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Novel Systemic Treatments in High Grade Ovarian Cancer

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Abstract

Most patients with ovarian cancer present at an advanced stage and are never cured. To improve outcomes a variety of novel systemic strategies are being developed. Traditional cytotoxic chemotherapy is being optimised, anti-angiogenic strategies are already in the clinic and several PARP inhibitors have gained regulatory approval. In addition, immunotherapy is showing promise and novel targeted strategies including against folate receptor alpha are also generating excitement. As our therapeutic choice increases, a challenge will be how to best utilize the options available. Here we discuss recently established and other emerging therapies with a focus on key concepts rather than detailed synopses of trial designs and outcomes.

Keywords: ovarian cancer, PARP inhibitors, immunotherapy, antiangiogenic therapy

1. Introduction

Over a quarter of a million women are diagnosed with epithelial ovarian cancer (EOC¹) each year and it is responsible for around 140,000 deaths worldwide. There is no effective screening program so the majority present with advanced disease. Despite improved surgical technique most patients are never cured. Novel systemic treatments are needed both to prolong overall survival *with* the disease but also increase the fraction of patients in whom cure is achieved. A variety of distinct but complementary approaches are discussed here.

¹In this chapter, EOC refers also to primary peritoneal and fallopian tube carcinoma. Definitions of platinum-sensitive, resistant and refractory are as per the relevant citation.

2. Chemotherapy in ovarian cancer

Despite the emergence of alternate antineoplastic strategies, chemotherapy remains the backbone of EOC treatment. Although EOC is chemosensitive, with most patients responding initially, the majority will eventually relapse and subsequent responses are poorer. Efforts are being made to try and enhance the efficacy of 'traditional' cytotoxic chemotherapy. These include manipulation of dosing schedules, efforts to understand resistance and discovery of novel agents. These strategies are discussed in this subsection.

2.1. Dose-dense chemotherapy

Dose densification refers to the administration of an agent more frequently than in the 'standard' regimen. It can imply dose intensification (i.e. increasing the net $\text{mg}/\text{m}^2/\text{week}$) but some authors use it to describe splitting the standard scheduled dose into weekly fragments while maintaining the same (rather than increased) dose intensity [1].

The rationale for dose-dense treatment stems from the Norton-Simon hypothesis (**Figure 1**).

The rationale for dose densification extends beyond the Norton-Simon hypothesis. Firstly, the pharmacokinetics of a dose-dense approach may reduce toxicity. For example, paclitaxel-induced myelosuppression is dependent on the time during which the plasma level exceeds 50 nM [3]. This is considerably shorter for 80 mg/m^2 weekly compared to 240 mg/m^2 q3w [4]. Secondly, weekly paclitaxel may confer an additional anti-angiogenic effect compared to q3w scheduling [5].

Weekly paclitaxel was initially studied in the recurrent setting. Notably in one trial patients resistant to the q3w regimen achieved an objective response rate (ORR) of 25% with the weekly regimen possibly due to the additional anti-angiogenic effect of this schedule [6].

Weekly paclitaxel has also been studied in the adjuvant setting (**Table 1**).

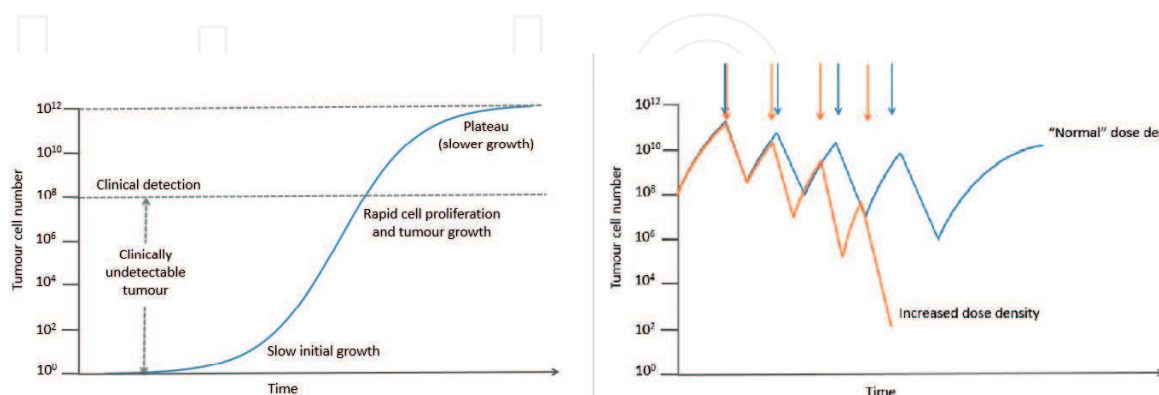


Figure 1. The Norton-Simon hypothesis assumes a Gompertzian model of tumour growth (left). This was combined with their observation that after treatment, smaller tumours regress faster than larger ones. Crucial to their mathematical model is the fact that 'log-kill' is not constant for a given dose of therapy but instead depends on tumour size, being greater for smaller tumours. Their model predicts that a dose-dense approach is more likely to eradicate a tumour [2].

Study	Eligibility	Treatment	Efficacy (months)	Safety (grade ≥ 3 , $P < 0.001$)
JGOG 3016 [10]	Stage II-IV	Carbo q3w + either taxol q3w or weekly ¹	PFS 28.2 vs. 17.5 OS 100.5 vs. 62.2	Anaemia 69% vs. 44% Discontinuation due to tox. 60% vs. 43%
GOG 0262 [11]	Incompletely resected III or IV	As above + uncontrolled bevacizumab ²	PFS 14.7 vs. 14.0 (not significant)	Anaemia 36% vs. 16% Neutropenia 72% vs. 83%
MITO-7 [12]	Stage IC-IV	Carobplatin/paclitaxel either q3w or weekly ³	PFS 18.3 vs. 17.3 (not significant)	Neutropenia 42% vs. 50% Thrombocytopenia 1% vs. 7%

¹Carboplatin AUC 6, paclitaxel 180 mg/m² (q3w) or 80 mg/m² (weekly).
²Carboplatin AUC 6, paclitaxel 175 mg/m² (q3w) or 80 mg/m² (weekly). 84% of patients received bevacizumab.
³Carboplatin AUC 6, 175 mg/m² (q3w) or carboplatin AUC 2, paclitaxel 60 mg/m² (weekly).

