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Abstract:	Cytoreductive surgery is the mainstay of treatment for high grade epithelial ovarian cancer. Although for early stage disease outcomes following surgery alone are good, the risk of recurrence necessitates adjuvant chemotherapy for the majority of patients. Post-operative chemotherapy in advanced stage disease, or neoadjuvant chemotherapy followed by surgery has improved progression free survival (PFS) and overall survival (OS). However, despite the use chemotherapy, the rate of recurrence remains high. In recent years an increasing knowledge of the biology of ovarian cancer has led to a journey of drug discovery, facilitating the use of novel targeted agents such as VEGF inhibitors and more recently PARP inhibitors in the first line treatment of ovarian cancer.

Highlights

- Adjuvant chemotherapy following cytoreductive surgery is a mainstay of treatment for advanced disease and is also indicated for a proportion of patients with early-stage disease and high risk of relapse
- Improved understanding of the biology of ovarian cancer has led to integration of targeted therapies into treatment regimens
- Genomic testing is recommended for all patients with high-grade ovarian cancers and is now integral to management
- Prevention of first relapse is the key objective to improve survival

Adjuvant and post-surgical treatment in high grade epithelial ovarian cancer

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Abstract

Cytoreductive surgery is the mainstay of treatment for high grade epithelial ovarian cancer. Although for early stage disease outcomes following surgery alone are good, the risk of recurrence necessitates adjuvant chemotherapy for the majority of patients. Post-operative chemotherapy in advanced stage disease, or neoadjuvant chemotherapy followed by surgery has improved progression free survival (PFS) and overall survival (OS). However, despite the use chemotherapy, the rate of recurrence remains high. In recent years an increasing knowledge of the biology of ovarian cancer has led to a journey of drug discovery, facilitating the use of novel targeted agents such as VEGF inhibitors and more recently PARP inhibitors in the first line treatment of ovarian cancer.

Here, we outline the current evidence-based guidance for systemic therapies in ovarian cancer and highlight the ongoing research to improve patient outcome.

Key words

Adjuvant; chemotherapy; targeted therapies

1 Introduction

Epithelial Ovarian Cancer (EOC) can be segregated into Type 1 and Type 2 disease. Type 1 includes the more indolent tumour types such as low grade serous cancer, but also endometrioid, clear cell and mucinous carcinomas (1). Type 2 tumours, most commonly high grade serous ovarian cancer (HGSOC), are far more aggressive, develop rapidly and usually present with widespread disseminated disease. They also include undifferentiated cancers and carcinosarcomas (1). The hallmarks of HGSOC are severe cytologic atypia, high mitotic rates (2) and *TP53* mutations (3). HGSOC is the most common subtype of EOC, accounting for about 70% of cases. HGSOC predominantly effects post-menopausal women with >80% of cases being diagnosed over the age of 50 years.

Staging classifications are used to describe the extent of disease spread and to determine treatment and prognosis. Ovarian cancers are usually staged according to the FIGO (International Federation of Gynecology and Obstetrics) (4) but the AJCC (American Joint Committee on Cancer) TNM (Tumour, Node, Metastasis) (5) classification is also used. The FIGO staging system is the most powerful prognostic indicator (4). Early stage (FIGO stage I) ovarian cancer occurs in 20-25% of cases; most women present with advanced disease (FIGO stage II to IV).

The aim of front-line treatment is to delay or prevent recurrence. The long-term survival of HGSOC has changed little over the last 40 years (6) and the prognosis of women with advanced disease is poor. Better surgery and newer post-operative treatments are delaying recurrence and for some this might lead to an improved survival. For those experiencing relapse, the development of better therapies has improved the three- and five-year survival of patients with recurrent ovarian cancer.

2 Stage specific treatment

2.1 Early stage disease

Surgery is the primary modality of treatment for early EOC with the aim of resecting the tumour and to undertake thorough and accurate surgical staging. Approximately 30% of patients considered pre-operatively to have early (localised) stage I EOC will be upstaged after comprehensive surgical staging (7) (8).

