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Epithelial Ovarian Cancers: On-Target is Better than Near-Target

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Abstract

Epithelial ovarian cancer is the most common cause of gynecological cancer-related mortality worldwide. The discovery that PARP inhibitors block an essential DNA repair pathway in BRCA mutant cells has revolutionized the management of high-grade ovarian cancers. The cross talk among PARP inhibitors and other molecularly targeted therapies such as anti angiogenic drugs further broadens the scope of these agents. A paradigm shift in the management of ovarian cancer is rapidly emerging, potentiated by a better understanding of the underlying defective molecular pathways/mechanisms.

This is providing the opportunity for the clinicians to deliver an effective, yet less toxic and durable treatment to a molecularly selected patient population.

Keywords: Antiangiogenic; Inhibitors; Clinicians; Chemotherapy; Chemorefractory

Introduction

Ovarian cancer is the sixth most commonly diagnosed malignancy in women, and is the most lethal gynecologic malignancy. The annual incidence of ovarian cancer is 2,38,719 per year with 1,51,917 patients dying from it [1]. Treatment of ovarian cancer has progressed from surgery alone to addition of neo adjuvant chemotherapy [2] to intraperitoneal [3] and dose dense [4,5] chemotherapy as well as targeted agent and angiogenesis inhibitor.

The treatment of ovarian cancer involved significant change across the last few decades. The addition of adjuvant chemotherapy in early stage ovarian cancer has improved the 5 yr survival by 8% [6]. Platinum was the most active agent and later on studies confirmed usefulness of taxane addition to it and since then Platinum–taxane doublet became the standard of care in the chemotherapy regimen [7,8]. The outcome of relapsed ovarian cancer remains poor inspite of many permutations -combinations being tried. The commonly used drugs are gemcitabine, pegylated liposomal doxorubicin, irinotecan and etoposide, trabectedin [9-15] which has shown increment in progression free survival or clinical benefit.

In preclinical studies, ovarian cancer was shown to express (vascular endothelial growth factor) VEGF receptors [16,17]. Although the proportion of patients expression VEGF is small, there is conflicting result regarding its prognostic value [18,19]. So, the definite role of VEGF remains elusive. Many newer pathways and targets have been identified and many of them have been beneficial from the therapeutic point of view

The discovery of BRCA gene has enlightened the world with newer insight into tumor biology, response to platinum agents and a stage to test the role of poly (ADP ribose) polymerase (PARP) inhibitor. This communication will provide an insight into the current state of the targeted therapy in ovarian cancer and realistic prediction for forthcoming years.

Antiangiogenic Therapy

Bevacizumab

Angiogenesis has a vital role in tumor growth and metastasis, and VEGF represents a potent cytokine in this process. However, the influence of VEGF in ovarian cancer remains controversial. Ovarian cancer most commonly spreads along the peritoneum. So, it has been suggested by many authors that probably VEGF plays an important role. In one study, VEGF was significantly increased in tumor patients in comparison to controls and accumulates in ascites. The highest VEGF levels were found in patients diagnosed with advanced tumor stages, with tumors of poor differentiation, or in the group of solid/cystic-solid tumors. Patients with residual tumor after operation showed significantly higher levels of VEGF both before and after surgery as compared to tumor-free resected patients [19].

Targeting VEGF with bevacizumab was initiated after some evidence of response in ovarian cancer. In a phase II study of 60 patients, out of which majority were platinum resistant, 21% has a clinical response. Median PFS and overall survival were 4.7 and 17 months, respectively [20]. In another similar phase II study, it was combined with gemcitabine and carboplatin. The median PFS was 13.3 (95% CI, 11.3 to 15.3) months. The objective response rate was 69% [10]. Bevacizumab was also combined with pemetrexed in a phase II study in recurrent or persistent ovarian cancer (platinum sensitive population), median PFS was 7.9 months (95% CI, 4.6-10.9), with a median overall survival (OS) of 25.7 months (95% CI, 15.4-29.8). In the first line setting, a novel combnation of docetaxel, oxaliplatin and bevacizumab was tested in a phase II trial. Out of 132 pts (76.5% had advanced disease), the best overall confirmed response rate (complete response + partial response [measurable disease subgroup]) was 58.6% (95% CI 49%, 67%). The 12-month PFS rate for the measurable disease subgroup was 65.7% (95% CI 53.4%, 76.7%); median PFS was 16.3 (95% CI 12.6, 19.6) months. Median overall survival was 47.3 (95% CI 34.1, upper limit not applicable) months [21] Table 1.

