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REVIEW

Treatment of patients with recurrent epithelial ovarian cancer for whom platinum is still an option

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Background: Ovarian cancer remains the most deadly gynecologic cancer with the majority of patients relapsing within 3 years of diagnosis. Traditional treatment paradigms linked to platinum sensitivity or resistance are currently being questioned in the setting of new diagnostic methods and treatment options.

Design: Authors carried out review of the literature on key topics in treatment of recurrent epithelial ovarian cancer (EOC) when platinum is still an option; including secondary surgical cytoreduction, chemotherapy, novel treatment options, and maintenance therapy. A treatment algorithm is proposed.

Results: Molecular characterization of EOC is critical to help guide treatment decisions. The role of secondary cytoreductive surgery is currently being evaluated with results from Gynecologic Oncology Group (GOG) 213 and anticipated results from DESKTOP III clinical trials. Chemotherapy backbone has remained relatively unchanged but utilizing non-platinum-based regimens is under investigation. In addition, maintenance therapy with anti-angiogenic therapy and Poly (ADP-ribose) Polymerase (PARP) inhibitors has emerged as the standard of care. Novel combinations, including immunotherapy and anti-angiogenesis agents, may further change the current landscape.

Conclusions: The treatment of recurrent EOC is rapidly changing. Clinical trial design will need to continue to evolve as many novel therapies move to the upfront setting. Ultimately, the treatment of patients with recurrent EOC must incorporate individual patient and tumor factors.

Key words: ovarian cancer, platinum, maintenance therapy, molecular characterization

Introduction

Epithelial ovarian cancer (EOC) remains the most deadly cancer of the female genital tract with ~22 000 new cases and 14 000 deaths expected in 2018 in the USA [1]. While an initial disease-free interval is achieved in many patients, most will eventually relapse. This treatment free interval (TFI) has traditionally labeled patients as either platinum sensitive (relapse ≥6 months since last platinum agent) or platinum resistant (relapse <6 months since last platinum agent). While we understand that length of TFI from last platinum (TFIp) does correlate with response to subsequent platinum-based chemotherapy, this classification system likely needs adaptation as our understanding of EOC develops.

Alvarez et al. challenged this classic paradigm. They proposed a multi-step classification system based on two primary principles. First, EOC surveillance is not standardized. The utilization of CA-125 monitoring and more advanced imaging techniques allows for detection of recurrence sooner than traditional physical exam/symptom surveillance. Patients that would have previously been deemed platinum sensitive may now fall into the platinum resistant category and be excluded from further platinum therapy or clinical trials based merely on earlier identification of disease recurrence. Secondly, improved molecular understanding of the pathogenesis of EOC has altered the understanding of response to platinum-based chemotherapy and newer targeted therapies [2].

With these factors in mind, the classic rigid paradigm no longer seems applicable to patients with a platinum sensitive recurrence. With this in mind, the Gynecologic Cancer Intergroup proposed utilizing new nomenclature to describe patients in their disease course which will be utilized in this review [3]. Patients will be defined by their TFI from last platinum (TFIp), from last non-platinum (TFInp), or biologic agent (TFIb). Patients are subsequently characterized as those for whom platinum re-treatment is an option and those for whom it is not. In this article, we review the recent data on secondary cytoreductive surgery (CRS), molecular characterization and applications to treatment, agents for treatment of recurrent EOC for whom platinum is an option and evidence for maintenance therapy following treatment and finally, a discussion of the challenges in developing new treatment strategies given recent and ongoing clinical trial activity in front line therapy.

Secondary cytoreductive surgery

In a patient with first recurrence, one of the initial questions is whether additional surgical intervention is warranted. Multiple retrospective cohort studies have shown increased survival if optimal CRS is achieved [4–7]. Data to inform patient selection for secondary CRS were presented in the original DESKTOP OVAR trial (Descriptive evaluation of Preoperative Selection Kirteria for Operability in Recurrent Ovarian Cancer). This multi-institutional retrospective cohort study analyzed demographic, surgical, and treatment variables in 267 patients. Patients with completely resected tumors had significantly longer overall survival (OS) (45.2 versus 19.7 months). The size of residual tumor impacted OS and factors independently associated with complete resection were Eastern Cooperative Oncology Group performance status (PS) of 0, no residual tumor following initial surgery, and ascites <500 ml [5].

DESKTOP II prospectively validated the score developed in the first trial and predicted complete resection in 75% of patients who were score 'positive' [5, 8]. DESKTOP III, randomized patients with a 'positive' score to either second line chemotherapy alone or CRS followed by chemotherapy. OS data are still immature but progression free survival (PFS) was improved in those patients who underwent surgery (19.6 versus 14 months; hazard ratio (HR): 0.66 CI 0.52–0.83 $P < 0.0001$). In addition, 72% of patients achieved complete resection with acceptable toxicity in both arms [9]. Gynecologic Oncology Group (GOG) protocol 213, had two primary objectives [10]. The first assessed the impact of bevacizumab administered concomitantly with paclitaxel and carboplatin as well as in maintenance on OS (primary end point) among patients with one prior line of treatment. The second evaluated the impact of secondary CRS on OS in this same cohort. Patients who were deemed appropriate for secondary CRS were randomized to surgery followed by chemotherapy versus chemotherapy alone. Eligibility included a complete response (CR) to front line chemotherapy, no evidence of bowel obstruction, or need for parenteral nutrition and no evidence of carcinomatosis or parenchymal organ disease that was felt to be unresectable. Complete resection was achieved in 67% of patients. Despite this high level of complete resection, OS was, in fact, negatively impacted by secondary CRS with a median of 53.6 versus 65.7 months (HR = 1.28; 0.92–1.78) in favor of no surgery [11]. Subgroup analysis of GOG 213 patients with oligometastatic disease also found no benefit from resection [12].

