Review Article

The challenges and opportunities in ovarian cancer relapse—the role of second and third-line chemotherapy: literature review

Semini Greening[1], Nikita Sood*, Shibani Nicum[2]

[1]Oxford University Hospitals NHS Trust, Oxford, UK; [2]University College London (UCL) Cancer Institute, London, UK

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Correspondence to: Dr. Shibani Nicum. University College London (UCL) Cancer Institute, London, UK. Email: snicum@nhs.net.

Background and Objective: The aim of this article is to discuss the current therapies and also novel treatment approaches that are available to those women with relapsed ovarian, primary peritoneal and fallopian tube cancers. Throughout this review we will refer to these 3 tumour types collectively as ovarian cancer. Despite significant progress in the treatment of advanced ovarian cancer, for many women, the disease sadly remains incurable. The main goals of treatment in this setting are to improve survival, control symptoms and maintain quality of life.

Methods: Information used to write this literature review was collected from a Medline search of publications in English from 1970 to January 2021 and abstracts presented at the European Society of Medical Oncology conference (ESMO) 2020 and the American Society of Clinical Oncology Conference (ASCO) 2020.

Key Contents and Findings: Whilst platinum-based chemotherapy remains the mainstay of treatment of recurrent disease, the increasing use of poly(ADP-ribose) polymerase (PARP) inhibitors and anti-angiogenic agents as maintenance therapy have led to significant improvements in progression free survival (PFS) with women, as a result, living longer. For those who have a degree of resistance to platinum, options are more limited and palliative chemotherapy with drugs such as paclitaxel and pegylated liposomal doxorubicin (PLD) may be more appropriate. However, recent clinical trials have also highlighted the role of both PARP inhibition and anti-angiogenic agents in this setting. The role of surgery in prolonging survival in relapsed disease and the importance of tailored symptomatic care is also discussed.

Conclusions: Further research evaluating combinations of agents, novel therapeutic strategies and also the role of biomarkers in stratifying treatment decisions, is essential to improve outcomes for women with recurrent ovarian cancer.

Keywords: Ovarian cancer; relapse; treatment; novel agents

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Introduction

Almost 300,000 women are diagnosed with ovarian cancer worldwide each year, making it the 7th most common female cancer and the 5th leading cause of female deaths from cancer (1,2). Disease signs and symptoms are often non-specific leading to the majority of patients presenting with advanced disease (stage III or IV), which is associated with a poorer prognosis and a 5-year survival of less than 30% (3).

*, no affiliation.

Table 1 Search strategy of keywords

Number	Keywords
#1	Ovarian cancer [Title/Abstract]
#2	Recurrent ovarian cancer [Title/Abstract]
#3	Ovarian cancer recurrence [Title/Abstract]
#4	OR/1-3
#5	Treatment [Title/Abstract]
#6	Surgery [Title/Abstract]
#7	Chemotherapy [Title/Abstract]
#8	PARP inhibitors [Title/Abstract]
#9	Immunotherapy [Title/Abstract]
#10	Novel combinations [Title/Abstract]

The majority of ovarian cancers are epithelial (90%), with non-epithelial ovarian cancers comprising germ cell tumours (5%) and sex cord stromal tumours (5%). Epithelial ovarian cancers can be further classified into high-grade serous adenocarcinomas (70%), endometrioid adenocarcinomas (10%), clear cell adenocarcinomas (10%), mucinous adenocarcinoma (~3%) and low-grade serous carcinomas (<5%) (4).

Epithelial ovarian cancers are surgically staged according to the 2017 8th Edition AJCC and the FIGO Tumour, Node, Metastasis (TNM) classification system (5). A single system is now used for ovarian, fallopian tube, and peritoneal carcinomas, and available treatment decisions are dependent on whether a patient presents with early or late-stage disease. Throughout this review we will refer to these three tumour types collectively as ovarian cancer.

Despite optimal upfront treatment with a combination of radical surgery, chemotherapy and maintenance treatments with anti-angiogenic agents (the monoclonal antibody, bevacizumab) and poly(ADP-ribose) polymerase (PARP) inhibitors (niraparib and olaparib) the majority of newly diagnosed patients with stage III/IV ovarian cancer will relapse (6). We present the following article in accordance with the Narrative Review reporting checklist (available at https://gpm.amegroups.com/article/view/10.21037/gpm-21-29/rc).