Trial/author	Design/arms	Number of patients	Primary outcome	PFS	OS	Toxicity
Cannistra [30]	Phase II, platinum resistant	44	Response 15.9% PR	Median: 4.4 months	10.7 months	hypertension (9.1%), proteinuria (15.9%), bleeding (2.3%), and wound-healing complications (2.3%).
Burger et al. [20]	Phase II, Persistent/ recurrent disease, ½ prior chemo	62	PFS at 6 months and clinical response: 21%	4.7 months	17 months	GI 4.8% Hypertension: 9.6% Pain: 4.8%
Agustin et al. [31]	Phase II, bevacizumab with oral cyclophosphamide	70	PFS at 6 months	56% at 6 months, 7.2 mo	16.9 mo	GI(gastrointestinal) 5.7% Stroke: 2.8% Hypertension: 15.7% Proteinuria: 4.2%
Nimeiri et al. [32]	Phase II, recurrent persistent disease	13	Overall objective response : 3 responses (1 CR, 2 PR)	Not noted	Not noted	Hypertension 1 pt, nausea 1 pt, diarrhea 1 pt
ICON 7 [27]	Phase III randomized, paclitaxel carboplatin +/- bevacizumab with maintenance	1528	PFS and interim OS	22.4 mo *vs* 24.1 mo (P=0.04)	44.6 *vs* 45.5 months, p:0.85 Updated analysis [26]	Hypertension 18% *vs* 2%, VTE 7% *vs* 3%, GI 10 pts *vs* 3 pts
AURELIA [24]	Phase III randomized, platinum resistant, chemo with or without bevacizumab	361	PFS	6.7 mo *vs* 3.4mo (HR 0.48, P<.001)	16.6 mo *vs* 13.3 mo (HR 0.85, P<.174)	Hypertension 20% *vs* 7%, GI 2% *vs* 0%, VTE 5% *vs* 4%,
OCEANS [22,23]	Phase III randomized, platinum resistant, gemcitabine carboplatin with or without bevacizumab	484	PFS	12.4 mo *vs* 8.4 mo (HR 0.48, log-rank P<.0001)	33.6mo *vs* 32.9mo (hazard ratio=0.95; log-rank p=0.65)	Hypertension 17.4% *vs* <1%, proteinuria 8.5% *vs* <1%
GOG 218 [28]	Phase III randomized, paclitaxel carboplatin with bevacizumab +/- maintenance bevacizumab(bev)	1873	PFS	10.3 mo *vs.* 11.2 mo *vs* 14.1 mo respectively for CP *vs.* CP with bev *vs* CP with bev maintenance	No significant difference	Hypertension 16.5% in bev initiation group *vs* 22.9 in maintenance group *vs* 7.2% in control group, GI perforation 2.8%, 2.6% 1.2% respectively

Table 1: Summary of major trials with bevacizumab in ovarian cancer.

The above studies lead to further investigation on bevacizumab in platinum sensitive and refractory disease. In platinum sensitive disease, bevacizumab was studied in combination with gemcitabine and platinum.

The OCEANS trial was a randomised, multicentre, blinded, placebo-controlled phase-III trial. About 484 patients with platinum-sensitive recurrent ovarian cancer (recurrence 6 months after front-line platinum-based therapy) were enrolled. Patients were randomly assigned to carboplatin plus gemcitabine combined with bevacizumab or placebo for six to 10 cycles. Bevacizumab or placebo was continued till disease progression. PFS for the bevacizumab arm was superior to that for the placebo arm with a four-month improvement The preliminary report of the OCEANS study met its primary endpoint for progression free survival, and it showed benefit with hazard ratio [HR], 0.484; 95% CI, 0.388 to 0.605; log-rank P<.0001; median PFS was 12.4

v 8.4 months [22]. However, there was no improvement in the overall survival. This was also confirmed in the final publication of the same study [23]. Grade 3 or higher hypertension (17.4% versus 1%) and proteinuria (8.5% versus 1%) occurred more frequently in the bevacizumab arm. Three patients in the bevacizumab arm had reversible posterior leukoencephalopathy syndrome and two patients had GI perforation

