating the quality of life. The most common surgical approach for relieving large bowel obstruction is a diversion stoma. Venting gastrostomy is usually positioned to prevent the prolonged use of a nasogastric tube for decompression. Good symptomatic control can be achieved for bowel obstruction with medical treatment using a combination of glucocorticoids, opioid analgesics, antiemetics, and antisecretory drugs.[70] Insertion of peritoneal catheters (like PleurX peritoneal catheter drainage) and peritoneovenous shunts (like Leveen shunts) can reduce the admission for paracentesis and its complications.[71]

Metronomic Therapy in Ovarian Cancer

Metronomic therapy is described as the chronic administration of low, equally spaced, doses of chemotherapeutic drugs with therapeutic efficacy and low toxicity.

It has proved to modulate the host immune response and tilt the balance from immunosuppression to immunostimulation by several mechanisms. It also has an anti VEGF activity which results in an antiangiogenic effect. Basically, it acts by modulation of the tumor microenvironment.[72]

Various agents that have been used in ROCs include low dose oral cyclophosphamide and etoposide in combination with hormonal agents that have been elucidated earlier.[73] Some single and series case reports have also described the benefit of adding bevacizumab to metronomic therapy with cyclophosphamide.[74] Recently an article showed that a combination of pazopanib plus oral cyclophosphamide is a well-tolerated regimen with clinically relevant benefit in patients with platinum-resistant or -refractory EOC.[75] This form of therapy is especially important in a resource-constrained setting.

Evaluation of Patients with ROCs

According to GCIG criteria, recurrence based on serum CA 125 levels is defined as a serial elevation of serum CA 125. An imaging with Contrast enhanced Computed Tomography scans is essential for accurate staging of a recurrent disease. This can help in guiding treatment of the disease. Positron emission tomography (PET)-CT scans may reveal sites of disease not visible on CT scans. This becomes a valuable tool to select patients for secondary debulking surgery, by excluding additional sites of disease not seen on CT scans and not amenable to cytoreduction.[76] Diagnostic laparoscopy is only indicated when a secondary cytoreduction is planned to prevent futile laparotomies.

History of Chemotherapeutic Agents in Ovarian Cancer

Twenty years ago, women with advanced ovarian cancer were treated with the alkylating agents melphalan, cyclophosphamide, chlorambucil, and thiotepa—all as monotherapy.[77] A series of studies performed from the mid-1970s onward established cisplatin as one of the most active agents available for ovarian cancer.[78] The North Thames

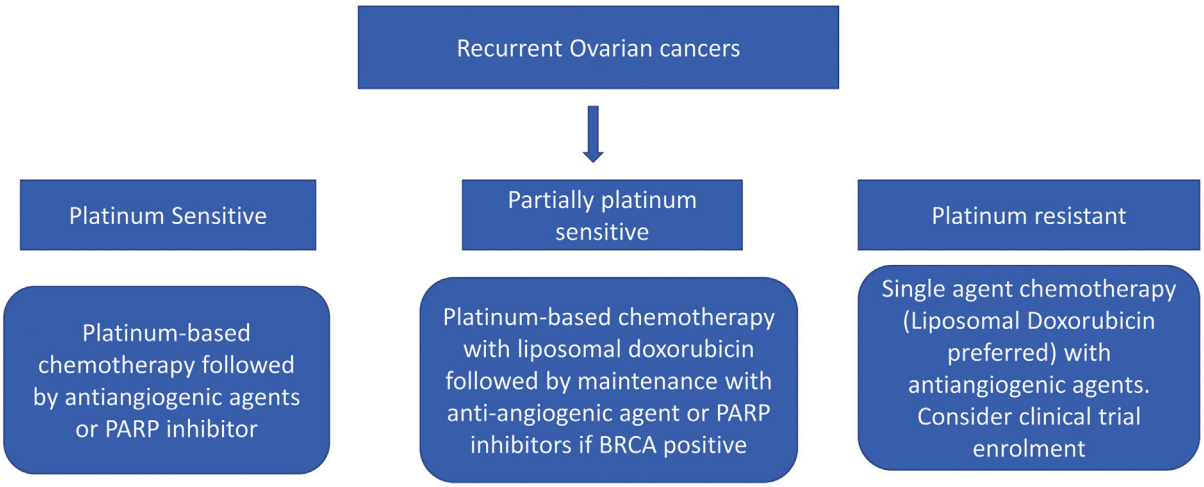

Fig. 2 Treatment algorithm for recurrent high grade serous ovarian carcinomas." There are several mechanisms of cellular resistance to platinum compounds that have been described in various in vivo and in vitro studies. These mechanisms can be classified in two groups.[5,83] NER defects are associated with an exceptional sensitivity to platinum compounds whereas defects of MMR correlate with resistance to the latter.[7,84] NER, nucleotide excision repair.

Cooperative Group reported the results of the first randomized comparison of first-line single-agent cisplatin with an alkylating agent (cyclophosphamide).[79] The possible clinical benefit from the addition of an anthracycline to cisplatin-alkylating agent regimens was studied. A meta-analysis of data from 10 trials showed a modest—but significant—improvement in survival of the triplet regimen.[80] After the discovery of taxanes, the taxane-platinum has become the standard of care. The randomized, controlled trials of first-line cisplatin-based dual therapy showed additional clinical benefit when cyclophosphamide was replaced by paclitaxel.[81,82]

Follow-up of Patients with ROCs

Monitoring is important to detect early signs of a second or subsequent relapse. CA 125 is most common tumor marker which is used for surveillance along with systemic examination. Imaging with ultrasound or CT scan is done only when clinically indicated or when a baseline CA 125 was normal. Most of the guidelines endorses a 3 to 4 monthly follow-up after a recurrence.

Summary

Platinum sensitive ROC (recurrence >12 months)—Rechallenge with platinum in combination with paclitaxel, gemcitabine, or PLD (based on toxicity profile) followed by antiangiogenic agents or PARP inhibitors (especially in BRCA mutant cases).

Partially platinum sensitive ROC (recurrence 6 to 12 months)—Rechallenge with platinum-based chemotherapy in combination with PLD followed by maintenance with anti-angiogenic agent. Consider PARP inhibitors if BRCA positive.

Platinum-resistant ROC (recurrence <6 months)—Single agent chemotherapy (PLD preferred) with antiangiogenic agents. Consider clinical trial enrolment.

The schema of the above has been depicted as a flowchart in ►**Fig. 2**.

Conclusion

The landscape of treatment for ROCs has shown extensive advances and refinements. Several molecular targeted therapies like anti-angiogenic agents and PARPi have shown activity in ROCs in addition to conventional chemotherapy. The utilization of these agents has gone a long way in improving survival in these sets of patients. Further progress is warranted especially in platinum-resistant ROC. Identification of newer targets and biomarkers is a paradigm for optimizing the care of this category of patients.

Conflict of Interest
None declared.

Acknowledgment
None declared.

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