Table 1. Comparison of phase III trials testing weekly paclitaxel in the adjuvant setting. All values given as weekly vs. q3w.

In JGOG 3016 patients derived both PFS and OS benefit from the dose-dense approach, whereas in GOG 0262, there was no PFS difference in the intention to treat (ITT) population [7–9]. The two trials, however, had key differences. Patients in GOG 0262 were allowed bevacizumab (BEV) in an uncontrolled fashion. Since weekly paclitaxel has an anti-angiogenic effect, this may have been negated by the addition of BEV in 85% of the trial population. Consistent with this, in those who didn't receive BEV, weekly paclitaxel improved PFS (14.2 vs. 10.3 months). Pharmacogenomic differences in the two trial populations may also have been important. There are consequently unanswered questions about dose-dense chemotherapy which may be answered by two phase III trials yet to report. In the 3-arm ICON 8 trial (NCT01654146), q3w carboplatin/paclitaxel is compared to 2 dose-dense regimens without BEV. In ICON 8B (NCT01654146), bevacizumab use is allowed but is controlled and pre-specified.

2.2. Understanding resistance to facilitate chemosensitization

EOC is initially chemosensitive so efforts to understand resistance could improve outcomes. Acquired resistance is secondary to diverse mechanisms which includes alterations to DNA repair and/or response to DNA damage. Mk-1775 is an anti-Wee1 tyrosine kinase inhibitor (TKI) that may sensitize cells to chemotherapy by abrogating the G2 checkpoint (crucial in P53 deficient cells) causing premature entry into mitosis [10]. It has shown promising results in several phase II trials [11]. In a different approach, the 2-arm PiSARRO trial (NCT02098343) involves the addition of APR-246 (capable of restoring mutant P53 to wild-type confirmation) to platinum-based therapy with the aim of restoring the apoptotic-response to chemotherapy-induced DNA damage. There are many other pre-clinical and early clinical efforts aiming to reverse chemoresistance including efforts to target primary resistance by targeting cancer stem cells and epithelial to mesenchymal transition [12].

2.3. Novel chemotherapeutic agents

Lurbinectedin is a recently discovered marine-derived antineoplastic agent that has a multi-modal mechanism of action similar to trabectedin. It showed promising results in a phase II

trial in platinum-resistant EOC and is being investigated in a phase III trial against either PLD or topotecan [13]. It has also shown *in vitro* synergy with cisplatin raising hopes of clinical application to reverse platinum resistance [14]. Trabectedin itself is undergoing phase III testing in patients with platinum partially-sensitive disease (NCT01379989).

3. Antiangiogenic strategies in ovarian cancer

Key mediators of physiological angiogenesis include products of the vascular endothelial growth factor (VEGF) gene family including VEGF-A (often abbreviated to VEGF), VEGF-B, C and D and placental growth factor. The receptor family includes VEGFR-1, 2 and 3. Different combinations of ligand-receptor interaction result in diverse outcomes such as promotion of survival, proliferation of endothelium, increased permeability and lymphangiogenesis. The binding of VEGF-A to VEGFR-2 is most important in endothelial proliferation and the regulation of permeability [15].

In physiology VEGF is important for the cyclical angiogenesis that takes place in the female reproductive tract [16]. Many tumour cell lines overexpress VEGF and in one series over 97% of human ovarian lines had overexpression [17]. Clinically, expression levels have been found to be an independent prognostic factor in several studies [18] and have also been found to correlate with peritoneal dissemination and ascites formation [19].

Given the role of VEGF in physiology as well as pre-clinical and observational data supporting a role for VEGF in cancer, several VEGF-directed therapies exist.

3.1. Bevacizumab

Bevacizumab (BEV) is a humanized monoclonal antibody able to bind all VEGF-A isoforms [20]. It is the most extensively studied of the antiangiogenic agents in EOC. Two phase III studies (GOG-218 and ICON7) tested adjuvant BEV. In GOG-218 [21] patients received 6 cycles of carboplatin/paclitaxel q3w and either 1) placebo (cycles 2–22), 2) BEV induction (cycles 2–6) then placebo maintenance (7–22) or 3) BEV induction (cycles 2–6) then maintenance (7–22). BEV was given at 15 mg/kg. The median PFS was 14.1 months in the BEV throughout arm compared to 11.2 months in the induction-only arm and 10.3 months for the control. Overall survival was not significantly different. 22.9% developed grade ≥ 2 hypertension in the BEV throughout arm vs. 7.2% in the control arm. In ICON7 [22], high-risk patients were given carboplatin/paclitaxel q3w with either placebo or bevacizumab (7.5 mg/kg) for cycles 2–18. Median PFS was 19.0 months in the BEV arm vs. 17.3 months (HR 0.81, $p < 0.01$). Among patients with incompletely resected IIIC or IV disease the median PFS was 15.9 vs. 10.5 months in the control arm. Bleeding (39 vs. 11%), hypertension (18 vs. 2%), thromboembolism (7 vs. 3%) and GI perforations (10 vs. 3 patients) were higher with BEV. Mean global QoL score was higher, at 54 weeks, in the control arm (76.1 vs. 69.7 points - EORTC questionnaire) [23]. Recent exploratory analysis of a ‘high-risk’ subgroup revealed significantly increased OS (restricted means) in the BEV group of 39.3 vs. 34.5 months [24].

There were similarities and differences between these trials. Both suggested greater benefit in a subpopulation with higher stage and suboptimal debulking. They also agreed that QoL was not improved with BEV. Conversely, different doses and durations of treatment were used and overall survival data also differed, perhaps confounded by the 40% crossover in GOG 218. BEV received regulatory approval from the EMA using 15 mg/kg [25] although ESMO guidelines supported the 7.5 mg/kg dose used in ICON7, which is also prescribed in the UK currently [26]. Analysis of both trials showed greatest separation of the PFS curves at the end of BEV treatment (12 or 15 months), raising questions about extending maintenance duration. This is being investigated in the phase III BOOST study (NCT01462890).