The AURELIA trial was the first randomised phase-III trial evaluating bevacizumab in combination with chemotherapy in platinum-resistant ovarian cancer. He study enrolled 361 patients with ovarian cancer that progressed in less than 6 months after completion of platinum-based therapy. Pegylated liposomal doxorubicin 40 mg/m2 on day 1 every 4 weeks (n=126), weekly paclitaxel at 80 mg/m2 on days 1, 8, 15, and 22 every four weeks (n=115), or topotecan at 4 mg/m2 on days 1, 8, and 15 every four weeks or 1.25 mg/m2 on days 1 to 5

every three weeks (n=120) were administered. Bevacizumab (10 mg/kg every two weeks or 15 mg/kg every three weeks) was given until progression, unacceptable toxicity, or consent withdrawal. There was a three months prolongation of PFS with the addition of bevacizumab. The OS trend was not significant [24]. AURELIA is the first of the bevacizumab combination studies to show an improvement in abdominal/GI symptom and other patient-reported outcomes. At week 8/9, a ≥ 15% improvement in abdominal/GI symptoms on the EORTC QLQ-OV28 was reported by 21.9% of patients in the bevacizumab/chemotherapy group versus 9.3% patients in the chemotherapy-alone group (difference=12.7%, p 0.002) [25].

Following these results, there was enthusiasm for using bevacizumab in the first line settings. In the ICON7 study, newly diagnosed ovarian cancer that was either high-risk early-stage disease (International Federation of Gynecology and Obstetrics [FIGO] stage I-IIa, grade 3 or clear cell histology) or more advanced disease (FIGO stage IIb-IV), with an Eastern Cooperative Oncology Group performance status of 0-2, were enrolled and randomly assigned in a 1:1 ratio to standard chemotherapy (six 3-weekly cycles of intravenous carboplatin [AUC 5 or 6] and paclitaxel 175 mg/m2 of body surface area) or the same chemotherapy regimen plus bevacizumab 7·5 mg per kg bodyweight intravenously every 3 weeks, given concurrently and continued with up to 12 further 3-weekly cycles of maintenance therapy. They concluded that there was no OS benefit with bevacizumab, however. In poor prognosis patients, there was a significant difference in survival [26,27]. In another trial, bevacizumab used in first line improved the PFS compared to standard chemotherapy arm by 4 months [28].

In all of the above trials, the most common end point is progression free survival. But even with overall survival as secondary endpoint, none of these trials have shown any benefit. The reason may be crossover design. However, in ICON7, a high risk group had improved survival.

Till date, all the trials utilizing bevacizumab in ovarian cancer has improved the PFS. A cost effective analysis however concluded that the use of bevacizumab in first line is not cost effective [29].

Aflibercept

Aflibercept is a heterodimeric molecule consisting of domains of vascular endothelial growth factor 1 (VEGFR1) and VEGFR2 with immunoglobulin G Fc. Although it has a lower molecular weight than bevacizumab, it possesses a higher affinity for VEGF isoforms including VEGF-A, VEGF-B, and placental growth factor. In a preliminary phase II study, aflibercept was given in chemorefractory disease. Primary end point was repeat paracentesis response rate (RPRR). Out of a total 16 pts, the RPRR was 62.5% (95% CI 35.4%-84.8%). Aflibercept 4 mg/kg every 2 weeks was effective at controlling malignant ascites, reducing the interval between repeat paracenteses [30-33]. Another phase II randomized study involved 55 patients, where aflibercept was compared to placebo. Mean time to repeat paracentesis was significantly longer with aflibercept than with placebo (55.1 [SE 7.3] *vs* 23.3 [7.7] days; difference 31.8 days, 95% CI 10.6-53.1; p=0.0019). However, the frequency of fatal gastrointestinal events was higher with aflibercept [34]. When RECIST was used as a primary endpoint, aflibercept did not meet its primary end point, as shown in a phase 2 randomized studies [35]. When combined with chemotherapy like docetaxel, the overall response rate in 54%, as shown in a phase 1-2 trial [36]. The current Australia and New Zealand Gynecological Oncology Group (ANZGOG) REZOLVE II study aims to address whether the intraperitoneal administration of aflibercept could result in OS advantages not.

Nintedanib

Nintedanib, an oral triple angiokinase inhibitor of VEGF receptor, platelet-derived growth factor receptor, and fibroblast growth factor receptor, has shown activity in phase 2 trials in this setting. In a phase II trial, nintedanib was used as maintenance after standard platinum based chemotherapy in recurrent ovarian cancer. Thirty-six-week PFS rates were 16.3% and 5.0% in the nintedanib and placebo groups, respectively (hazard ratio, 0.65; 95% CI, 0.42 to 1.02; P=0.06) [37]. This was followed by a phase III trial where advanced ca ovary patients were randomized to receive six cycles of carboplatin (AUC 5 mg/mL per min or 6 mg/mL per min) and paclitaxel (175 mg/m2) in addition to either 200 mg of nintedanib (nintedanib group) or placebo (placebo group) twice daily on days 2-21 of every 3-week cycle for up to 120 weeks. Total 1366 patients were randomized. Median progression-free survival was significantly longer in the nintedanib group than in the placebo group (17.2 months [95% CI 16.6-19.9] *vs* 16.6 months [13.9-19.1]; hazard ratio 0.84 [95% CI 0.72-0.98]; p=0.024). Gastrointestinal side effects were significantly higher in the nintedanib group (21% *vs.* 2%) [38]. So, Nintedanib seems to be a useful agent in anti-angiogenesis, but more data end investigation is required to improvise on tolerability.