While the final OS results from DESKTOP III are pending, the results of the two studies are thus far very consistent when comparing PFS. In GOG 213, the median PFS of the completely resected patients versus those patients who underwent no surgery was 21.4 versus 16.5 months (HR = 0.68; 0.51–0.90)—very similar to that reported in DESKTOP III. In both trials, target lesions were resected in the surgery arm making PFS difficult to interpret. The OS findings from DESKTOP III are therefore of critical importance, for if they confirm the surgical end points of GOG 213, recommendations for secondary CRS in this setting may be abandoned.

Molecular characterization

Role of tumor profiling

Tumor profiling ideally identifies molecular alterations that can be therapeutically manipulated to induce an anticancer effect. These actionable mutations can be identified with next generation sequencing or immunohistochemistry among other techniques. The challenge in solid tumors, in general, and in EOC specifically, is pinpointing the driver mutations, which are critical to successful application of targeted therapies. Additional challenges include spatial and temporal tumor heterogeneity, redundant pathways, and a relatively low identification of molecular alterations that have an available, regulatory-approved, and clinically validated therapeutic agents.

BRCA identification

Clearly, the best current example of tailored therapy selection for EOC has been the therapeutic effect demonstrated with poly (ADP-ribose) polymerase inhibitors (PARPi) in patients with germline or somatic *BRCA (g or s BRCA)* mutations. *BRCA* testing is recommended for all patients with EOC, and this information can trigger cascade testing in relatives, provide important prognostic information for patients, and inform treatment planning. Currently, most clinicians are performing germline testing, but there is growing interest in tumor testing with reflexing to germline determination. This approach may help us focus germline testing; however, current tumor testing for *BRCA* is less reliable than germline testing and the presence of reversion mutations may lead to false negatives [13]. The utility and uptake of tumor testing and high throughput panel testing will continue to grow as additional targeted agents are developed that depend upon specific genetic alterations beyond just *BRCA* mutations. With the recent publication of SOLO-1 demonstrating an unprecedented improvement in PFS with use of the PARPi, olaparib following front line platinum-based induction chemotherapy among patients with *g* or s*BRCA* mutation, the imperative to identify *BRCA* mutations close to the time of diagnosis will become standard of care so this molecular characterization should be known for recurrent EOC in the future [14].

Table 1. Summary of randomized trials on chemotherapy backbone

Trial	Treatment	RR (%)	PFS (months)	HR	OS (months)	HR
ICON4/AGO-OVAR-2.2 [81] *(n = 802)*	Carboplatin or cisplatin	54	10	0.76 $P = 0.0004$	24	0.82 $P = 0.02$
	Carboplatin or cisplatin + paclitaxel	66	13		29	
Pfisterer et al. [82] *(n = 356)*	Carboplatin	31	6	0.72 $P = 0.0031$	17	0.96 $P = 0.7349$
	Carboplatin + gemcitabine	47	9		18	
CALYPSO [83] *(n = 976)*	Carboplatin + pegylated Liposomal doxorubicin	–	11	0.821 $P = 0.005$	31	0.99 $P = 0.94$
	Carboplatin + paclitaxel	–	9		33	

RR, objective response rate; PFS, progression free survival; HR, hazard ratio; OS, overall survival.

Homologous recombination deficiency status

An important concept discovered during the development of PARPi was that there are genetic or epigenetic alterations other than *BRCA* that confer sensitivity to PARPi and that prevent high fidelity double strand DNA break repair via homologous recombination.

Understanding homologous recombination deficiency (HRD) status may potentially prioritize between competing PARPi and non-PARPi regimens. For example, one current clinical quandary is whether to use a PARPi or bevacizumab as maintenance therapy in the patients with recurrent EOC for whom induction platinum is an option. The surprising finding across all PARPi maintenance trials (discussed below) is that there is a statistically significant treatment effect in those who are *BRCA* wild type and HRD negative. Nonetheless, the magnitude of effect is not nearly as sizeable as seen for the *BRCA* or HRD+ cohorts, which calls to question whether other strategies potentially would be superior for patients who lack demonstrable DNA repair deficiencies.

Currently, the only validated biomarker for patient selection of PARPi is germline or somatic *BRCA*. This may change as results of ongoing studies evaluate alternative biomarkers.

Options for treatment

Chemotherapy backbone

The standard of care for patients with recurrent EOC for whom platinum is an option has been a platinum-containing regimen. When considering which chemotherapy backbone to use, there are four options with differences in schedule, toxicity profile, and in the case of single agent versus doublet chemotherapy, efficacy. These are summarized in Table 1.

Substitution of other standard cytotoxics does not provide superior or even equivalent oncologic outcomes when compared with platinum-based regimens. This concept was demonstrated in MITO 8, a study of patients with TFIp of 6–12 months who were randomized to platinum-based chemotherapy versus non-platinum-based chemotherapy with an end point of OS which found no improvement in OS by delaying platinum-based therapy (21.8 versus 24.5 months; HR = 1.38; 95% CI 0.99–1.94; $P = 0.06$) [15].