Methods

A systematic literature review of published studies from 1970 to January 2021 was conducted using the Medline database and abstracts presented at ESMO 2020 and ASCO 2020. The literature search was limited to publications in English and included high quality systematic reviews, meta-analysis and randomised controlled trials where possible. However lower levels of evidence were also reviewed and are included where higher levels of evidence did not exist. The reference lists of identified articles were also reviewed for other potentially relevant papers. All authors contributed to the literature search independently and subsequently agreed upon publications used herein. During revision a further Medline search using the relevant keywords (*Table 1*) was performed to ensure that published studies to September 2021 were included.

Recurrent disease

It is well recognised that the most important predictor of prognosis and probability of response to subsequent lines of therapy is the time to relapse after platinum-based treatment. Patients are often categorised by their platinum-free interval (PFI), with those who have progressed within 6 months of platinum-based chemotherapy being classified as platinum-resistant and those with an interval greater than 6 months being described as having platinum-sensitive disease. Patients who progress whilst receiving platinum-based chemotherapy are considered to have platinum-refractory disease (7). However, these definitions have been challenged as it is clear that platinum sensitivity is a continuum: approximately 30% of women who require retreatment within 5–12 months of prior platinum will respond again compared to 60–70% of those with a PFI of 24 months (8). Typically subsequent responses to platinum are shorter than for the initial response, although this is not always the case for patients with BRCA 1/2 mutations. Treatment decisions are made factoring in this PFI, as well as prior treatments received, previous treatment related toxicity, disease burden, symptoms, BRCA 1/2 mutation status, patient fitness and wishes and the availability of clinical trials. Asymptomatic patients, with a rising CA125 and limited radiological evidence of relapse, can continue to be monitored as early treatment has been shown to have a negative impact on quality of life without impacting survival (9). The main goals of therapy in this setting are to prolong progression free survival (PFS) and to improve symptom control. The below discussed findings are summarised in *Table 2*.

Table 2 Summary of treatment options in recurrent ovarian cancer

Treatment (reference of relevant publications included in review)	Key facts
Carboplatin and paclitaxel (10)	Generally considered for those women with a treatment free interval of >6 months
	Clinically meaningful benefit of carboplatin/paclitaxel doublet over carboplatin monotherapy
	Doublet associated with moderate neurotoxicity in up to 20% of patients
	Large prospective trial but included relatively high proportion of taxane naive patients
Carboplatin and gemcitabine (11)	Generally considered for those women with a treatment free interval of >6 months
	Improvements in mPFS and RR in combination arm
	Significant haematological toxicity seen in combination
	No significant difference in overall survival or QoL
Carboplatin and PLD (12)	Generally considered for those women with a treatment free interval of >6 months
	Largest phase III trial completed in recurrent setting
	Generally well tolerated, with improvements seen in mPFS and RR but without significant change in OS
	Post-study treatment differences may have affected OS data
Weekly paclitaxel (13,14)	If unsuitable for platinum rechallenge e.g., PFI <6 months or cannot tolerate platinum
	Generally well tolerated, variable response rates seen
	Phase II trials with relatively small numbers
PLD (15)	If unsuitable for platinum rechallenge
	Cochrane review demonstrated efficacy of 4 weekly treatment
	Toxicity associated with higher doses e.g., hand-foot syndrome; lower starting dose of 40 mg/m^2 recommended
Gemcitabine (16)	If unsuitable for platinum rechallenge
	Meta-analysis demonstrated no real difference in OS or PFS of gemcitabine *vs.* PLD
	Higher incidence of neutropenia and hand-foot syndrome
PARP inhibition (olaparib, niraparib, rucaparib) (17-30)	Maintenance in platinum sensitive relapse is now SOC regardless of BRCA status
	Also used in frontline setting with degree of response dependent on presence of BRCA mutations/HRD
	Phase III data demonstrating efficacy of all 3 agents, generally well tolerated with slightly different toxicity profiles although haematological toxicity is common
Anti-angiogenic treatment (bevacizumab and cediranib) (31-36)	Intravenous (bevacizumab) used in combination with chemotherapy and as maintenance until progression
	PFS improvement without demonstrable OS benefit
	Higher rates of serious (grade 3/4) complications of the gastrointestinal tract e.g., perforation if evidence of serosal bowel involvement
	Oral (cediranib) anti-angiogenic treatment used in combination with chemotherapy and as maintenance only within clinical trials
	Toxicities include hypertension and diarrhoea, benefit of treatment unclear given duration of maintenance treatment needed for survival advantage