Trebananib

Trebananib inhibits the binding of angiopoietins 1 and 2 to the Tie2 receptor, and thereby inhibits angiogenesis. Two phase I studies have shown that Trebananib in combination with liposomal doxorubicin, topotecan or paclitaxel carboplatin has some clinical effectiveness [39,40]. This was later confirmed by a phase III trial, the TRINOVA 1 study, where recurrent ca ovary with platinum free interval less than a year was randomized to single agent paclitaxel or combination with Trebananib. The primary endpoint was progression free survival. Over 900 patients were included in the study. Median progression-free survival was significantly longer in the Trebananib group than in the placebo group (7.2 months [5.8-7.4] *vs* 5.4 months [95% CI 4.3-5.5], respectively, hazard ratio 0.66, 95% CI 0.57-0.77, p<0.0001). Incidence of grade 3 or higher adverse events was similar between treatment groups [41].

Pazopanib

Pazopanib is a novel tyrosine kinase inhibitor specifically designed to impair angiogenesis by abrogating vascular endothelial growth factor receptor 2 (VEGFR-2) to exert its function. Pazopanib inhibits VEGF-induced endothelial cell proliferation *in vitro* and angiogenesis *in vivo* and demonstrated antitumor activity in mouse models [42]. In the initial phase 2 study as a single agent in recurrent ovarian cancer, 11 of 36 patients (31%) had a CA-125 response to Pazopanib, with median time to response of 29 days and median response duration of 113 days. Overall response rate was 18% in patients with measurable disease at baseline [43]. It was tested as a maintenance strategy after completion of first line therapy. In the AGO OVAR trial, over 900 patients after completion of surgery and standard taxane platinum chemotherapy, were randomized to Pazopanib 800 mg once daily versus placebo, for 2 yrs. The primary endpoint was PFS. It was observed that maintenance Pazopanib prolonged progression-free survival compared with placebo (hazard ratio [HR], 0.77; 95% CI, 0.64 to 0.91; P=0.0021; median, 17.9 *vs.* 12.3 months, respectively). Overall

survival data to this point did not suggest any benefit. Almost a third of the patients had grade 3/4 hypertension [44]. However, there is evidence that the effect of pazopanib may not be the same amongst Asians. In a study where the data from the Asian patients in AGO-OVAR study as well as data from a separate east Asian study were analyzed, Pazopanib maintenance had a detrimental effect on median progression-free survival versus placebo in East Asian patients from the combined studies (n=354; 17.9 vs. 21.5 months; hazard ratio, 1.114; 95% confidence interval, 0.818-1.518; P=0.4928). Pazopanib maintenance showed a disadvantage in overall survival in East Asian patients from AGO-OVAR16 versus placebo (hazard ratio, 1.706; 95% confidence interval, 1.010-2.883; P=0.0465) [45]. So, further studies are warranted, especially from Asian subcontinent.

Sunitinib and sorafenib

Sunitinib and sorafenib are multikinase inhibitors which have been studies in ovarian cancer. In a phase II study of 30 patients, majority were platinum sensitive, more than 30% response was seen in only 5 patients. Overall median progression-free survival was 4.1 months [46]. Another phase II study also produced a modest response rate of 8% [47]. In a randomized phase II trial, the two dosing schedules of Sunitinib (4 week on 2 week off versus continuous) was tested. They concluded that 4 week/2 week regimen is preferred as far as response rate and survival is concerned [48].

Similarly, sorafenib was also studies in various phase 1 and 2 trials. In cases post multiple lines of therapy, no patients (out of 11) experienced a partial response or complete response or stable disease lasting longer than 6 months according to RECIST criteria in one study [49]. In a study by GOG group, only modest 3.5% patients had partial response [50]. In the recurrent setting, sorafenib has been combined with gemcitabine in a study from Princess Margaret hospital. Only 23% patients maintained response at 6 months. The median time to progression was 5.4 months, and the median overall survival was 13.0 months [51]. As maintenance strategy after front line therapy, sorafenib was tested in a phase 2 trial. There was no significant difference in progression free survival, and there were increased toxicities in the sorafenib arm [52]. Sorafenib was combined with standard platinum taxane in recurrent platinum sensitive disease, where the response rate and the median PFS improved with combination, albeit at the cost of increased toxicity [53]. However, in the first line setting, combination with standard chemotherapy did not improve efficacy and substantially increased toxicity [54].