In young women, fertility-sparing surgery could be considered for early stage disease. Adequate non-fertility sparing surgery consists of peritoneal washings prior to mobilisation of the tumour, bilateral salpingo-oophorectomy, hysterectomy, multiple peritoneal biopsies, omentectomy, appendicectomy (if there is mucinous histology) and pelvic and para-aortic lymph node dissection up to the renal veins (9).

The prognosis is generally good for patients with fully evaluated early stage EOC, however, the recurrence risk is significant enough to recommend adjuvant chemotherapy for a majority of patients with high grade histology.

The data supporting post-operative adjuvant chemotherapy in early stage disease has come from two large European trials, ACTION and ICON1. These showed that adjuvant platinum-

based chemotherapy was superior to observation alone in early stage EOC (10). Long term follow-up substantiated these results along with highlighting the importance of adequate staging and the effect of adjuvant therapy was most evident among the high grade subtypes of ovarian cancer (11) (12).

Carboplatin-based chemotherapy is the treatment of choice. Adjuvant chemotherapy with carboplatin alone or in combination with paclitaxel should be offered to patients with early stage high grade ovarian cancer (stage I – IIA) (13). The decision to use combination chemotherapy is largely derived from data treating patients with more advanced disease. The optimum duration of adjuvant chemotherapy remains controversial; six cycles are usually recommended, particularly if carboplatin monotherapy is used, but OS using three cycles of carboplatin and paclitaxel was similar to six cycles (13). Extending treatment using maintenance low-dose paclitaxel following three cycles of carboplatin and paclitaxel has not been shown to improve the recurrence-free interval (14) (15).

2.2 Advanced stage disease

Chemotherapy and cytoreductive surgery are the cornerstones of treatment for advanced ovarian cancer. The aim is to remove all macroscopic disease followed by post-operative chemotherapy as this is associated with increased OS and PFS (16) (17) . Neoadjuvant (pre-operative) chemotherapy is increasingly being offered to patients with poor performance status at presentation, low albumin levels and in those with very extensive tumour dissemination where complete cytoreduction is difficult to achieve, or will would be associated with significant morbidity (9) (17). Interval surgery is followed by post-operative chemotherapy.

Platinum-based treatments remain the backbone of chemotherapy for advanced ovarian cancer (**see Table 1**). Carboplatin and paclitaxel have been the standard of care for more than 15 years, and attempts to improve the results of treatment by adding a third drug (18) (19) or increasing the dose of treatment (20) has not led to an improvement in outcome. Debate has continued for many years about the added value of intraperitoneal therapy, but the most recent large-scale trial comparing this treatment modality to current standard chemotherapy failed to show a benefit (21). Similarly, the initial studies with weekly paclitaxel compared with three-weekly paclitaxel showing both a PFS and OS benefit have not been confirmed by subsequent trials (22) (23) (24). Substitution of paclitaxel by docetaxel or pegylated doxorubicin has not altered the median PFS (25) (26) (**see Table 1**). Thus, six cycles of three-weekly chemotherapy with carboplatin and paclitaxel is recommended for all patients with FIGO stage II-IV disease following surgery. Alternatively, it may be given as neoadjuvant chemotherapy, commonly for 3-4 cycles and then following interval debulking surgery.

The results of this treatment have remained remarkably constant over a decade of clinical trials with a median PFS of EOC of around 18 months for patients undergoing primary debulking surgery. Results from neoadjuvant studies have been consistently worse than this and debate continues about whether the reasons for this are tumour biology, the effect of primary surgery or both.

Over the last decade, newer studies that incorporate therapies that target either the tumour vasculature or DNA repair mechanisms have led to significant improvements in the PFS and have altered the landscape of treatment of women with advanced ovarian cancer.