Bev has also been studied for recurrence. In AURELIA [27], patients with platinum-resistant disease and ≤ 2 prior lines of chemotherapy were given single agent investigator-choice chemotherapy either alone or with BEV continued until progression/toxicity. Median PFS was higher in the BEV arm, 6.7 vs. 3.4 months with an ORR of 27.3 vs. 11.1%. Of the 113 patients with baseline ascites 17% required paracentesis in the control arm vs. 2% in the BEV arm and PROMs for GI symptoms were better with BEV [28]. OS was not significantly different in the context of 40% crossover but a recent exploratory analysis suggestive a survival advantage in those who received BEV during or after the study [29]. Adverse events were consistent with previous studies. BEV has been granted FDA and EMA approval for this indication.

In the OCEANS study [30], the addition of BEV to carboplatin/gemcitabine in patients with platinum-sensitive disease resulted in a median PFS of 12.4 months vs. 8.4 months. OS was not significantly (38% crossover). Hypertension, proteinuria and non-CNS bleeding were significantly more common in the BEV arm. BEV was also tested in the platinum-sensitive setting with carboplatin/paclitaxel, in the factorial GOG-213 trial [31]. Median OS with BEV was 42.2 months compared to 37.3 months without ($p = 0.056$). BEV has EMA regulatory approval in this setting.

3.2. VEGFR tyrosine kinase inhibitor (TKI) therapy

Whereas BEV binds directly to VEGF, VEGFR TKIs affect signalling via competitive inhibition of the intracellular kinase domain. They have the advantage of being orally bioavailable and multitargeted. Conversely, plasma concentration is unpredictable and off-target effects narrow the therapeutic window.

Cediranib inhibits VEGFR-1,2 and 3 and c-Kit. ICON 6 [32] randomised patients with recurrent platinum-sensitive disease to chemotherapy plus: placebo concurrently + maintenance (Arm A), cediranib concurrently + placebo maintenance (Arm B) or cediranib concurrently + maintenance (Arm C). Median PFS was 11 months in Arm C vs. 8.7 months in Arm A ($p < 0.0001$). Recent OS data [33] by restricted means showed 34.2 months vs. 29.4 months in Arms C and A respectively (95% CI for the difference: -0.1 -9.8). During chemotherapy grade ≥ 3 fatigue (16 vs. 8%), diarrhoea (10 vs. 2%), hypertension (12 vs. 3%), febrile neutropenia (7 vs. 3%) and thrombosis (3 vs. 1%) were higher with cediranib. 48% discontinued treatment due to toxic effects in Arm C compared to 17% in Arm A and 37% in B. Although recent analysis showed no detriment in

QOL at 1 year [34], filing for regulatory approval for cediranib had been previously withdrawn. Nonetheless cediranib maintenance is undergoing investigation in ICON9 (see below).

Pazopanib inhibits VEGFR1,2 and 3, c-Kit and PDGFR. The AGO-OVAR 16 study [35] evaluated first-line maintenance pazopanib. PFS was 17.9 months for pazopanib compared to 12.3 months for control. Grade 3/4 adverse events were significantly higher for pazopanib including hypertension (30.8%), neutropenia (9.9%) and diarrhoea (8.2%). Discontinuation due to AEs occurred in 33% in the pazopanib arm compared to 5.6% in the placebo arm. Regulatory approval filing was withdrawn due to perceived imbalance in benefit–risk ratio.

Other VEGFR TKIs have been studied in ovarian cancer [35]. Nintedanib was given in the first-line setting with chemotherapy and then maintenance. Again, a PFS benefit was seen but no significant OS advantage [36]. Other multitargeted VEGFR TKIs such as sunitinib and sorafenib have also been studied with similar outcomes. As a class the TKIs appear to have some effect however their multi-targeted nature and unpredictable bioavailability means that their perceived risk:benefit ratio has not led to any regulatory approvals as yet.

3.3. Other antiangiogenic strategies

The Ang-Tie pathway is distinct from the VEGF axis, involved in vascular remodelling. Trebananib is peptide-Fc fusion protein that binds Angiopoietin 1 and 2 and prevents interaction with Tie on endothelium. Although promising results were seen in phase II [37], a phase III trial (TRINOVA-2) [38] failed to meet its PFS endpoint and a third terminated early for futility (NCT01493505).

3.4. Combination therapy

Vascular disrupting agents (VDAs), in contrast to inhibiting formation of new vessels, target existing tumour vasculature. The VDA's combretastatin and fosbretabulin disrupt the endothelial cytoskeleton (by binding tubulin) aiming to cause endothelial detachment and eventual vessel obstruction. Tumour vasculature lacks pericytes and smooth muscle making them selectively susceptible. Fosbretabulin is being examined for synergy with bevacizumab and chemotherapy in platinum-resistant disease in a phase II/III trial (NCT02641639).

There is pre-clinical rationale for the combination of VEGF-targeted therapy with poly (ADP-ribose) polymerase inhibitors (PARPi); anti-VEGF induced hypoxia can impair DNA repair and sensitize otherwise insensitive cells to PARPi. In a phase II trial of olaparib and cediranib [39] PFS with the combination was prolonged (17.7 vs. 9.0 months) and, consistent with pre-clinical rationale, the difference was most marked in BRCA wild-type patients. Grade 3/4 toxicity however was 70% with the combination vs. 7% for olaparib monotherapy. The combination is currently undergoing phase III testing (ICON 9). The combination of bevacizumab and olaparib in first-line maintenance is also being studied (NCT02477644).

Combining VEGF blockade and immunotherapy also has pre-clinical rationale (see below). Combinations of anti-angiogenesis and chemotherapy have been discussed in the paragraphs above. Of note, an early phase trial of pazopanib with carboplatin/paclitaxel was terminated early because of toxicity (GI perforations and myelotoxicity).