Overall, both sunitinib and sorafenib seems to have modest clinical benefit and the lack of promising phase 3 trials comes in the way of these agents being used for routine clinical practice.

Cediranib

Cediranib is an oral tyrosine kinase inhibitor (TKI) of vascular endothelial growth factor receptor VEGFR-1, VEGFR-2, VEGFR-3, and c-kit. Several phase I studies have shown its effective dose to be 45 mg [55,56]. A phase 2 study involving 74 patients of recurrent ovarian cancer was undertaken. In platinum sensitive group, 10 (26%) partial responses (PR) and 20 (51%) stable disease (SD) were confirmed while in the platinum resistant arm there were no confirmed PR and 23 pts (66%) had SD. The main grade 3/4 toxicities observed at the 30 mg starting dose were hypertension (27%), fatigue (20%) and diarrhea (14%) [57]. Cediranib was also tested in combination with olaparib for

recurrent platinum sensitive ovarian cancer. Median PFS was 17.7 months (95% CI 14.7-not reached) for the women treated with Cediranib plus olaparib compared with 9.0 months (95% CI 5.7-16.5) for those treated with olaparib monotherapy (hazard ratio 0.42, 95% CI 0.23-0.76; p=0.005). This study proved that the combination is quite effective in improving PFS. This was followed by a large randomized phase 3 trial ICON6, in platinum sensitive cancer. In this study, Cediranib was given with chemotherapy, as well as continued into maintenance, compared to placebo. In this study, Cediranib was started at 20 mg OD. Addition of Cediranib to chemotherapy resulted in improvement of PFS from 8.7 months to 9.9 months, and if continued as maintenance, it further improved the PFS to 11 months, which is statistically significant with hazard ratio 0.56, 0.44-0.72, p<0.0001. Diarrhea, neutropenia, hypertension, and voice changes were significantly more common, during chemotherapy with Cediranib, and diarrhea, hypothyroidism and voice changes were more common during maintenance. Poor compliance with Cediranib was noted during maintenance treatment with toxic effects being the most common cause for discontinuation [58]. So, we have evidence from large phase 3 trial supporting the use of Cediranib in routine practice.

Integrin receptors

Integrin receptors are involved in endothelial cell adhesion, migration, and proliferation. Integrin subunits α5β3 located on vascular endothelial cells and ovarian tumour cells has a prime role in tumour invasion and angiogenesis. In a phase II, multicenter, single-arm, two-stage study in platinum-resistant, advanced epithelial ovarian or primary peritoneal cancer, 16 patients were enrolled in stage 1, Volociximab was administered at 15 mg/kg IV every week until progression of disease or drug intolerability. Safety data are available on all 16 patients; 14 were evaluable for efficacy. One patient had stable disease at 8 weeks. The remaining 13 progressed on treatment. Twelve patients (75%) experienced study-related adverse events (AEs); the most common (≥ 20%) were headache and fatigue. Three patients experienced possible study-related serious AEs (SAEs): reversible posterior leukoencephalopathy syndrome, pulmonary embolism, and hyponatremia.

Poly (ADP-ribose) polymerase inhibitors (PARP inhibitors) and BRCA mutations

Hereditary breast and ovarian cancer (HBOC) due to mutations in BRCA1 andBRCA2 is the most common cause of hereditary forms of both breast and ovarian cancer and occurs in all ethnic and racial populations. The overall prevalence ofBRCA1/2 mutations is estimated to be from 1 in 400 to 1 in 800 [59-62]. BRCA1 interacts with several proteins involved in cellular pathways, including cell cycle progression, gene transcription regulation, DNA damage response, and ubiquitination [63,64]. BRCA2 appears to be involved in the DNA repair process. Studies in homologous knockout mice suggest that BRCA 2 is a caretaker to maintain the genomic integrity.

According to a combined analysis of 22 population-based studies in which cases were unselected for family history, the average risk for breast cancer in BRCA1 mutation carriers by the age of 70 years was 65% (95% confidence interval [CI]: 44-78%) and for ovarian cancer was 39% (95% CI: 18-54%) for BRCA 1 [65]. For BRCA 2, risk estimates to age 70 for both breast and ovarian cancer were 45% (95% CI: 33-54%) and 11% (95% CI: 4-18%), respectively [65]. Various

recent evidence is coming up that BRCA associated tumors have better prognosis [66-68].