The combination of pegylated liposomal doxorubicin (PLD) and trabectedin, a novel cytotoxic derived from the marine tunicate *Ecteinascidia Turbinatanata,* that acts as a DNA minor groove binder that leads to double strand DNA breaks, has been studied as a platinum-based substitution in patients with a TFIp of 6–12 months [16–18]. An improvement of PFS of 4 months of PLD alone was seen [19]. The phase III ORCHYD trial evaluated the efficacy of trabectedin and PLD versus PLD in patients with PSR EOC in the third line (NCT01846611). This study was closed early for futility and results have not yet been presented. The results of the INOVATYON trial (NCT01379989) are still awaited. This is a phase III randomized trial in patients with TFIp of 6–12 months to trabectedin and PLD versus carboplatin and PLD.

Maintenance therapy

Continuance of some form of active therapy in patients demonstrating a response to induction therapy is highly desired since eventual progression is an expected vicissitude [20]. Several agents and strategies have been reported, including anti-angiogenics (AA) and PARPi, which have provided strong evidence of a treatment effect. Studies evaluating immune-oncology agents such as anti-programmed cell death protein-1 (PD-1) or anti-programmed cell death ligand-1 (PD-L1) are ongoing.

There are essentially two broad concepts of maintenance therapy: secondary maintenance and switch maintenance. Fundamentally, these terms could apply to maintenance treatment in the primary setting as well. Studies that are evaluating secondary maintenance are generally designed as a treatment combination, commonly chemotherapy and a biologic, where one or more agents, but not the induction regimen, is continued until progression or some defined duration of therapy [10, 21, 22]. In contrast, switch maintenance therapy involves a therapy that is new to the treatment plan following a desired response to induction therapy. An example would be administration of a novel agent following treatment with 4–6 cycles of platinum-based chemotherapy [23–26]. In addition, many maintenance trials allow for the initiation of a maintenance regimen after both

Table 2. Summary of randomized trials with maintenance anti-angiogenesis therapy in platinum sensitive EOC

Trial	Treatment	RR (%)	PFS (months)	HR	OS (months)	HR
TRINOVA-1 [42]	Paclitaxel weekly	–	5.6	0.66 Subgroup 95%	–	–
(*n* = 435[a])	Paclitaxel weekly + trebananib	–	7.6	CI 0.52–0.84	–	
OCEANS [21]	Gemcitabine + carboplatin	57	8.4	0.48 $P < 0.0001$	33.6	0.96 $P = 0.65$
(*n* = 484)	Gemcitabine + carboplatin + bevacizumab	79	12.4		32.9	
GOG 213 [10]	Paclitaxel + carboplatin	59	10.4	0.61 $P < 0.0001$	37.3	0.82 $P = 0.045$
(*n* = 674)	Paclitaxel + carboplatin + bevacizumab	79	13.8		42.2	
ICON6 [22]	Platinum + paclitaxel	–	8.7	0.67 $P = 0.0003$	21.0	
(*n* = 456)	Chemotherapy + concurrent cediranib	–	9.9		25.0	
	Chemotherapy + cediranib + maintenance cediranib	–	11.0	0.56 $P < 0.0001$	26.3	0.77 $P = 0.11$
AGO-OVAR 2.21 [43]	Gemcitabine + carboplatin + bevacizumab	–	11.7	0.807 $P = 0.0128$	28.2	0.833 $P = 0.787$
(*n* = 682)	Pegylated liposomal doxorubicin + carboplatin + bevacizumab	–	13.3		33.5	

EOC, epithelial ovarian cancer; RR, objective response rate; PFS, progression free survival; HR, hazard ratio; OS, overall survival; PFI, platinum free interval.
[a]Platinum sensitive (PFI 6–12 months).

a CR and 'partial' response (PR). This arguably is a 'switch' of therapeutic strategies after a PR and not a maintenance therapy by the purest definitions. Since most patients in this setting ultimately develop progressive disease, continuance of treatment to progression or unacceptable toxicity is often prescribed. Utilization of this trial design mandates the incorporation of OS end points to help elucidate true benefit from this strategy.

The anti-angiogenesis strategy. The relationship between factors driving the development of tumor-associated vasculature and outcomes in EOC has been well documented [27–41]. Table 2 outlines the AA agents that have undergone formal evaluation in large prospective randomized trials [10, 21, 22, 42, 43]. As can be seen, agents targeting the vascular endothelial growth factor (VEGF) isoforms (e.g. bevacizumab) or its receptors (e.g. cediranib) have undergone the most intensive investigation.

The remaining trial evaluating trebananib evaluated this novel AA agent as a secondary maintenance strategy—that is, once chemotherapy induction was complete, continuance on the AA agent was assessed for survival end points [42].

Recently, a direct comparison of carboplatin, bevacizumab (concurrent and maintenance) with either gemcitabine or PLD demonstrated superior PFS of 11.7 versus 13.3 months respectively (HR = 0.807; 95% CI 0.681–0.956; $P = 0.0128$) and a trend towards improvement in OS (HR = 0.833; 95% CI 0.680–1.022) for the PLD doublet [43]. These data support prioritization of a PLD/carboplatin backbone when a bevacizumab based approach is selected in recurrent EOC when platinum is an option.