3.5. Predictive biomarkers in anti-angiogenic therapy

Given the relatively modest median PFS benefits and lack of OS benefit in some trials combined with toxicity and economic considerations, biomarkers for patient selection are needed. None have yet been validated for routine use although many have been suggested. Studies have been retrospective and focussed on different markers including gene-expression signatures, serum and tissue proteomic biomarkers. There have been some intriguing results including a 63-gene signature that identifies an immune subgroup that may be harmed by bevacizumab treatment [40]. Prospective validation is needed for this and other candidate markers.

4. PARP inhibitor therapy

DNA constantly undergoes single and double-strand breaks (SSBs/DSBs). SSBs are repaired predominantly by base excision repair (BER). PARPs are nuclear proteins with diverse functions including in BER and chromatin remodelling. PARP-1 is the most abundant member which upon binding to SSBs activates its ADP-ribosyltransferase catalytic domain allowing PARylation and recruitment of DNA repair effectors [41]. DSBs are mostly repaired by homologous recombination (HR) or non-homologous end joining (NHEJ), the latter being error-prone [42]. HR involves a number of key proteins including BRCA1, BRCA2, RAD51 and PALB2. A detailed discussion is beyond the scope of this chapter but the process of HR is reviewed here [43]

4.1. Homologous recombination repair in ovarian cancer

The Australian Ovarian Cancer Study Group screened 1001 patients with stage I-IV ovarian cancer for point mutations or large deletions in BRCA genes. 14.4% of patients overall had a germline mutation (including 17.1% with serous histology) [44]. A similar frequency was found in The Cancer Genome Atlas (TCGA) [45] although globally the prevalence varies between ethnic groups. In addition to germline mutations, BRCA genes can be somatically mutated, epigenetically silenced or the protein inactivated through post-translational mechanisms, e.g. EMSY amplification [46]. Various series have found somatic mutations of BRCA in 3–6% of EOC [47]. In contrast to somatic mutations, epigenetic silencing by promoter methylation is a dynamic process and may be harder to quantify. Studies report prevalence in the region of 5–30% of ovarian cancers.

However, BRCA1 and 2 are just two of many proteins involved in HR. TCGA undertook exomic analysis of 316 ovarian cancers as well as studies of promoter methylation, RNA expression and copy number changes [45]. Pathway analysis demonstrated that 51% of tumours had either mutations or silencing of components in the HR pathways. (**Figure 2**).

4.2. PARP inhibitors in ovarian cancer

HR deficiency (HRD) in EOC provides a target that can be exploited therapeutically. It was noted that cells with non-functioning PARP develop increased nuclear foci of Rad51 implying an increased burden of lesions being repaired by HR in these cells [48]. Farmer et al. [49] tested

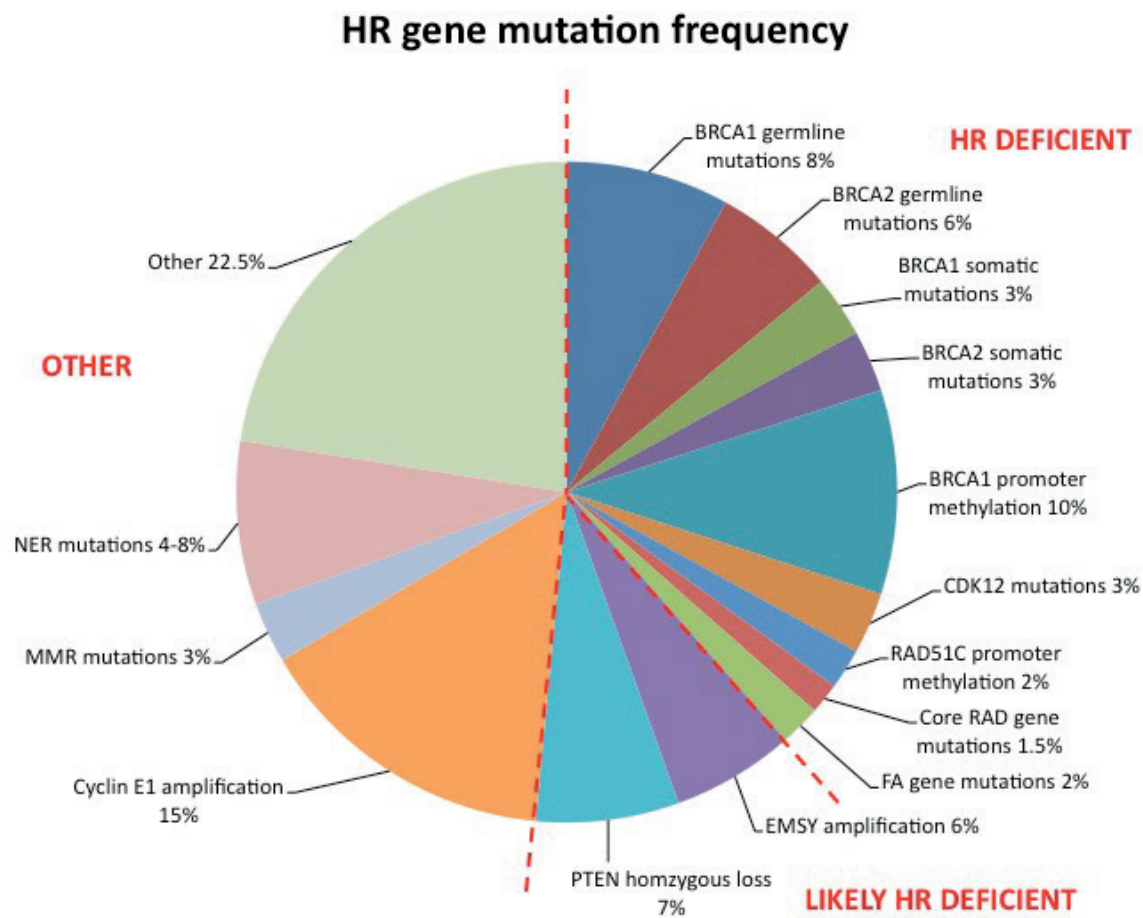


Figure 2. Distribution of HR gene mutations in EOC. Adapted from Ref. [47].

the hypothesis that BRCA 1/2 dysfunction would hypersensitize cells to PARP inhibition and were able to demonstrate this in BRCA deficient cell lines. This example of ‘synthetic lethality’ whereby either defect alone is tolerable but the combination is fatal has been exploited in the generation of a family of drugs, the PARP inhibitors. (**Figure 3**).