2.3 Targeted treatments

2.3.1 Angiogenesis inhibitors

Pre-clinical studies have shown that vascular endothelial growth factor (VEGF) is frequently expressed by EOC cell lines and is associated with disease progression *in vivo* (27). Decreasing VEGF receptor expression reduces tumour vascularisation, angiogenesis and prolongs survival (28). Bevacizumab is a monoclonal antibody targeting VEGF-A and was the first targeted therapy to be introduced for EOC treatment. It is approved for use in combination with carboplatin and paclitaxel and then as maintenance therapy based on the outcome of two clinical trials (GOG-218 and ICON-7) showing improvement in PFS (29) (30). Neither ICON-7 nor GOG-218 demonstrated an increase in OS by addition of bevacizumab in the whole population. However, addition of bevacizumab to carboplatin and paclitaxel showed benefit in patients with higher risk of disease due to stage III with incomplete surgery (>1cm residual disease) or FIGO stage IV/inoperable disease, with a 9.5 month difference in median OS (31). This was confirmed in further retrospective subgroup analysis of ICON-7 (32). Post-hoc analysis of GOG-218 also indicated a significant benefit in OS in the bevacizumab group for patients with stage IV disease (33). In view of the ICON-7 data some physicians restrict use of bevacizumab to higher risk patients with stage III-IV and residual disease >1cm and use the lower dose of bevacizumab that was given in ICON-7.

The current recommended schedule according to the EMA and FDA approval is 15mg/kg every 21 days for up to 22 cycles (15 months). However, there is ongoing debate regards the optimum dose and duration of bevacizumab treatment in light of evidence that lower dosage (7.5mg/kg for 18 cycles) results in similar PFS with lower toxicity and cost (30). The toxicity profile of prolonged treatment is manageable for most patients, and the recent results of the phase III BOOST trial comparing 15 vs 30 months of bevacizumab showed no improvement in PFS or OS with more prolonged therapy (34).

Not all countries use bevacizumab for first line therapy and in some regions its use is restricted to patients with a poorer prognosis. Also, the decision may be influenced by the availability of bevacizumab for recurrent disease, either in combination with platinum-based therapy, or at later relapse when non-platinum-based drugs are used (35) (36). Re-introducing bevacizumab for treatment of recurrent disease is outside its licence, although there is evidence that repeated use is clinically useful (37).

2.3.2 PARP inhibitors

Maintenance treatment with Poly (ADP-ribose) polymerase (PARP) inhibitors has become a key component of the treatment of recurrent ovarian cancer post-platinum-based chemotherapy and recently the same strategy has been applied to first-line treatment after chemotherapy. PARP inhibitors work via the principle of ‘synthetic lethality’, exploiting a

deficiency in the repair of double strand breaks (DSBs) in DNA by homologous recombination (HR) repair. HR deficiency is particularly evident in tumours with a *BRCA* mutation, whether germline or somatic in origin but it is also present in a proportion of *BRCA* wild-type tumours.

Inherited susceptibility to HGSOC is mostly associated with germline *BRCA1/2* mutation. Heterozygous carriers of *BRCA1/2* mutations have increased lifetime risk of developing ovarian cancer (*BRCA1* 40-60%, *BRCA2* 11-30%) (9). Approximately 15-20% of HGSOC tumours carry a germline *BRCA1* or *BRCA2* mutation and somatic mutations are found in approximately 8% of cases.

Data from The Cancer Genome Atlas suggests that up to 50% of all HGSOC have detectable germline and/or somatic mutations, epigenetic silencing via DNA methylation of genes involved in HR or other mutations that make the tumour HR repair deficient (38) (3) (39) (40) (41).

Initially, PARP inhibitor therapies were investigated in EOC patients harbouring germline or somatic *BRCA1/2* mutations but it soon became clear that although these patients derived the greatest benefit, significant clinical improvement was seen in patients with *BRCA* wild-type tumours (42) (43). Further studies were performed in patients that included women with a *BRCA* mutation or with *BRCA* wild-type tumours (44) (45) (46). Evaluation of HR repair gene mutations or measurement of HRD by genomic scarring assays did not on their own identify responders and non-responders (45) (46). In all trials, it was the response to platinum-based therapy that best identified patients likely to benefit and olaparib, niraparib and rucaparib are now approved for clinical use in the maintenance setting for any patient with relapsed platinum-sensitive mutated high grade ovarian cancer following a response to platinum-based therapy. A long-term response lasting many years is seen in a proportion of patients and this may influence clinicians' decisions about whether to use these drugs in the first-line setting (below) or for recurrent disease (47) (48).