The PARPi strategy. There are currently five PARP inhibitors in use or under study in EOC: olaparib, niraparib, rucaparib, talazoparib, and veliparib. PARPi are under investigation both as monotherapy treatment in the recurrent setting as well as under study and approved as switch maintenance. The results from three randomized phase III (NOVA, SOLO2, ARIEL3) trials and one phase II (Study 19) trial are surprisingly consistent when looking at PARPi in the switch maintenance setting [23–26]. However, significant differences in trial design, eligibility, patient populations, and assessment techniques distinguish them (Table 3). Each of these trials follows a placebo-controlled, switch maintenance design, in which eligible patients are first treated with a platinum-based induction regimen, and if they demonstrate a response, they are randomized to PARPi versus placebo. Notably, patients with a best response of stable disease to induction chemotherapy were not included in these studies whereas they were included in studies of bevacizumab. Similar to the trial designs mentioned above for secondary maintenance, response to induction therapy in these trials did not need to be complete before randomization.

Unique to ARIEL3, ORR was collected from those patients entering the trial with measurable disease in each of the step-down cohorts. As might have been expected, patients with g or s*BRCA* cancers achieved further response (38%) when treated with rucaparib [26].

Review of these secondary versus switch maintenance and the outcomes from well-controlled phase III clinical trials suggest that both have merit in patients with recurrent EOC for whom platinum is an option. Only one trial to date has demonstrated an OS advantage (GOG-0213) and the current availability of both classes of agents will challenge attaining this goal in subsequent trials due to crossover. Ongoing trials are looking into combinations of both AA agents and PARPi as maintenance strategies and others will assess the impact of either or both of these agents in combination with various immune-oncology agents such as anti PD-1/PD-L1 or CTLA-4 inhibitors. For example, ICON 9 (NCT03278717) is a randomized phase III trial of recurrent EOC for whom platinum is an option. This study randomizes patients who have had a PR or CR platinum-based chemotherapy to either olaparib alone or olaparib plus cedirinib. The primary end point is PFS with secondary end points to include OS, safety, health

Table 3. Summary of randomized switch maintenance clinical trials in patients receiving PARP inhibitors for recurrent platinum sensitive EOC

PFS (inv review—primary)	Rucaparib	Placebo	HR	*P*
sBRCA	16.8 months	5.4 months	0.23	$P < 0.0001$
sBRCA + HRD	13.6 months	5.4 months	0.32	$P < 0.0001$
ITT	10.8 months	5.4 months	0.37	$P < 0.0001$
PFS (BICR—primary)	**Niraparib**	**Placebo**	**HR**	***P***
sBRCA	21.0 months	5.5 months	0.26	$P < 0.0001$
sBRCA + HRD	NA	NA	NA	
All non-*gBRCA* (*sBRCA*+ HRD + HRC)	9.3 months	3.9 months	0.45	$P < 0.001$
ITT (FDA analysis)	11.3 months	4.7 months	0.42	Not Given
PFS (inv review—primary)	**Olaparib**	**Placebo**	**HR**	***P***
SOLO-2—*gBRCA*	19.1 months	5.5 months	0.30	$P < 0.0001$
Study 19—ITT	8.4 months	4.8 months	0.35	$P < 0.0001$
Study 19—*gBRCA*	11.2 months	4.3 months	0.18	$P < 0.0001$

EOC, epithelial ovarian cancer; *sBRCA*, somatic *BRCA* mutation; *gBRCA*, germline *BRCA* mutation; HR, hazard ratio; HRD, homologous recombination deficiency; HRC, homologous recombination compliant; ITT, intent-to-treat; BICR, blinded independent central review (imaging and clinical); NA, not applicable.

related quality of life and PFS2. Stratification includes HRD but eligibility is not biomarker based.

The immune-oncology strategy. For now, a bevacizumab-containing regimen or PARPi represents new standards of care for patients with recurrent EOC for whom platinum remains an option with improved PFS (both) and OS (bevacizumab). The challenge remains to further improve PFS and OS outcomes among a broader biomarker population of EOC patients. Immunotherapy appears potentially promising, but the ideal sequencing and combinations of immunotherapy with chemotherapy and other novel agents have yet to be determined.

Evasion of immune surveillance is one of the established hallmarks of cancer [44, 45]. EOC is a valid potential target for immuno-oncology agents given that over 50% of patients have tumor infiltrating lymphocytes (TILs) at the time of diagnosis and the presence or absence of TILs is prognostic [46]. EOC also carries a significant mutational load [47]; however, we see a very modest response seen to immune checkpoint inhibitors thus far, with response rates from 11% to 25%, when used as a single agent in the recurrent, platinum resistant setting [48–50].

Combinations of immune checkpoint inhibitors with other agents are likely to improve the efficacy and durability of responses seen with monotherapy use of any tested agent. Rational combination partners with immune checkpoint inhibitors include molecules that cause DNA damage, chemotherapy, and AA agents.

Chemotherapy combined with an immune checkpoint inhibitor capitalizes on the complimentary effects on the immune system imparted by each component. Chemotherapy alone may modulate dendritic cells, enhance MHC1 presentation on tumor cells, and lead to immunogenic cell death. In addition, studies have demonstrated that the percentage of TILS increased in immunocompetent mouse models when treated with both platinum and taxane agents [51, 52].