Following this, further work began on designing a PARP inhibitor (PARPi) suitable for clinical use. Early agents mimicked the substrate-enzyme interaction between NAD⁺ and the catalytic domain of PARP1/2 and further optimization led to the design of Compound 47, that would be developed as Olaparib [50]. Since Olaparib, several agents have been developed (discussed later) designed to inhibit PARP 1/2 catalytic activity.

In addition to catalytic inhibition, a distinct antitumour mechanism of PARPi, ‘PARP-trapping’ has been described. Trapped PARP-DNA complexes were more cytotoxic than unrepaired SSBs in PARP deficient cells and different PARP inhibitors had different PARP-trapping potency which was not correlated with their catalytic inhibitory properties [51].

4.3. Olaparib

Olaparib is an orally bioavailable small molecule with a nicotinamide moiety that competes with NAD⁺ for binding to PARP. The MTD for olaparib was established from early phase

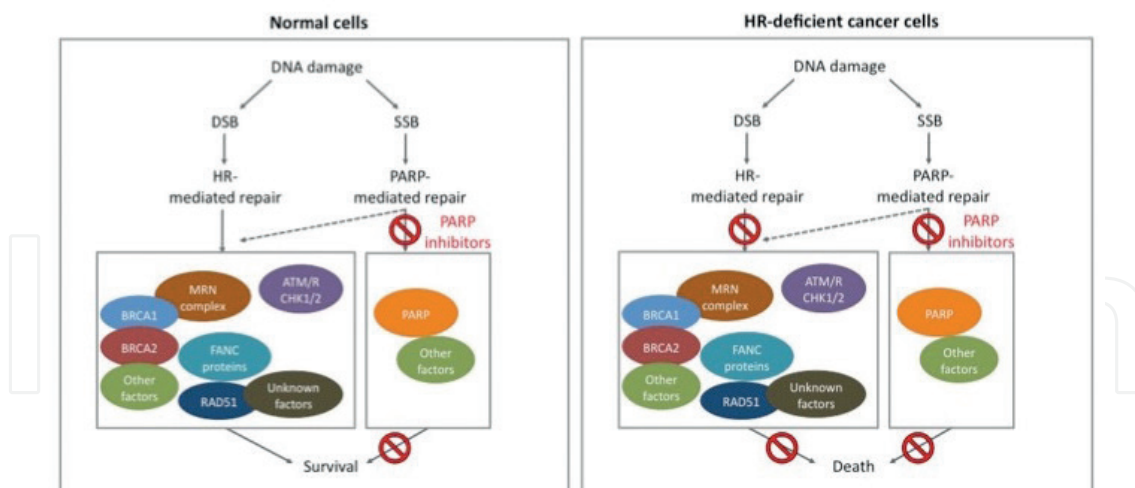


Figure 3. Schematic of synthetic lethality of PARP inhibition in HR deficient cells.

trials at 400 mg BD. Objective responses were seen mainly in patients with germline BRCA mutations (gBRCAm) [52]. Further support for the efficacy of olaparib in the gBRCAm population came from a proof-of-concept phase II where the ORR in the 400 mg BD cohort was 33% including some complete responses (CRs) [53]. Of note, one heavily pre-treated patient developed acute myeloid leukaemia (AML) 9 months after cessation.

A further phase II study gave 193 heavily pre-treated EOC platinum-resistant/unsuitable patients with gBRCA mutations olaparib at a dose of 400 mg BD [54]. The ORR was 31%. AEs were similar to those seen in earlier trials with a grade 3/4 rate of 54% including anaemia (17%) and fatigue (6%). Two patients developed leukaemia and one myelodysplastic syndrome, all were heavily pre-treated (25, 26 and 34 cycles each). These results (along with other applicant-submitted data) earned olaparib FDA approval as monotherapy for patients with gBRCA mutations after three prior lines. The recent phase III SOLO3 study randomised patients with gBRCA mutations who have received at least 2 prior lines of platinum-based therapy and who are deemed at least partially platinum-sensitive to either Olaparib 300 mg BD or single agent chemotherapy of investigators choice [55]. Results are awaited. While the previous formulation of Olaparib required 16 capsules a day, the current tablet formulation requires only four raising hopes that some of the gastrointestinal toxicity will be mitigated.

In the aforementioned studies olaparib was given as monotherapy for treatment of 'active' disease. In contrast, Study 19 randomised patients with recurrent platinum-sensitive cancer with at least 2 prior lines to maintenance olaparib or placebo post-chemotherapy [56]. In a pre-defined subset analysis of patients with known germline or somatic BRCA mutation (most retrospectively determined), median PFS in the gBRCAm group was 11.3 vs. 4.3 months with Olaparib and placebo respectively (HR 0.18). OS was not significantly different (23% crossover). The findings led to EMA approval. SOLO2 was a phase III double-blind placebo-controlled study in patients with recurrent platinum-sensitive EOC who had received at least 2 prior chemotherapy lines. Patients either got maintenance olaparib 300 mg BD or placebo. Investigator-assessed median PFS was 19.1 vs. 5.5 months (HR 0.30). Median PFS2 was also

improved from not reached vs. 18.4 months (HR 0.5) and OS data are immature. Although nausea (76% vs. 33%) and vomiting (37% vs. 19%) were higher in the olaparib arms, grade 3/4 events were infrequent (2.6% for both). Grade 3/4 anaemia occurred in 20%. Patient-reported outcomes showed no detriment for olaparib [57].

The phase III SOLO1 has completed accrual and randomised patients with BRCAm following first-line platinum-based chemotherapy to either Olaparib 300 mg BD or placebo.

4.4. Niraparib

Niraparib is a potent PARP1 and PARP2 inhibitor whose pharmacokinetics allows once daily dosing. A phase I dose escalation trial established the MTD as 300 mg/day. Dose-limiting toxicities included fatigue, reversible pneumonitis (in the context of recent chest wall irradiation) and reversible grade 4 thrombocytopenia. Of the 20 patients with gBRCA mutations and evaluable tumours the ORR (at doses between 80 and 400 mg) was 40% [58].