Table 2 (*continued*)

Table 2 (*continued*)

Treatment (reference of relevant publications included in review)	Key facts
Immunotherapy (37,38)	Limited therapeutic benefit demonstrated with check point inhibitors in the relapsed setting
	Combination treatment and biomarker driven treatment currently being explored within clinical trials
Secondary cytoreductive surgery (39,40)	Evidence of benefit seen in strictly selected cohorts of patients at first relapse
Supportive treatment	Symptomatic relief of ascites, pleural effusions and bowel obstruction
	Consider use of TPN for symptomatic benefit despite, no survival benefit demonstrated

mPFS, median progression free survival; RR, response rate; QoL, quality of life; PLD, pegylated liposomal doxorubicin; OS, overall survival; PFI, platinum free interval; PARP, poly(ADP-ribose) polymerase; SOC, standard of care; HRD, homologous recombination deficiency.

Chemotherapy for patients with a platinum free interval >6 months

For patients with a platinum free interval of greater than 6 months platinum-based therapy remains the mainstay of treatment. This can be with carboplatin monotherapy, which is generally easy to administer and well tolerated and may provide reasonable response rates (RR) in patients unfit or unwilling to receive combination chemotherapy. However, several studies have demonstrated the benefit of combination chemotherapy in the setting of platinum sensitive recurrent disease. The ICON4/OVAR2.2 study compared single-agent carboplatin with a doublet regime of carboplatin and paclitaxel, demonstrating a 7% improvement in 2-year survival rate in the combination arm (57% versus 50% in the monotherapy arm) and a 5-month improvement in median survival (29 versus 24 months; 95% CI for difference 1–11 months) (10). Despite this clinically meaningful benefit retreatment with carboplatin and paclitaxel was associated with moderate neurotoxicity in up to 20% of patients, leading to the exploration of alternative combination regimens.

The Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) group demonstrated the role of doublet carboplatin-gemcitabine chemotherapy in platinum sensitive recurrent ovarian cancer, with patients receiving a median of 6 cycles of chemotherapy in both arms. Improvements in median PFS (8.6 versus 5.8 months; 95% CI: 5.2–7.1 months) and RR (47.2% versus 30.9%) were seen in the combination chemotherapy arm, without any statistically significant differences in quality of life scores (11).

The CALYPSO trial compared two doublet combinations in platinum sensitive recurrent ovarian cancer, with the combination of carboplatin-pegylated liposomal doxorubicin (PLD) showing non-inferiority to carboplatin-paclitaxel. Furthermore, a favourable toxicity profile was demonstrated in the carboplatin-PLD arm, suggesting this may be a better treatment option in this group of patients (12).

Both these combinations regimens are routinely considered for patients with relapsed platinum sensitive disease.

Chemotherapy for patients with a platinum free interval <6 months

In this cohort of patients with a poorer overall prognosis, treatment decisions should be made focusing on quality of life and symptom control. Although retreatment with platinum can be considered often alternative, platinum-sparing regimens including weekly paclitaxel, PLD, gemcitabine and oral etoposide or suitable clinical trials are considered.

Weekly paclitaxel at a dose of 80 mg/m^2 has been shown to be effective even in patients who have developed resistance to prior doublet chemotherapy with carboplatin and paclitaxel, and two phase II randomised studies have demonstrated RRs ranging from 43% (13) to 56% (14) in cohorts of platinum-resistant patients.

Four-weekly PLD monotherapy has also been shown to be efficacious in patients with platinum resistant disease. A Cochrane review assessing the efficacy and safety of PLD in relapsed epithelial ovarian cancer found that in platinum-resistant disease, the median PFS and overall survival (OS) for PLD monotherapy was 15 and 54 weeks respectively. Toxicity included severe hand-foot syndrome, which

occurred more frequently at doses of 50 mg/m^2 (15) and therefore clinically the routinely administered starting dose is 40 mg/m^2.