DNA damages result from errors in replication, production of reactive oxygen species, and exposure to ultraviolet rays and ionizing radiation. These lesions that result from these noxious events include point mutations, single strand breaks (SSBs), and double strand breaks (DSBs), intrastrand and interstrand cross-links. Cells employ multiple types of DNA repair mechanisms: base excision repair (BER), nucleic acid excision repair (NER), homologous recombination(HR), single strand annealing (SSA), Mismatch Repair (MMR), and non-homologous end joining (NHEJ) to repair these damages on a regular basis [69].

PARP, poly (ADP-ribose) polymerases, is a family of proteins with enzymatic properties, scaffolding properties, and recruiting ability for other necessary DNA repair proteins. PARP is involved in single strand repair (BER). Inhibition of the PARP enzyme leads to persistence of spontaneously occurring single-strand breaks (SSBs) and subsequent formation of double-strand breaks (DSBs) as the SSBs stall and collapse replication forks, leading to DSBs. These DSBs cannot be repaired by the defective homologous recombination (HR) pathway in BRCA-mutated cells thereby resulting in cell death. In addition, another DNA repair pathway, the no homologous end joining (NHEJ) pathway, also plays a role in the anti-cancer mechanism of action of PARP inhibitor [70]. In addition, PARP inhibitors may also function by trapping PARP-1 and PARP-2; PARP trapping occurs when the PARP enzyme is trapped on DNA by a PARP inhibitor. These PARP-DNA complexes then have the ability to interfere with DNA replication [71].

Olaparib

A Phase I dose-finding study evaluated the tolerability, pharmacokinetics, PARP inhibitory activity, and antitumor activity of olaparib in Japanese patients with solid tumors. Olaparib was well tolerated up to the 400 mg b.i.d. dose in Japanese patients with solid tumors. Preliminary evidence of antitumor activity was observed [72]. In another study, 50 patients were treated: 48 had germline BRCA1/2 mutations; one had a BRCA2 germline sequence change of unknown significance, and another had a strong family history of BRCA1/2-associated cancers that declined mutation testing. Of the 50 patients, 13 had platinum-sensitive disease, 24 had platinum-resistant disease, and 13 had platinum-refractory disease (according to platinum-free interval). Twenty (40%; 95% CI, 26% to 55%) achieved Response Evaluation Criteria in Solid Tumors (RECIST) complete or partial responses and/or tumor marker (CA125) responses, and three (6.0%) maintained RECIST disease stabilization for more than 4 months, giving an overall clinical benefit rate of 46% (95% CI, 32% to 61%). Median response duration was 28 weeks. There was a significant association between the clinical benefit rate and platinum-free interval

across the platinum-sensitive, resistant, and refractory subgroups (69%, 45%, and 23%, respectively). Post hoc analyses indicated associations between platinum sensitivity and extent of olaparib response (radiologic change, P=0.001; CA125 change, P=0.002) [73]. In a study involving BRCA mutated patients of multiple tumors, the ovarian cancer subgroup had response rates of 31% [74,75]. A proof of concept trial was undertaken for patients with BRCA mutations treated with olaparib. A 400 mg twice daily dose of olaparib led to a response rate of 33% [76]. Olaparib was also investigated in combination with carboplatin. In a phase I trial it was found that 400 mg BD is well tolerated along with standard dose of carboplatin [77]. However, Olaparib in combination with cisplatin 75 mg/m2 was not considered tolerable in standard doses [78]. In a phase 2 randomized study of platinum sensitive disease, who had received up to 3 lines of chemotherapy, olaparib was combined with taxane carboplatin and continued as maintenance. Out of 178 patients, 38% had BRCA mutation positivity. Progression-free survival was significantly longer in the olaparib plus chemotherapy group (median 12.2 months [95% CI 9.7-15.0]) than in the chemotherapy alone group (median 9.6 months [95% CI 9.1-9.7) (HR 0.51 [95% CI 0.34-0.77]; p=0.0012), especially in patients with BRCA mutations (HR 0.21 [0.08-0.55]; p=0.0015). The most common grade 3 or higher adverse events during the combination phase were neutropenia and anemia [79]. The combination of olaparib and Cediranib was investigated in a phase 2 randomized trial, where the combination seems to improve PFS in women with recurrent platinum-sensitive high-grade serous or endometrioid ovarian cancer [80]. Olaparib was tested as a maintenance strategy in platinum sensitive recurrence after response to platinum agents. The primary endpoint was PFS, analyzed for the overall population and by BRCA status. 136 patients were assigned to olaparib and 129 to placebo. BRCA status was known for 131 (96%) patients in the olaparib group versus 123 (95%) in the placebo group, of whom 74 (56%) versus 62 (50%) had a deleterious or suspected deleterious germline or tumor BRCA mutation. Of patients with a BRCA mutation, median PFS was significantly longer in the olaparib group than in the placebo group (11.2 months [95% CI 8.3-not calculable] vs. 4.3 months [3.0-5.4]; HR 0.18 [0.10-0.31]; p<0.0001); similar findings were noted for patients with wild-type BRCA, although the difference between groups was lower (7.4 months [5.5-10.3] vs. 5.5 months [3.7-5.6]; HR 0.54 [0.34-0.85]; p=0.0075). At the second interim analysis of overall survival (58% maturity), overall survival did not significantly differ between the groups (HR 0.88 [95% CI 0.64-1.21]; p=0.44); similar findings were noted for patients with mutated BRCA (HR 0.73 [0.45-1.17]; p=0.19) and wild-type BRCA (HR 0.99 [0.63-1.55]; p=0.96). They concluded that there is significant effect of olaparib on sensitive disease as maintenance, especially in the BRCA mutated group [81]. The SOLO 1 and SOLO 2 trials are ongoing, results are awaited [82] Table 2.