The pivotal phase III NOVA trial enrolled patients with platinum-sensitive disease who had received at least two prior lines of chemotherapy and who had measurable disease of <2 cm post-treatment [59]. Patients were randomised to niraparib 300 mg or placebo as maintenance till PD or unacceptable toxicity. Patients were stratified into gBRCA mutations vs. those without. Those without gBRCA mutations were further stratified into those with or without a positive HRD score (see below) and a predefined cut-off. PFS in the gBRCA mutated group was 21 vs. 5.5 months in the niraparib and control arms respectively (HR 0.30) and 12.9 vs. 3.8 months (HR 0.45) in the HRD positive cohort.

QUADRA is an ongoing single-arm phase II trial in patients pre-treated with 3–4 lines of chemotherapy and who were platinum sensitive at first recurrence regardless of BRCA mutation status. Patients who entered the trial underwent testing for homologous recombination deficiency (HRD) using a validated commercial assay. This assesses tumour samples for three SNP array-based ‘signatures’ of genomic instability (loss of heterozygosity, telomeric allelic imbalance and large scale transition) to derive an overall ‘HRD score’ that should predict sensitivity to PARP inhibition [NCT02354586].

PRIMA is an ongoing phase III of niraparib maintenance after 1st line chemotherapy. Unlike SOLO1, patients are enrolled on the basis of HRD score rather than gBRCA mutation status.

4.5. Rucaparib

Rucaparib is another orally bioavailable PARPi with both catalytic inhibitory and PARP-trapping activity, the potency of the latter being equivalent to olaparib [60].

Rucaparib was granted accelerated FDA approval largely based on composite data from 2 phase II studies. 106 patients with gBRCA mutations who had received at least 2 prior lines of chemotherapy received continuous rucaparib at 600 mg BD [61]. The confirmed ORR by RECIST was 54%. Toxicity at \geq grade 3 included anaemia (27%), fatigue (15%), transient AST/ALT elevation (13%), vomiting (6%) and nausea (4%).

Part 1 of the ARIEL2 trial (from which the gBRCA mutation data was pooled in the above analysis) enrolled 206 patients who had been received at least 1 prior platinum containing chemotherapy regimen and who had progressed after at least 6 months after their most recent course [62]. Patients were prospectively divided into three subgroups based on their HRD status: 1) germline or somatic BRCA mutations 2) BRCA wild-type and LOH-high 3) BRCA wild-type and LOH-low. LOH was assessed using a next generation sequencing assay and a cut-off of 14% was assigned using microarray and survival data from TCGA. Based on this pre-specified score, PFS was 12.8 months, 5.7 months and 5.2 months in the BRCA mutated, BRCA wild-type/LOH-high and BRCA wild-type/LOH-low subgroups. Although median PFS was similar in the latter groups, the HR for PFS was significantly in favour of the LOH-high subgroup (0.62 95% CI 0.42–0.90), and ORR by RECIST (29% vs. 10%) and 1 year survival (28% vs. 10%) were also better for the LOH-high subgroup. Of note, LOH exists on a continuum and exploratory post-hoc analysis revealed that a cut-off of 16% provided better discrimination between the two subgroups [63]. Also importantly, there were patients in the LOH-negative group with very good partial and even complete responses (by ca125). In this single arm phase II study, it is not possible to exclude the possibility that LOH-high tumours simply have a better prognosis and that LOH is a prognostic rather than predictive marker. In order to address this question (in a maintenance setting at least) the NGS assay is being prospectively applied in the phase III Ariel 3 study which is investigating maintenance rucaparib in platinum-sensitive ovarian cancer. The phase III Ariel 4 study is will compare rucaparib as an active treatment vs. standard of care chemotherapy in platinum-sensitive disease after at least 2 prior lines.

4.6. Veliparib

Another orally bioavailable PARP inhibitor, veliparib is far less potent at PARP-trapping than the previously mentioned agents although it is a more potent catalytic inhibitor than niraparib and has been shown to cross the blood–brain barrier [51]. In a phase I trial 40% of the 28 BRCAm positive evaluable patients had an ORR at the MTD (400 mg BD). Commonest toxicities were nausea, vomiting and lymphopenia and 2 patients had grade 2 seizures [NCT01472783].

In a phase II trial in patients with gBRCAm who had been treated with 3 or fewer prior regimens (median 2) and of whom 60% were platinum resistant, the ORR was 26% (35% in the platinum-sensitive cohort). Grade 3 fatigue, nausea and neutropenia occurred in 6%, 4% and 2% respectively with no other grade 3 toxicities. Veliparib is currently being explored in phase III trial concurrently with carboplatin/paclitaxel and then continued as maintenance (NCT02470585, see below).

4.7. Talazoparib

Talazoparib is a novel PARPi that traps PARP approximately 100-fold more efficiently than olaparib and rucaparib and exhibits cytotoxicity at nanomolar (compared to micromolar) concentrations) [60]. At an MTD of 1 mg/kg, 5/12 patients with BRCAm ovarian cancer achieved

an ORR with a 24% and 18% rate of G3 anaemia and thrombocytopenia respectively [64]. Given its unique potency for trapping, there is hope that it may have efficacy as a second line agent for patients who have progressed on a previous PARPi [65].

4.8. Combination therapy with PARP inhibitors

PARPi were originally developed as potential chemo/radiosensitizers. There is obvious rationale in combining PARPi with other agents, especially in tumours that are HR proficient. When combining PARPi with chemotherapy, rational combination necessitates consideration of the mechanism of action of the chemotherapy plus the relative catalytic inhibitory/trapping properties of the PARPi. For example, PARPi combination with topo-1 inhibitors is synergistic primarily because of catalytic PARP inhibition whereas synergy with alkylating agents relies on trapping too [66]. Several PARPi/chemotherapy combinations are in trials, reviewed here [67]. Synergistic toxicity (e.g. myelotoxicity) will have to be borne in mind. PARPi/VEGFR targeting combinations have previously been discussed. Other targeted combinations include PI3K/MTOR pathway inhibitors, HSP90 and CHK1/2 inhibitors [67]. Finally, talazoparib had immunomodulatory effects in a pre-clinical mouse model; studies looking at immunotherapy with PARPi are underway (NCT0257172).