A meta-analysis of 6 randomised controlled trials compared gemcitabine to PLD in the setting of platinum resistant recurrent ovarian cancer, and demonstrated no significant differences in OS or PFS. Toxicity profiles varied, with significantly more neutropenia noted with gemcitabine treatment and more hand-foot syndrome in patients treated with PLD (16).

PARP inhibitors in recurrent ovarian cancer

There have been significant advances in the treatment of ovarian cancer with the recognition of the importance of PARP enzyme inhibition. These agents exploit the DNA repair vulnerabilities of ovarian cancer cells due to deficient homologous recombination repair (HRR) pathways. Hereditary mutations in BRCA 1/2 genes are present in approximately 20% of patients, and in addition mutations in genes such as RAD51C, RAD51D, BRIP1, BARD1, PALB2, lead to deficient HRR in up to 50% of high grade serous ovarian cancers (17).

Whilst the most significant benefit of PARP inhibitors has been in patients with known germline or somatic BRCA 1/2 mutations, efficacy has also been demonstrated in those women with high grade tumours that demonstrate homologous recombination deficiency (HRD) through mutations (RAD51C, RAD51D, BRIP1 and others) and in ovarian tumours with high loss of heterozygosity (LOH), a genomic signature associated with HRD. The results of three important phase III trials, SOLO2, NOVA and ARIEL3 have led to the licensing of the PARP inhibitors, olaparib, niraparib and rucaparib respectively in the maintenance treatment of platinum sensitive relapsed ovarian cancer. All three agents have been shown to be orally efficacious and are generally well tolerated, but have slightly different toxicity profiles, which is helpful in terms of increasing patient choice (18).

The phase III, SOLO2 trial prospectively evaluated the role of the PARP inhibitor olaparib in BRCA 1/2 mutated patients with recurrent platinum-sensitive ovarian cancer. Maintenance treatment with olaparib provided a significant improvement in PFS [19.1 versus 5.5 months in placebo arm; hazard ratio (HR) 0.30 (95% CI: 0.22–0.41), P<0.0001], without impacting quality of life (19) and at 5 years 28.3% of patients in the olaparib arm compared to 12.8% of those in the placebo arm were alive and had still not received subsequent treatment (20). Study 19, a randomised controlled phase II, trial also confirmed the benefit of olaparib in the BRCA wild type population: retrospective analysis demonstrated a median PFS of 7.4 months for women treated with olaparib (95% CI: 5.5–10.3 months) *vs.* 5.5 months for placebo (95% CI: 3.7–5.6 months; HR, 0.54; 95% CI: 0.34–0.85; P=0.0075). These data led to the licensing of olaparib in the maintenance setting in women with platinum sensitive relapsed disease (21).

The activity of single agent olaparib versus non-platinum-based chemotherapy has also been demonstrated in the phase III SOLO3 trial, where heavily pre-treated BRCA 1/2 mutated patients (who had received 2 or more lines of platinum-based chemotherapy) were randomised to receive treatment with single agent olaparib or physician's choice of non-platinum chemotherapy. A significant improvement of objective RR [72.2% versus 51.4%; odds ratio (OR), 2.53 (95% CI: 1.40–4.58); P=0.002] and median PFS [13.4 versus 9.2 months; HR 0.62 (95% CI: 0.43–0.91); P=0.013] was seen in the olaparib arm compared to chemotherapy (22). Although platinum retreatment remains the standard of care for this group, the SOLO3 trial has provided important evidence for using olaparib in BRCA 1/2 mutation carriers who are unable to receive platinum due to toxicity, hypersensitivity or patient preference.

The results of the phase III NOVA trial expanded the routine use of maintenance PARP inhibitors to women with relapsed platinum-sensitive disease regardless of whether they had evidence of defective DNA repair due to a BRCA1/2 mutation or HRD. Although even within this trial the greatest benefit was seen in patients with germline BRCA1/2 mutations, with a PFS of 21.0 months versus 5.5 months in favor of niraparib for germline BRCA1/2 mutated cancers (95% CI: 0.17–0.41, HR =0.27, P<0.0001). There was also an improvement in the median duration of PFS in other cohorts: a PFS of 12.9 versus 3.8 months in favor of niraparib for non-BRCA HRD tumors (95% CI: 0.24–0.59 months, HR =0.38, P<0.0001) and a PFS of 9.3 versus 3.9 months in favor of niraparib for the overall non-BRCA cohort (95% CI: 0.34–0.61, HR =0.45, P<0.001). In the exploratory population of HRD-negative and non-BRCA patients the median PFS for niraparib was 6.9 versus 3.8 months for placebo (95% CI: 0.36–0.92, HR =0.58, P=0.02) (23).