Table 4. Summary of randomized of clinical trials in women receiving PARP inhibitors for recurrent Platinum sensitive EOC

	ORR (%)	PFS (months)
Rucaparib		
Study 10 [65]	59.5	NA
ITT		
ARIEL 2 [67]		12.8
BRCAmut	80	
LOH High	29	5.7
LOH Low	10	5.2
Niraparib		
Phase 1 [24]		NA
BRCAmut	40 (50 in PSen)	
BRCAwt	16 (33 in PSen)	
Quadra II [68]		
BRCAmut	39	NA
BRCAwt	21	
Olaparib		
Study 42 [84]	34 (46 in PSen)	6.7 (9.4 in PSen)
Velaparib		
Coleman et al. [72]	26 (35 in PSen)	8.2

EOC, epithelial ovarian cancer; *BRCAmut*, somatic or germline *BRCA* mutation; *BRCAwt*, *BRCA* wild type; LOH, loss of heterozygosity; ITT, intent-to-treat; ORR, objective response rate; PFS, progression free survival; PSen: platinum sensitive); NA, not applicable.

There is mechanistic rationale for combining AA with immunotherapy. VEGF is a highly immunosuppressive molecule with both direct and indirect inhibition of T-cell function, stimulation of regulatory T-cells, inhibition of dendritic function, and induction of abnormal tumor vasculature which decreases tumor

T-cell trafficking [44, 53–57]. There is already demonstration of the safety and efficacy for this combination in non-squamous, non-small-cell lung cancer (NSCLC). In the IMpower150 study, patients with chemotherapy naïve, stage IV or recurrent non-squamous NSCLC were randomized to carboplatin, paclitaxel, and atezolizumab followed by atezolizumab maintenance, the same plus bevacizumab with and following chemotherapy versus carboplatin, paclitaxel and bevacizumab followed by bevacizumab maintenance. In comparing the second two arms, the PFS favored combination atezolizumab and bevacizumab (HR = 0.617; 0.517–0.737; $P < 0.0001$) as did the OS (HR = 0.780; 0.636–0.956; $P = 0.0164$). Patients were allowed to participate regardless of PD-L1 status and all patients showed benefit, but subset analysis of those with higher PD-L1 benefited more (HR = 0.44 for PD-L1 high, 0.50 for PD-L1 low, and 0.77 for PD-L1 negative) [58]. ATALANTE (GINECO-OV236b/NCT 02891824) is a phase III randomized trial enrolling patients with recurrent EOC and randomizes to platinum-based chemotherapy, bevacizumab, and placebo followed by bevacizumab and placebo maintenance versus platinum-based chemotherapy, bevacizumab and atezolizumab followed by bevacizumab and atezolizumab maintenance until progression. The primary end point is PFS with secondary end points inclusive of time to second subsequent therapy or death, OS, and safety. This study is actively accruing patients and results are expected in 2023.

Combination of PARPi and chemotherapy

Combinations of PARPi and chemotherapy have proved challenging with dose modifications required on both sides. Oza reported on the combination of paclitaxel and carboplatin with olaparib compared with chemotherapy alone in the PSR setting. Overlapping toxicity of myelosuppression required dose reduction of the carboplatin to AUC4 and olaparib to 200 mg b.i.d. (capsule formulation). This randomized phase II trial demonstrated no significant difference in ORR based on the addition of olaparib to chemotherapy; however, there was a clear improvement in PFS for maintenance olaparib versus placebo supporting development of olaparib for switch maintenance [59]. Even single agent chemotherapy combinations with PARP inhibition has proven difficult, as significant bone marrow toxicity was observed limiting adequate doses of either the PARPi or the cytotoxic chemotherapy [60–63].

Non-cytotoxic treatments instead of platinum

A number of PARPi have been evaluated as monotherapy treatment in recurrent EOC. In this setting, indications have been specific to patients harboring g or s *BRCA* mutations. Table 4 outlines the various trials investigating PARPi in recurrent EOC. Olaparib was the first PARPi to obtain approval in g*BRCA* EOC with ≥3 lines of therapy. This was based on a phase II study which demonstrated a 33% ORR ($n = 137$) and a 45% ORR among PS EOC. Importantly, 56% of patients were progression free at 6 months [64].

Based on data from two large open label trials (Study 10 and ARIEL2) in recurrent EOC, rucaparib was the second PARPi to receive an indication in recurrent EOC [65–67]. This approval was in patients with ≥2 prior therapies in the setting of either g or s *BRCA*. In the integrated analysis of both trials, rucaparib achieved an ORR of 54% [66]. ARIEL2 was designed to identify and curate the cut-off of the test to identify a set of 'BRCA-like' tumors that garnered more benefit from PARPi compared with *BRCAwt* tumors. Tumors identified as 'BRCA-like' achieved ORR of 30% and a median PFS of 7.1 months, indicating success of the test to predict efficacy. This test was then used to stratify patients in the ARIEL-3 maintenance study noted above [67].

The phase II QUADRA study (open label, single arm) enrolled 463 patients evaluating niraparib (300 mg po qd) until progression in patients with relapsed EOC who have received ≥3 prior regimens. The primary end point for this study was overall response rate (ORR) among EOC patients who were HRD+ and for whom platinum therapy was still an option. This study demonstrated the efficacy of monotherapy nirparib in heavily pretreated, HRD+ recurrent EOC with ORR of 29% and duration of response (DOR) was 9.2 months [68].