4.9. Resistance to PARP inhibitors

Several putative mechanisms of resistance have been described. These include a secondary mutation in BRCA which either restores the correct open reading frame (i.e. where the original mutation caused a frameshift) or which fully reverts the original mutation to wild-type. This also causes platinum resistance and in one study of platinum resistance in BRCAm patients, 46% had acquired a secondary BRCA mutation [68]. Other mechanisms include upregulation of P-glycoprotein and loss of 53BP1 (which usually promotes NHEJ and prevents HR). Knowledge of the specific resistance mechanism may have clinical relevance as some (e.g. secondary mutations) cause platinum resistance too whereas others do not. Also, 53BP1 loss causes resistance in BRCA1 but not BRCA2 deficient tumours.

5. Immunotherapy in ovarian cancer

In 2003 Zhang and colleagues showed that the presence or absence of tumour-infiltrating lymphocytes (TILs) in EOC is an independent prognostic factor (in multivariate analysis) for PFS and OS. Of 174 patients, those with TILs had a median overall survival of 50.3 months compared to 18.0 months in the 72 patients without [69]. Tumour-associated antigens discovered in EOC include mesothelin, Her2, NY-ESO and ca125 amongst others [70].

Around 50% of EOC has genomic/epigenetic changes in genes implicated in HRD [45]. Therefore there is a subset of EOC with a higher mutational burden possibly more likely to benefit from immunotherapy. Analysis of TCGA data showed a significantly higher predicted neoantigen load in HRD vs. HR proficient tumours [71]. In addition, BRCA1/2 status and neoantigen load

were independent predictors of OS in multivariate analysis and BRCA mutated tumours had an increased TIL burden and PD-L1 expression. Lastly, tumour burden/volume is an important factor in predicting the response to immunotherapy [72]. Ovarian cancer is unusual as patients presenting *de novo* with bulky disease can be treated with radical surgery to no residual disease. Although the majority relapse, there is a window of time where disease remains undetectable. Given the data that exists on enhanced effectiveness of immunotherapy in patients with a low overall tumour burden, this may present a window of opportunity to maximise effectiveness of this therapeutic approach.

5.1. Checkpoint blockade

Co-inhibitory checkpoints usually act to minimize collateral tissue damage during immune-activation. Upregulation of these checkpoints can subvert anti-tumour immunity. The binding of CTLA-4 to B7.1/B7.2 is one such inhibitory interaction that can be prevented by the anti CTLA-4 monoclonal antibody ipilimumab.

In a phase I study including 2 patients with ovarian cancer, one patient had a 43% reduction in ca125 levels while the other developed a plateau in ca125 levels despite rapidly rising levels before treatment [73]. In a follow-up study of 9 patients one developed a radiologic PR with complete resolution of mesenteric lymphadenopathy. Three others achieved radiographic and ca125-defined stable disease of 2, 4 and >6 months duration. In a phase II study of 40 patients with recurrent platinum-sensitive EOC (NCT01611558), 50% developed at least G3 toxicity and the ORR was 10.9% by RECIST. A phase II trial testing a combination of nivolumab and ipilimumab for recurrent ovarian cancer is currently underway (NCT02498600).

A trial using another CTLA4 antagonist, tremelimumab, is currently enrolling patients for phase I trials in combination with olaparib (NCT02571725, NCT02485990).

Another inhibitory checkpoint interaction is between PD-1 (on T-cells) and PD-L1 (that may be upregulated on tumour cells and their microenvironment). Avelumab, a fully humanised IgG1 anti-PD-L1 antibody, was tested in a phase Ib trial in 124 patients with platinum resistant/refractory disease after a median of 4 lines of therapy [73, 74]. The drug was well tolerated with a grade 3/4 adverse event rate of 6.4%. ORR in this heavily pre-treated population was 9.7% and the relationship between germline BRCA status and probability of response is being investigated. Avelumab is currently being tested in two randomised phase III trials. The three-arm JAVELIN Ovarian 200 study (NCT02580058) is recruiting patients with their first platinum resistant/refractory relapse and randomising to either Avelumab or PLD alone or in combination. In JAVELIN Ovarian 100 (NCT02718417) patients with previously untreated III/IV ovarian cancer are randomised to carboplatin and paclitaxel followed by placebo or avelumab maintenance or carboplatin and paclitaxel with concurrent *and* maintenance avelumab.

Atezolizumab is also a fully humanized IgG1 anti-PD-L1 antibody. In the phase III ATALANTE trial (NCT02891824) patients with platinum-sensitive relapse are being randomised to platinum-based chemotherapy with concurrent and maintenance bevacizumab + placebo (control arm) or bevacizumab + avelumab (experimental arm). The combination of bevacizumab and avelumab is a rational one based on evidence that endogenous VEGF signalling has a variety

of immunomodulatory effects. VEGF-A has been postulated to suppress dendritic cell maturation, increase the presence of immunosuppressive CD34+ haematopoietic progenitor cells in the tumour microenvironment and inhibit T-cell maturation [75]. Another trial combining atezolizumab with bevacizumab (NCT02839707) in a phase II/III setting is randomising platinum resistant patients between 3 arms each containing PLD with either bevacizumab alone (control), atezolizumab alone or bevacizumab and atezolizumab.

Instead of targeting PD-L1, pembrolizumab is a humanized anti PD-1 antibody. Keynote-028 included 26 EOC patients. 1 patient had a CR and 2 had PR by RECIST. The median duration of response was not reached (range 24.9+ to 26.5+) [76]. There are currently several ongoing phase I/II trials with pembrolizumab both as monotherapy and in combination with chemotherapy, niraparib and various small molecule inhibitors in the frontline and recurrent settings (NCT02865811, NCT02520154, NCT02440425, NCT02674061).