The role of single agent niraparib was also evaluated in a large single arm, open label phase II trial, QUADRA, in women who had been heavily pre-treated (exposed to 3 or more prior chemotherapy regimens). In this cohort,

clinically relevant activity of niraparib was demonstrated in patients with HRD-positive platinum sensitive disease, which included patients with non-BRCA HRD mutations (24).

The third approved PARP inhibitor is rucaparib, which can be used as monotherapy for BRCA-mutated patients or as maintenance treatment after a response to platinum-based chemotherapy (regardless of BRCA status). The efficacy of rucaparib has been evaluated in the phase III ARIEL2 and ARIEL3 trials. In ARIEL2, patients with recurrent platinum-sensitive ovarian cancer were classified by HRD status (BRCA1/2 mutant, BRCA wild-type and LOH high, or BRCA wild-type and LOH low), with all patients receiving rucaparib monotherapy. Median PFS was highest in the BRCA1/2 mutant group (HR 0.27, 95% CI: 0.16–0.44, P<0.0001), 12.8 months compared to 5.7 months in the LOH high group (HR 0.62, 95% CI: 0.42–0.90, P=0.011) and 5.2 months in the LOH low group (25). In ARIEL3, pre-treated women (2 or more lines of previous platinum-based therapy) with recurrent platinum sensitive disease were randomised 2:1 to receive rucaparib maintenance or placebo, regardless of their BRCA1/2 or HRD status. Rucaparib significantly improved PFS, with the most marked improvement seen in those women with BRCA1/2 mutant disease [16.6 versus 5.4 months with placebo; HR 0.23 (95% CI: 0.16–0.34); P<0.0001] but benefit was also demonstrated in the HRD group [13.6 versus 5.4 months; HR 0.32 (95% CI: 0.24–0.42); P<0.0001] and in the intention-to-treat cohort [10.8 versus 5.4 months; HR 0.36 (95% CI: 0.30–0.45); P<0.0001] (26). This study confirmed the use of PARP inhibitors in the maintenance setting, irrespective of BRCA/HRD status.

The use of PARP inhibitor maintenance in platinum sensitive relapse is now a standard of care for women regardless of BRCA1/2 status, and recent data from the phase III trials, SOLO1, PRIMA, PAOLA1 and VELIA (27-30) has expanded the role of these agents into the frontline setting, with the degree of response again dependent on the presence of a BRCA1/2 mutation or HRD.

Anti-angiogenic treatment in recurrent ovarian cancer

Agents blocking angiogenesis, by inhibiting vascular endothelial growth factor receptor (VEGFR), have demonstrated activity in the treatment of advanced ovarian cancer and the monocloncal antibody, bevacizumab (Avastin), is licensed in the treatment of newly diagnosed and relapsed disease.

Initial trials in women with multiply relapsed ovarian cancer demonstrated the activity of bevacizumab as a monotherapy (31). A subsequent phase III trial, OCEANS, investigated the efficacy of bevacizumab in combination with platinum based chemotherapy. Women with recurrent platinum-sensitive disease were randomised to receive standard chemotherapy with gemcitabine-carboplatin and placebo or the same doublet chemotherapy with bevacizumab. Placebo/bevacizumab maintenance was then continued until disease progression. The trial demonstrated a 4-month statistically significant improvement of PFS in the bevacizumab treated group (12.4 versus 8.4 months placebo; HR 0.48; 95% CI: 0.388–0.605; P<0.0001) and overall RR (79% versus 57%) although this did not translate into an improvement in OS (32).

The role of bevacizumab in patients with platinum-resistant disease was evaluated in the phase III randomised AURELIA trial, where progressing patients received single-agent chemotherapy (PLD, weekly paclitaxel or topotecan) alone or in combination with bevacizumab until disease progression. Participants were allowed to crossover to single-agent bevacizumab after progression on chemotherapy alone. The addition of bevacizumab to chemotherapy significantly improved PFS (6.7 months with bevacizumab versus 3.4 months with chemotherapy alone) and objective RR (27.3% versus 11.8%; P=0.001) although again no difference in OS was seen (33). AURELIA demonstrated that bevacizumab was most active in combination with weekly taxol with a 53% RR and a median PFS of 10.4 months (33).