More recently the activity of maintenance therapy with PARP inhibitors has been investigated in the front-line treatment setting (**see Table 2**). The SOLO1 trial in women with *BRCA* mutated tumours showed a significant improvement in PFS with olaparib maintenance after first-line platinum based chemotherapy. The risk of disease progression or death being 70% lower with olaparib compared to placebo (49). Whilst OS data are awaited, the five year follow up showed that 48% of patients with stage III-IV disease remained free of progression after a 2-year course of olaparib compared to 21% patients receiving placebo (50). This study underlines the importance of testing all patients with high grade ovarian cancer for the presence of a *BRCA* mutation.

Three further randomised trials with maintenance PARP inhibitors have been conducted in patients with or without *BRCA* mutations. All three used a PARP inhibitor after primary therapy with surgery and chemotherapy. One, with veliparib (VELIA trial) included a trial arm with veliparib given during chemotherapy and another, PAOLA-1 added olaparib to bevacizumab (51) (52). The third study, PRIMA, used either niraparib or placebo and was open to all patients who responded to first-line platinum-based chemotherapy. It demonstrated that maintenance niraparib provided clinical benefit with prolonged PFS in all patients irrespective of tumour HRD status (53). On this basis, approval has been given by the FDA and EMA to treat any patient responding to front-line treatment. Tumours were

centrally tested for HRD using Myriad Genetics MyChoice test and randomisation was stratified by this result. The greatest benefit of niraparib was seen in the groups with a *BRCA* mutation or HRD positive *BRCA* wild-type groups. In the PAOLA-1 trial, olaparib was added to bevacizumab and compared to bevacizumab alone. Although a significant benefit was seen in the intention to treat population receiving the combination, the greatest effect was seen in patients with a *BRCA* mutation or *BRCA* wild-type and high Genomic Instability Score (GIS) using the Myriad MyChoice HRD assay (52). In the GIS low subgroup, the addition of olaparib did not improve the PFS compared to bevacizumab alone. In most countries, the license for this combination is restricted to the GIS high group (HRD positive). There was no arm comparing olaparib alone, so it remains unclear if the effect of combining olaparib and bevacizumab was additive. A similar benefit of veliparib was seen in the VELIA trial with no evidence that combining chemotherapy with veliparib was superior to chemotherapy alone (51) (**see Table 2**). Veliparib has not been submitted for approval in ovarian cancer.

Whilst all results have demonstrated significant improvements in PFS, particularly among patients with *BRCA* mutations or HRD tumours, long-term outcome results, in particular OS are not yet available. The results from SOLO1 cast little doubt on the the benefit of olaparib in *BRCA* mutated ovarian cancer. Similar results are seen among this group with niraparib. There is a strong recommendation with these results to recommend PARP inhibitor maintenance therapy in all patients with a *BRCA* mutation who do not have disease progression after first-line therapy (54) (55). Intermediary endpoints, such as the PFS2 (time from randomisation to the second progression after treatment for recurrence) provides encouraging results for longer term follow up. However, it is important to await OS results and see what the effect of cross-over to a PARP inhibitor on relapse has on this result. Nevertheless, resistance to PARP inhibitor therapy on treatment or its failure to control disease long-term are two areas where further research is needed. These are two related but separate issues. It is important to understand what causes a failure on therapy and whether other drugs in combination with PARP inhibitors can overcome resistance (56) (57). Similarly, it is important to know whether PARP inhibitors alone or in combination are effective in re-treating patients whose cancer has relapsed some while after first-line PARP inhibitor therapy.

In conclusion, from the data available all patients with high grade ovarian tumours should be tested for a *BRCA* mutation. In some countries this can be done for germline and somatic mutations. In others, tumour *BRCA* testing can be done. Guidelines recommend that this is a valuable addition to the initial evaluation of patients with ovarian cancer (58). Increasingly, it will become possible to test HRD in addition, although currently this test is expensive and not available in all countries.

2.4 Future therapies with Immune checkpoint inhibitors

Immunotherapy is a rapidly advancing field in cancer treatment and has revolutionised patient care in a number of tumour types. Two key immune checkpoint pathways have been targeted – cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed death 1 (PD-1)/ programmed death ligand 1 (PDL-1). These immune checkpoints are essential

negative regulators of T-cell immune function. Pharmacological inhibition of these targets reduces the ability of cancer cells to evade host immune recognition (59).