The unanswered question is the performance of PARPi compared with platinum-based chemotherapy in a patient for whom platinum therapy is still an option. A randomized phase II trial of single agent olaparib compared with PLD in g*BRCA* mutated EOC demonstrated superior ORR but no difference in PFS. The trial did not meet the primary end point of superiority, which was unexpected, but this is postulated to be due to higher than expected efficacy of PLD in g*BRCA* EOC [69]. There are two ongoing studies of PARPi monotherapy compared with physician's choice chemotherapy, SOLO3 (olaparib), and ARIEL4 (rucaparib) (NCT02282020, NCT02855944).

Across a number of targeted therapies, there are growing data to indicate that single agents will not be adequate to achieve durable efficacy. PARP inhibition is no exception given the existence of innate, acquired, and adaptive resistance to therapy [70]. Certainly, there are a proportion of tumors with g or *BRCA* mutation that do not respond to PARPi. Further, the median DOR to PARPi when used as monotherapy, even in *BRCA* tumors, is ∼8 months [64, 67, 71, 72]. This supports the development of adaptive resistance to PARPi. Thus, the exploration of combination therapies with PARP inhibition has been of great interest.

The combination of PARPi with AA therapies developed out of the concept that synthetic lethality may occur in the tumor microenvironment when hypoxia from AA therapy leads to development of HRD [73]. This would provide a mechanism of sensitivity to PARPi outside of the presence of *BRCA* mutation. Phase I studies of PARPi have been successfully completed with bevacizumab and cediranib [73, 74]. A phase II study of olaparib and cediranib compared with olaparib alone demonstrated improved PFS in the combination arm (17.7 versus 9.0 months) irrespective of *BRCA* mutational status with the benefit of combination therapy greatest in the *BRCAwt* status cohorts [75]. A randomized phase II trial (OTOVA, NCT03117933) is comparing weekly taxol versus olaparib versus olaparib/cediranib in platinum resistant EOC; however, this includes patients with TFIp of <12 months. Phase III trials in two settings have launched to assess this combination: (i) NRG-GY004 recurrent EOC compared with standard platinum-based chemotherapy and (ii) NRG-GY005 recurrent EOC compared with physician's choice chemotherapy for patients in which platinum is no longer an option (NCT02446600; NCT02889900). The combination of olaparib and bevacizumab was explored in a phase I trial which