The role of oral anti-angiogenic agents such as, cediranib, a tyrosine kinase inhibitor targeting VEGF receptor 1, 2 & 3, has also been explored. A phase II trial demonstrated single agent activity of cediranib (34) and led to its evaluation in combination with chemotherapy in women with relapsed disease. The Phase III ICON6 trial evaluated the combination of cediranib with platinum-based chemotherapy and as ongoing maintenance treatment in relapsed platinum sensitive ovarian cancer. An improvement was seen in PFS and OS in patients receiving oral cediranib with chemotherapy and as continued maintenance, although toxicities including diarrhoea, neutropenia and hypertension were noted (35,36). Although cediranib is not currently licensed for treatment of relapsed ovarian cancer, its role is being further evaluated in combination trials such as ICON9.

Combination therapies

The results of combination trials, using agents synergistically to improve the efficacy and durability of responses seen with monotherapy, have been promising in ovarian cancer. The addition of cediranib to the PARP inhibitor, olaparib was explored in a phase II randomised trial in recurrent platinum-sensitive ovarian cancer. Here, women receiving cediranib plus olaparib had an improved PFS (17.7 months) versus those treated with olaparib monotherapy (9 months) (41). The Phase III GY004 trial further explored the activity of olaparib, the combination of olaparib and cediranib compared to platinum doublet chemotherapy in women with BRCA stratified platinum sensitive recurrent ovarian cancer. Although no OS differences were seen between the treatment arms, the combination of olaparib and cediranib still demonstrated significant activity in the treatment setting (41) and the combination is being further explored in the maintenance setting within the international phase 3 trial, ICON9. In the platinum resistant setting, the phase II randomised OCTOVA trial evaluated the role of olaparib alone or olaparib in combination with cediranib and the final results of both trials are awaited.

The role of PARP inhibitors in combination with other anti-angiogenic agents e.g., bevacizumab has also been explored. In a chemotherapy sparing Phase II trial (AVANOVA/ENGOT-OV24), women with relapsed platinum-sensitive disease received niraparib alone or niraparib with bevacizumab. Patients treated with the combination had a median PFS of 11.9 versus 5.5 months [HR 0.35 (95% CI: 0.21–0.57), P<0.0001] in those treated with niraparib alone, and this benefit was shown to be independent of HRD status (42).

In the first-line setting, the combination of maintenance olaparib and bevacizumab was shown to significantly improve PFS in patients with HRD (regardless of BRCA status) in the phase III PAOLA1 study (29), and this is the combination has now been licensed in newly diagnosed patients. The Phase II OVARIO study, evaluating niraparib and bevacizumab treatment in the first-line maintenance setting has not identified any safety concerns with the combination and results for survival are awaited (43).

Immunotherapy in recurrent ovarian cancer

Whilst immunotherapy with check-point inhibitors has led to practice changing outcomes in other tumour types, its role in ovarian cancer remains to be clearly established. Modest activity of pembrolizumab, a programmed death receptor 1 (PD1) inhibitor, as monotherapy in recurrent ovarian cancer was demonstrated in a large open label phase II KEYNOTE-100 study (44) and a small phase II single arm trial of nivolumab has also demonstrated RRs of 15% in programmed death ligand 1 (PD-L1) positive platinum resistant disease (37). Avelumab has been evaluated in combination with chemotherapy in an attempt to improve responses in the frontline and relapsed settings within the Javelin 100 and 200 trials respectively.

Recent results of the phase III randomised Javelin 200 trial, where an unselected population of women with platinum-resistant or refractory ovarian cancer received avelumab in addition to PLD, demonstrated that the combination was well tolerated but did not lead to an improvement in PFS or OS benefit (38). Although in pre-specified analysis those women who had PD-L1-positive tumours appeared to benefit from the addition of avelumab as they demonstrated an improved OS (18.4 *vs.* 12.7 months) compared with PD-L1-negative patients. In this setting it appears that there may be a potential role for PD-L1 expression as a predictor of clinical benefit from avelumab, although overall the activity of the combination was not overwhelming in platinum resistant ovarian cancer.