In EOC, some early phase clinical trials have shown only modest clinical benefit of anti-PD-1 and anti-PDL-1 therapies with a response rate of approximately 10% (60). The phase III JAVELIN 100 trial explored frontline avelumab as monotherapy or in combination with chemotherapy compared to standard of care (carboplatin/paclitaxel) in treatment naïve stage III/IV EOC patients. The study was discontinued after an independent panel determined the study would not meet its end point of PFS (61) (62).

First-line combination therapy of PDL-1 inhibitor atezolizumab and bevacizumab similarly failed to demonstrate improval of PFS for EOC patients (63) (64). Therefore, there are currently no approved immune checkpoint inhibitor regimens for the treatment of EOC. However, there is a good scientific rationale for combining PARP inhibitors with immune check point inhibitors and this has led to a number of first-line trials comparing this combination (65). Four phase III trials have now been completed or are about to finish (ATHENA, DUO, ENGOT-ov43/GOG-3036 and FIRST (66) (67) (68) (69)) and the results are awaited with interest.

3 Summary

Chemotherapy, whether as an adjuvant following surgery for early ovarian cancer or as part of the treatment for advanced disease remains a major component of the treatment for ovarian cancer. Surgery and in particular complete removal of macroscopic disease is a key element in the treatment of advanced ovarian cancer. The high failure rate of chemotherapy in producing long-term control has led to the development of molecularly targeted therapies, built on the growing knowledge of the biology of ovarian cancer. Genomic testing, particularly for *BRCA* mutations has now become an integral part of evaluation and therapy with PARP inhibitors. Prevention of first relapse remains the key objective and further improvement of the results of first-line treatment remains to be a major area of research strategy.

Conflicts of interest

GEW – no conflicts of interest

JAL – Advisory Boards and Lecture Fees: AstraZeneca; GlaxoSmithKline, MSD/Merck, Clovis Oncology, Neopharm, Artios Pharma, Regeneron, Eisai, VBL Theraeutics. Grants: AstraZeneca, MSD/Merck

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Table 1: Summary of clinical trials investigating post-operative platinum chemotherapy in combination with paclitaxel.

Systemic anti-cancer treatment	**Trial**	**Year**	**Median PFS (months)**	**Ref**
Cisplatin + cyclophosphamide vs Cisplatin + paclitaxel	GOG 111	1996	13 18	(1)
Cisplatin + cyclophosphamide vs Cisplatin + paclitaxel	OV10	2000	11.5 15.5	(2)
Carboplatin + docetaxel vs Carboplatin + paclitaxel	SCOTROC1	2004	15 14.8	(3)
Carboplatin + paclitaxel	GOG 182	2009	16	(4)
Carboplatin + Pegylated liposomal doxorubicin vs Carboplatin + paclitaxel	MITO-2	2011	19 16.8	(5)

Table 2: Summary of clinical trials investigating the addition of first-line bevacizumab and/or PARP inhibitor to platinum-based chemotherapy. *<u>*BRCA*</u> mutation only. Homologous recombination deficiency (HRD).

Systemic anti-cancer treatment	**Trial**	**Year**	**Median PFS (months)**	**Ref**
Carboplatin + Paclitaxel + placebo	GOG 218	2011	10.3	(6)
Carboplatin + paclitaxel + bevacizumab (cycle 2 – 6)			11.2	
Carboplatin + paclitaxel + bevacizumab (cycle 2 – 22)			14.1	
Carboplatin + Paclitaxel	ICON7	2011	22.4	(7)
Carboplatin + paclitaxel + bevacizumab			24.1	
Carboplatin + paclitaxel - olaparib*	SOLO1	2018	49.9	(8)
Carboplatin + paclitaxel - placebo			13.8	
Carboplatin + paclitaxel – niraparib	PRIMA	2019	HRD – 21.9 Overall - 13.8	(9)