Nivolumab, a PD-1 blocking antibody, was given to 20 patients with platinum resistant EOC. 40% of patients developed G3/4 toxicity (lymphopenia, anaemia, hypoalbuminaemia, maculopapular rash, fever, ALT increase). Three patients (15%) had an OR including 2 CRs. One of these was in a patient with clear cell carcinoma (often chemoresistant) and this response was ongoing at the time of study reporting [77]. As with the pembrolizumab data, although the ORR was modest, there was evidence of durable responses in both studies. Nivolumab is being studied in several ongoing trials including in combination with ipilimumab for (NCT02498600), in combination with bevacizumab (NCT02873962) and with a vaccine against the tumour-associated antigen WT1 (NCT02737787).

5.2. Adoptive T-cell therapy

Adoptive T-cell therapy (ATT) involves the direct administration of various types of anti-tumour T-cells to the patient. Given the prognostic value of TILs (see above), TIL-based ATT seems logical. In one study, 13 patients who had no residual disease after surgery and adjuvant therapy were treated with TIL infusion. A matched control group was followed up concurrently [78]. In this small study 3 year OS was 100% in the TIL group vs. 67.5% in the control group. TIL-based trials are ongoing (NCT02482090, NCT01883297). Another ATT approach involves using chimeric antigen receptor (CAR) T-cells that have been engineered to express a CAR with an extracellular single chain variable fragment incorporating immunoglobulin heavy and light chains capable of targeting any extracellular target (not just those complexed with MHC). There are currently over 20 trials registered on ClinicaTrials.gov testing CAR-T-cell-based therapy in ovarian cancer against targets including Her2, mesothelin, folate receptor- α (FR α) and NY-ESO-1.

5.3. Other approaches

The field of immunotherapy is advancing rapidly and various other approaches are in early phase trials. Vaccine based therapy has yielded objective responses demonstrating proof-of-concept, for example using a dendritic cell whole-tumour based approach [79]. Although clinical trials for vaccines have been disappointing, various techniques for optimisation are leading to renewed enthusiasm [80]. Another approach used a tri-functional antibody, catumaxomab,

which binds to epithelial cell adhesion molecule (EpCAM), CD3 (found on T-cells) and has an Fc portion that is recognised by various cells including macrophages. This allows immune cells to colocalize with tumour and cause cytotoxicity. EpCAM positive cells are found in 70–100% of malignant effusions and in a phase II study intraperitoneal (IP) administration of catumaxomab significantly improved the puncture free interval in heavily pre-treated patients [81]. It was given EMA approval for IP administration but the manufacturer withdrew this for commercial reasons in July 2017. One of the problems of ‘targeted’ immune therapy such as this is toxicity with systemic administration. Consequently, IP administration may be the only viable route with some therapies.

5.4. Combinations

Combination immune therapy PARP inhibitors, VEGF therapy and chemotherapy have already been mentioned. In addition, checkpoint inhibition has recently been combined with epacadostat, an inhibitor of 2,3-dioxygenase (IDO). IDO activation in tumours is associated with immune escape via T-cell dysfunction. Combining epacadostat and pembrolizumab has shown efficacy in patients with EOC although randomised trials are needed to ascertain the effect of epacadostat over and above pembrolizumab monotherapy [82].

6. Other novel agents

The aforementioned systemic strategies are of most relevance because they are either already in (or close to) the clinic. There are however various other strategies being explored, some of which have already been trialled in clinical studies. One approach involves targeting folate receptor and, specifically, the α isoform (FR α). This receptor is absent from normal ovarian epithelium but expressed on the majority of EOC [83]. The receptor has been targeted by various classes of therapy including folate-drug conjugates, small molecule FR α inhibitors, monoclonal antibodies, vaccines and oncolytic viruses. The phase III trial of vintafolide (folate conjugated with a derivative of vinblastine) in combination with PLD (NCT01170650) was discontinued for futility. Further trials of folate-drug conjugates are ongoing [84]. Farletuzumab, a monoclonal antibody that causes antibody and complement- dependant cellular cytotoxicity is being investigated in combination with platinum-based chemotherapy in patients with relapsed EOC and low ca125 following promising sub-group analysis from a previous phase III trial (NCT02289950). Phase I results for ONX-0801, a FR α -targeted thymidylate synthase inhibitor that accumulates in EOC cells generated a PR in 5/11 patients at the MTD with 4/4 FR α expressing tumours showing response [85].

Aside from FR α targeting therapy, there are multiple other targeted strategies in EOC in pre-clinical and early clinical phases. Cell cycle targeting with WEE-1 inhibition has been discussed but other strategies including CHK1/2 inhibition with prexasertib (which yielded a PR in 5/13 patients in cohort 1 of a recent phase II trial [86]) are being explored. PI3k/AKT/mTOR, Her2 and molecules in the apoptotic machinery are amongst a plethora of other avenues being explored. As our understanding of the molecular basis of EOC progresses, future

therapies are likely to employ biomarker or other selection criteria within trial protocols. For example, clear cell ovarian carcinoma is known to harbour mutations in the PI3K/AKT/mTOR pathway and the GOG-0268 trial of temsirolimus in addition to carboplatin/paclitaxel as first-line therapy was restricted to the clear cell population for this reason. Beyond the 'traditional' histological subtyping of EOC, analysis of TCGA data and recent advances in bioinformatics as led different groups to propose various molecular classifications of high grade serous EOC. Once such classification proposes four subtypes; mesenchymal, immunoreactive, differentiated and proliferative. Prospectively defined subgroup analysis of future trials using such novel molecular classifications may allow us to tailor therapy to maximise efficacy.

7. Conclusion

Several distinct strategies have been discussed. PARP inhibition have probably had the biggest clinical impact however mature OS data is awaited from many trials and further work is required to understand resistance and the potential role of combination therapy and sequencing of PARPi. Anti-angiogenic strategies have had a modest impact overall but research into patient selection may identify a subset who have more marked benefit. Similarly, with immunotherapy, the majority of patients do not show objective response but a subset has durable benefit. It seems, therefore that future success will depend on improved patient selection for trials, possibly through continued progress in understanding the molecular landscape of EOC. While progress has been made, there is a long way to go and the next few years should see continued incremental benefit in this difficult to treat disease.

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