Although to date there has been limited benefit from immunotherapy it may be that novel combinations, e.g., with an antiangiogenic agent such as bevacizumab, which are thought to have immunosuppressive properties and upregulate PDL1 expression, or PARP inhibitors, which may enhance intratumoural immune cell infiltration, may be more successful and these are being explored in ongoing clinical trials.

In a small phase II study the activity of the anti-PD1 therapy nivolumab together with bevacizumab was dependent on the platinum free interval with a greater progression-free survival of 8.1 months (45). Similarly, the anti-PD1 therapy pembrolizumab given with the PARP inhibitor niraparib has shown promising antitumour activity in recurrent ovarian cancer, regardless of platinum or HRD/BRCA status (46). The combination of durvalumab and olaparib has also demonstrated disease control rates of 81% and objective RRs of 63% in a phase II trial (47) and this combination is currently being evaluated in the phase III setting. The outcomes of further studies investigating immunotherapy combinations, such as ATALANTE, a phase 3 trial in women with platinum sensitive recurrence, evaluating a combination of atezolizumab and bevacizumab

and a number of front line phase 3 trials such as DUO, FIRST and ATHENA are also awaited.

Secondary cytoreductive surgery

For women with longer treatment free intervals and limited disease relapse there may be a role for secondary cytoreductive surgery, although there has been conflicting evidence from two recent large phase 3 trials. The GOG-0213 Phase III trial of 485 women failed to show improvement of OS in women with recurrent platinum-sensitive ovarian cancer who were treated with secondary cytoreductive surgery compared to chemotherapy alone, and also identified significant morbidity in the post-operative period (39). Conversely, a clinically meaningful survival benefit was demonstrated in the DESKTOP III trial of 407 women with recurrent platinum-sensitive ovarian cancer when patients were selected by a positive AGO-Score (PS ECOG 0, ascites ≤500 mL and complete resection at initial surgery). Here, patients randomised to receive surgery and chemotherapy had a median OS of 60.7 versus 46.2 months in those treated with chemotherapy alone (P=0.03) (40). Importantly, the DESKTOP III study did not include many patients who had exposure to PARP inhibitor therapy; the role of further cytoreductive surgery in this growing cohort of patients also needs to be explored.

Symptomatic treatment

Despite the progress made, recurrent disease remains incurable and a multidisciplinary approach including expert palliative care input is vital (48,49). Commonly patients develop ascites and pleural effusions, requiring recurrent drainage or indwelling catheters for symptomatic relief; or malignant bowel obstruction, requiring surgical and palliative care input, often with a combination of therapies including analgesia, anti-emetics, corticosteroids and subcutaneous octreotide infusions (50). The use of total parental nutrition may be considered in selected patients with late stage disease, perhaps even as an alternative to chemotherapy, although a Cochrane review has not confirmed a benefit in terms of quality of life (51). Trials are planned to evaluate the role of total parental nutrition in later stages of disease.

Conclusions

Recent trials of PARP inhibitors and anti angiogenic agents have led to significant improvements in progression-free of women with relapsed disease, however there still remains a significant need to improve OS. Furthermore as we use these agents in earlier lines of treatment, we will need to employ new strategies in those who relapse. The role of retreatment with a PARP inhibitor, and potentially maximising benefit by combining with other therapies, including other DNA damaging agents, is therefore an area of significant interest.

Although the initial promise of immunotherapy has not been realised, the results of a number of trials of combination therapy are awaited and it is hoped that, even if negative, they will provide an improved understanding of the tumour microenvironment in ovarian cancer. This will be fundamental in the development of treatments that can overcome potential immunosuppressive factors. It may be that cell based therapy, which includes adoptive T cell receptor therapy or chimeric antigen receptor T cell (CAR T) therapy, may be an alternative treatment approach for immunologically "cold" ovarian cancer.

Whatever the treatment strategy is, it is likely that biomarkers stratification will be essential in identifying those women who are most likely to benefit from therapies and spare those who are not likely to respond the toxicities of treatment. It is hoped that this approach of developing novel therapeutics with companion diagnostic tests, may lead to the personalisation of treatment and improved outcomes for women with recurrent ovarian cancer.

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Footnote

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