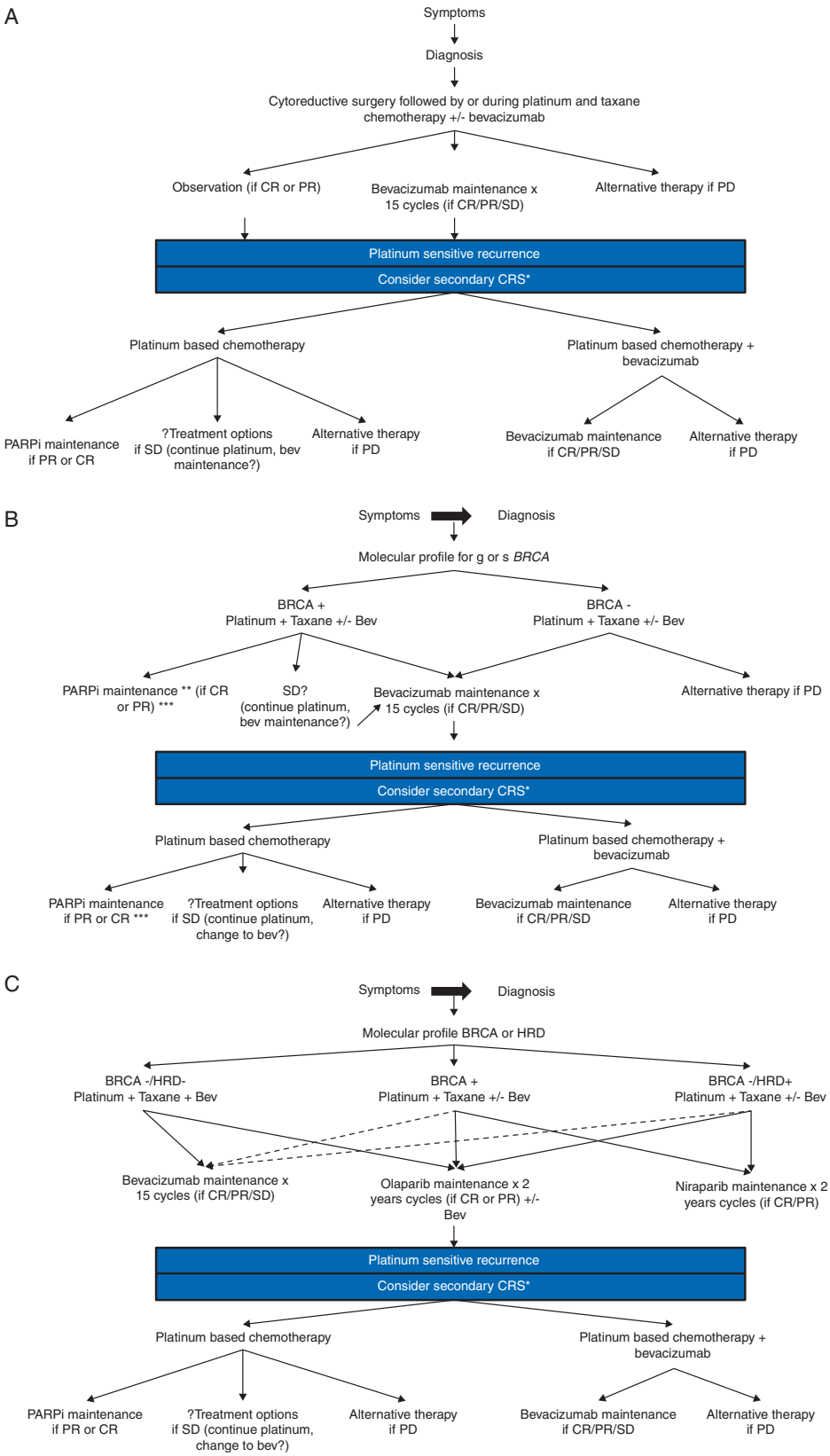

Figure 1. Treatment algorithm for patients diagnosed with epithelial ovarian cancer. CR, complete response; PR, partial response; SD, stable disease; CRS, cytoreductive surgery; Bev, bevacizumab. (A) Current treatment algorithm. (B) Algorithm incorporating results of SOLO-1. (C) Hypothetical algorithm incorporating the potential positive results of PRIMA and PAOLA-1.*Controversial, see text. **At the time of publication Olaparib is the only approved PARPi for this indication. ***preferred method if BRCA positive. Solid lines, preferred treatment option, dashed lines, allowable treatment option.

demonstrated acceptable toxicity and promising efficacy [73]. This combination is being explored in the first line maintenance setting in the PAOLA-1 trial (NCT02477644). Rucaparib in combination with bevacizumab as a maintenance strategy is also being investigated in a phase I followed by a randomized phase II trial of upfront ovarian cancer in MITO25 (NCT03462212).Niraparib has also been successfully combined with bevacizumab in a phase I trial. Impressively, this combination achieved a 50% response rate [76]. The AVANOVA2 trial (NCT02354131) will assess the impact on PFS of three options: (i) niraparib alone, (ii) combination of bevacizumab and niraparib, and (iii) sequential bevacizumab followed by niraparib all in patients with recurrent disease for whom platinum is still an option. This study is still recruiting patients at the time of this publication.

As described previously, combinations of immune-oncology agents (anti PD-1 and PD-L1 currently) with either PARPi or AA agents are of great interest as maintenance strategies or as doublet (or triplet) therapies, and studies are under way to best evaluate how and when to use these combinations.

Discussion

Conclusions

In summary, the landscape of treatment options for patients with recurrent EOC is changing. First, the role for secondary CRS is in question given the recent data from GOG 213. As we await mature data from DESKTOP III we must carefully contemplate the role surgery plays in this patient population.

Secondly, while our chemotherapy backbone has remained relatively unchanged for the past decade, newer therapies both as maintenance following and instead of traditional cytotoxic therapy are being developed. Indications may be specific to molecular or genetic subsets of patients; therefore, molecular and genetic profiling should be confirmed at the time of recurrent disease but ideally identified at time of diagnosis. When discussing maintenance therapy in the recurrent setting following induction platinum-based therapy, both AA and PARPi are viable options; however, as the indications for use of these agents in primary treatment changes, so will their use in recurrent disease. For example, the FDA recently approved the use of bevacizumab in upfront EOC. While we now have data for use of bevacizumab in multiple treatment lines, we must still consider how its routine use in upfront treatment may alter our decision to incorporate it into later lines [77] (Figure 1A). Similarly, the positive results of SOLO1 and recent FDA approval of Olaparib maitenance in *gBRCA* patients in the upfront setting will change the standard of care for *gBRCA* patients and may impact how we consider treatment of those who do later recur [78, 79]. Unlike bevacizumab, there is not yet data for re-treatment with a PARPi after prior exposure and therefore, selection of treatment plans in the setting of recurrence may be complicated (Figure 1B). Does it make sense to re-use a PARPi in the setting of prior maintenance use if (i) a patient recurred remote from use of the PARPi or (ii) recurred while taking the PARPi? Is there a difference? The ongoing OReO trial (NCT03106987) will attempt to address this question. This is a randomized phase III trial, which enrolls patients who have progressed or relapsed following PARPi maintenance have responded to platinum-based therapy and are then randomized to olaparib or placebo maintenance. With the current landscape, the sequence and combination of treatments will need to be individualized. Figure 1B attempts to help readers weigh the possible options. For BRCA positive patients, the authors recommend PARPi maintenance in the absence of previous PARPi therapy. Beyond this, patient clinical factors (e.g. disease distribution, patient performance status, ongoing toxicities, etc.), molecular profile, and previous treatments must be taken into account when choosing optimal treatment.