Study drug	Study design	Number of patients	Outcome	toxicity
Olaparib, study 42 [74]	Phase II, 3 or more lines of therapy	193	ORR 34% Median DoR: 7.9 mo ORR platinum resistant: 30% DoR of sensitive vs. resistant: 8.3 vs. 8.0.mo	None related to olaparib

Olaparib [79]	Phase 2 randomized platinum sensitive olaparib +/- Cediranib	90	Median PFS 17.7 mo *vs.* 9. mo, hazard ratio 0.42, 95% CI 0·23–0.76; p=0.005	Fatigue 12 *vs.* 5 pts Diarrhoe 10 *vs.* nine Hypertension 18 *vs.* none
Olaparib [80]	Phase 2 randomized, olaparib maintenance in platinum sensitive after response to platinum	136 *vs.* 129	PFS: BRCA mut- 11.2 *vs.* 4.3 mo Wild type: 7.4 *vs.* 5.5 mo Booth were statistically significant	Fatigue 7% *vs.* 3% Anemia 5% *vs.* <1% Severe Adverse Event: 18% *vs.* 9%
Olaparib [78]	Phase 2 randomized platinum sensitive paclitaxel carboplatin +/- olaparib with maintenance	81 *vs* 81	PFS 12.2 *vs* 9.6 mo More with BRCA mutation 95% CI 9.1-9.7) (HR 0.51 [95% CI 0.34-0.77]; p=0.0012	Alopecia 74% *vs* 59% Nausea 69% *vs* 57% Neutropenia 49% *vs* 39%, diarrhoe 42% *vs* 27%, headache 33% *vs* 9%, peripheral neuropathy 31% *vs* 19%, dydpepsia 26% *vs* 12%
Iniparib [82]	Phase 2 single arm, at least post 1 line chemo, BRCA mutation positive	12	SD: 1 pt PD: 11 pts	Asthenia 83% Constipation 25% Diarrhoe: 25% Nausea 25% Abdominal pain 16.7% Anemia 16.7%
Iniparib [83]	Phase 2 single arm platinum resistant along with gemcitabine and carboplatin	19	ORR 31.6% Median PFS: 5.9 months	Not available
Veliparib [86]	Phase 2 randomized in pretreated BRCA mutant cases, cyclophosphamide oral =/- veliparib	38 *vs.* 37	CR : 1 in each arm PR: 3 in combination, 6 in cyclophosphamide alone	Lymphopenia 13 *vs* 3 pts,anemia 7 *vs* 2 pts, fatigue 4 *vs* 0 pts
Veliparib [85]	Phase 2, up to 3 lines previous chemo, BRCA mutant	50	Platinum sensitive ORR: 35%, platinum resistant ORR: 20%	Grade 3: fatigue n=3, nausea 2, leukopenia 1, neutropenia 1, dehydration 1, and ALT 1. Grade 2 events >10% were: nausea 46%, fatigue 26%, vomiting 18%, and anemia 14%.
Rucaparib [88]	Phase 2 BRCA mutation positive cancers	44	12 out of 13 ovarian patients has ORR lasting more than 12 weeks Median duration of response DoR: 179 days	Grade 3 : Nausea 3% Grade 2: Fatigue 19% Headache 6% Anemia 5% Nausea 5%

Table 2: Summary of important trial for PARP inhibitors.