Carboplatin + paclitaxel – placebo			HRD – 10.4 Overall - 8.2	
Carboplatin + paclitaxel + bevacizumab – olaparib + bevacizumab Carboplatin + paclitaxel + bevacizumab – placebo + bevacizumab	PAOLA-1	2019	Overall - 22.1 HRD- 37.2 Overall - 16.6 HRD - 17.7	(10)
Carboplatin + paclitaxel + veliparib – veliparib Carboplatin + paclitaxel + placebo – placebo	VELIA	2019	HRD – 31.9 *BRCA* - 34.7 HRD – 20.5 *BRCA* - 22	(11)

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Multiple choice questions

Question 1

1) A 65 year old woman was diagnosed with stage IIIA HGSOC and underwent primary debulking surgery where all macroscopic disease was resected. Which of the following is the best treatment option?

    a. Hormonal therapy

    b. Single agent carboplatin

    c. Doublet platinum-based chemotherapy

    d. Single agent paclitaxel

    e. Clinical surveillance

Answer 1

a. F

b. F

c. T

d. F

e. F

Carboplatin and paclitaxel combination chemotherapy have been the standard of care post-operative regimen for advanced EOC for >15 years.

Question 2

2) A 51 year old woman has undergone sub-optimal cytoreductive surgery followed by post-operative carboplatin and paclitaxel chemotherapy for stage IVA HGSOC. Genetic testing showed a germline deleterious *BRCA2* mutation. Which of the following would you recommend?

    a. Clinical surveillance post-chemotherapy

    b. Maintenance treatment with bevacizumab

    c. Maintenance treatment with olaparib

    d. Maintenance treatment with single agent paclitaxel for 12 months

e. Maintenance treatment with bevacizumab and olaparib

Answer 2

a. F

b. F

c. F

d. F

e. T

Until recently, bevacizumab was most commonly used in patients with sub-optimally debulked tumours or stage IV ovarian cancer. The more recent data from the SOLO1 trial showed a significant improvement in PFS with olaparib after first-line platinum based chemotherapy in women with a *BRCA* mutation (50). Overall survival data is awaited but the five year follow up showed a 27% improvement of remaining disease free at 2 years of olaparib compared to placebo (50). The PAOLA-1 trial combined bevacizumab and olaparib. Whilst comparative data using olaparib with or without bevacizumab do not exist, the presence of sub-optimally debulked stage IV disease would be an indication to use bevacizumab combined with olaparib in a patient with a *BRCA* mutation

Question 3

3) A 40 year old woman with a germline *BRCA1* mutation has an incidental diagnosis of HGSOC at the time of oophorectomy for an right sided ovarian torsion. What should be the next step in management?

   a. Doublet platinum-based chemotherapy

   b. Single agent carboplatin

   c. Completion of surgical staging

   d. Olaparib

   e. Clinical surveillance

Answer 3

a. F

b. F

c. T

d. F

e. F

Optimum clinical outcomes are achieved when comprehensive surgical staging is undertaken. As this patient’s diagnosis was incidental at the time of an emergency surgery for ovarian torsion completion staging was not undertaken. It is important for accurate prognostic information, would be influential on the decision to give carboplatin and paclitaxel chemotherapy and may indicate treatment with maintenance olaparib. All of these influence long term survical outcomes.

Practice Points

Cytoreductive surgery with complete removal of macroscopic disease is a key element in the treatment of advanced ovarian cancer.

Chemotherapy, whether as an adjuvant following surgery for early ovarian cancer or as part of the treatment for advanced disease remains a major component of the treatment for ovarian cancer.

Post-operative chemotherapy improves PFS and OS, however recurrence rates remain high.

Development of molecularly targeted therapies with VEGF and PARP inhibitors, built on the growing knowledge of the biology of ovarian cancer, has improved patient outcomes.

Genomic testing, particularly for *BRCA* mutations has now become an integral part of evaluation for patients with ovarian cancer.

Research Agenda

Prevention of first relapse remains the key objective and further improvement of the results of first-line treatment remains a major area for research.

There is a clear benefit of PARP inhibition on PFS for *BRCA* mutated ovarian cancer. It is important to await OS results.

Primary resistance to PARP inhibitor therapy and identifying strategies to circumvent the mechanisms of resistance is essential.

Assessment of the efficacy of re-treating with PARP inhibitors at time of cancer relapse.

Evaluation of PARP inhibitors in combination with checkpoint inhibitors in relapsed setting as well as first line therapy.