Finally, as molecular understanding of EOC continues to progress, so will the development of new therapeutics. For example, immune modulators including PD-1/PD-L1 inhibitors are currently under investigation and will likely play a role in treatment of recurrent EOC. While JAVELIN Ovarian 100 (a phase III RTC of chemotherapy naïve advanced EOC comparing chemotherapy versus chemotherapy followed by avelumab maintenance versus chemotherapy plus avelumab plus avelumab maintenance for up to 2 years) was terminated early at a planned interim analysis for failure to meet its primary end point, multiple studies combining immune modulators in both the upfront and recurrent setting are still under way [80]. In this changing landscape, we can no longer base treatment decisions solely on the traditional paradigm of 'platinum sensitive' versus 'platinum resistant'. A multistep treatment approach that incorporates multiple patient factors including molecular and genetic profiles will be necessary as we advance the care of patients with recurrent EOC. A lack of understanding of the most appropriate sequence of many of these therapeutics remains. As in a biomarker agnostic setting, how will clinicians choose which targeted agent to add to front line chemotherapy to obtain highest benefit and how will this impact what is selected at the time of recurrence? While the results of JAVELIN Ovarian 100 were negative, PRIMA (NCT02655016) and PAOLA-1 (NCT02477644), which, if positive, will dramatically change both front line and recurrent treatment paradigms. PRIMA is a randomized phase III trial evaluating niraparib switch maintenance following front line platinum-based chemotherapy among those patients with a response. The primary end point is PFS. PAOLA-1 is a randomized phase III trial that enrolled patients following response to front line platinum-based chemotherapy containing bevacizumab and randomized them to receive continued bevacizumab maintenance plus placebo versus bevacizumab and olaparib maintenance. The end point here is PFS and the primary assessment will be in the intent-to-treat population. In addition to these, in the recurrent setting, NRG-GY004 is expected to report as well and will provide the first analysis of PARPi versus chemotherapy. If all of these studies meet their primary end points, the treatment paradigm for patients with recurrent EOC becomes very complicated (Figure 1C).

Moving forward, clinical trial design will be imperative. Traditional drug development has started in the 'platinum resistant' (PR) patient population and sequentially progressed to the 'platinum sensitive' (PS) and then eventually upfront settings; however, in the era of new targeted therapies and novel trial design utilizing molecular characteristics, this traditional paradigm may not always be necessary. Table 5 illustrates PFS and HR for

Table 5. PFS and HR of bevacizumab and olaparib in sequential ovarian cancer patient populations

	Platinum resistant	Platinum sensitive	Upfront
Bevacizumab	*AURELIA* [85]	*GOG 213* [10]	*GOG 218* [86]
PFS	3.4 versus 6.7 months	10.4 versus 13.8 months	11.2 versus 14.1 months
HR	0.42 (0.32–0.53 $P < 0.001$)	0.628 (0.534–0.739 $P < 0.0001$)	0.908 (0.795–1.040 $P = 0.16$)
Olaparib	Study 42 [84]	SOLO 2 [25]	SOLO 1 [78]
PFS	6.7 months	19.1 versus 5.5 months	Not Reached versus 13.8 months
HR	*NA*	0.30 (0.22–0.41 $P < 0.0001$)	0.30 (0.23–0.41 $P > 0.0001$)

PFS, progression free survival; HR, hazard ratio; GOG, Gynecologic Oncology Group; NA, not applicable.

Table 6. Current platinum sensitive studies

Name	*N*	Population	Arms	Primary end point	NCT
AGO-OVAR 2.21 ENGOT ov18	682	PFI > 6 months	Gem/carbo/bev versus PLD/carbo/bev	PFS	NCT01837251
INOVATYON	618	PFI 6–12 months, 1–2 priors	PLD 30 mg/m^2 / carbo AUC 5 versus PLD 30 mg/m^2 / trabectedin 1.1 mg/m^2 q 21 days	OS	NCT01379989
MITO 23/ENGOT Ov-32	244	Recurrent EOC with BRCA or BRCAness	PC chemo versus trabectedin 1.3 mg/mg d1 q 21 days	OS	NCT02903004
ICON9	618	1st recurrence, PFI > 6 months, CR or PR to induction therapy	Olaparib 300 mg b.i.d. + cediranib 20 mg qd versus olaparib 300 mg po b.i.d.	PFS and OS	NCT03278717
AVANOVA part 2	103	PFI > 6 months	Niraparib versus niraparib + bevacizumab	PFS	NCT02354131
AVANOVA part 3	72	PFI > 6 months	Niraparib + bev + TSR042	PFS	Pending
ATALANTE	405	PFI > 6 months, 1–2 prior lines	Carboplatin doublet + atezolizumab + bev versus carboplatin doublet + bev + placebo	PFS	NCT02891824
OREO/ENGOT Ov38	136 BRCA 280 BRCAwt	Response to induction platinum therapy in recurrent setting; prior PARPi exposure	Olaparib 300 mg po bid versus placebo switch maintenance	PFS	NCT03106987
ANITA/ENGOT Ov 41/GEICO 69-O	414	TFIp > 6 months, <2 prior lines	Platinum doublet + placebo followed by niraparib + placebo versus platinum doublet + atezolizumab followed by niraparib + atezo	PFS	NCT03598270

CR, complete response; PR, partial response; PLD, pegylated liposomal doxorubicin; PFS, progression free survival; OS, overall survival; TFIp, treatment free interval from last platinum NCT, National Clinical Trial; PFI, platinum free interval.

the development of both bevacizumab and olaparib. The table demonstrates the similar hazard ratios in both the PS and upfront patient settings leading to the question: should we focus trial design initially in the upfront patient setting? Should we be expediting drug development of compounds with known efficacy to the population they are likely to benefit the most and focus our use of already scarce patient resources? However, this shift would leave a gap in knowledge for what to do in the recurrent setting. As discussed above, additional trials will be needed demonstrating efficacy of repeat exposure of newer regimens as our upfront treatment of EOC shifts. The landscape of treating EOC is changing at a rapid pace and our ability to adjust our methodology and treatment paradigms must continue to change as well in order to provide optimal care for our patients with recurrent ovarian cancer.

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