Iniparib

Iniparib in another PARP inhibitor, which had preliminary activity in breast cancer patients with BRCA mutation. It has also being studies in ovarian cancer. In a phase 2 single arm study, eligible patients had advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer, germline BRCA1 or BRCA2 mutation, measurable disease, and at least 1 previous treatment regimen of platinum/taxane chemotherapy. Patients received Iniparib 8 mg/kg intravenously on days 1 and 4 weekly, with imaging every 8 weeks. Treatment continued until disease progression or adverse events (AEs) prohibited further therapy. Twelve patients were treated on study, with median exposure to Iniparib of 7.5 weeks. The median number of previous chemotherapeutic regimens was 7. Treatment-related AEs (≥ 10%)

included asthenia (83.3%), constipation (25%), diarrhea (25%), nausea (25%), abdominal pain (16.7%), and decreased hemoglobin (16.7%). All treatment-related AEs were grades 1 or 2 with the following 2 exceptions: 1 grade 3 diarrhea and 1 grade 3 hypertension. One patient had stable disease lasting 2 cycles; the remaining 11 patients had progressive disease. The study did not proceed to second stage enrollment [83]. They concluded that Iniparib did not show any significant activity. Iniparib was combined with chemotherapy in phase 2 study. In this study, Iniparib was combined with gemcitabine and carboplatin in platinum sensitive tumors. Carboplatin (AUC 4; IV; day 1), gemcitabine (1000 mg/m2; IV; days 1 and 8), and Iniparib (5.6 mg/kg; IV; days 1, 4, 8, and 11) were given on a 21-day cycle. The primary endpoint was overall response rate (ORR; RECIST 1.0);

secondary endpoints were safety and progression-free survival (PFS). Analysis from the first 17 patients demonstrated an ORR of 70.6%, consisting of 12 confirmed responses. Preliminary analyses did not indicate a relationship between BRCA status and objective response. They concluded that the combination had activity in platinum sensitive disease [84]. However, due to failed phase III trials evaluating the role of Iniparib in breast cancer, further trials have been stopped as of now [85].

Veliparib

Veliparib is another potent small molecule inhibitor of PARP-1/2. In a phase 2 study of relapsed patients post upto 3 lines of chemotherapy and BRCA mutation positive, Veliparib was administered at 400 mg orally BID with one cycle being 28 days. Out of 50 patients, 30 patients (60%) were platinum-resistant. The median number of cycles administered was 6 (1-27). There was one grade 4 thrombocytopenia. Grade 3 adverse events were: fatigue (n=3), nausea (2), leukopenia (1), neutropenia (1), dehydration (1), and ALT (1). Grade 2 events >10% were: nausea (46%), fatigue (26%), vomiting (18%), and anemia (14%). The proportion responding was 26% (90% CI: 16%-38%, CR: 2, PR: 11); for platinum-resistant and platinum-sensitive patients the proportion responding was 20% and 35%, respectively. The most common reason for treatment discontinuation was progression (62%). Twenty-nine patients are alive; two with SD remain on Veliparib. The median PFS was 8.18 months [86]. It has also being tested in the combination setting with oral cyclophosphamide. In a randomized trial, 75 patients were enrolled and 72 were evaluable for response; 38 received cyclophosphamide alone and 37 the combination as their initial treatment regimen. Treatment was well tolerated. One complete response was observed in each arm, with three partial responses (PR) in the combination arm and six PRs in the cyclophosphamide alone arm. Genetic sequence and expression analyses were performed for 211 genes involved in DNA repair; none of the detected genetic alterations were significantly associated with treatment benefit. It was well tolerated and clinical activity was observed; the addition of Veliparib at 60 mg daily did not improve either the response rate or the median progression-free survival [87].

Rucaparib

Rucaparib was shown to be effective in preliminary *in vitro* studies. It was tested in 39 ovarian cell lines, that were each characterized for mutation and methylation status of BRCA1/2, baseline gene expression signatures, copy number variations of selected genes, PTEN status, and sensitivity to platinum-based chemotherapy. Drug interactions were also tested. Drug interactions with rucaparib were synergistic for topotecan, synergistic, or additive for carboplatin, doxorubicin or paclitaxel, and additive for gemcitabine. Synergy was most pronounced when rucaparib was combined with topotecan, which resulted in enhanced apoptosis, DNA fragmentation, and γH2AX formation. Importantly, rucaparib potentiated chemotherapy independent of its activity as a single agent [88]. These results led to further studies. In a phase 2 open label muticentre trial in proven BRCA-1/2 mutation carriers with advanced breast and or ovarian cancer, intravenous (i.v.) and subsequently oral rucaparib were assessed, using a range of dosing schedules, to determine the safety, tolerability, dose-limiting toxic effects and pharmacodynamic (PD) and pharmacokinetic (PK) profiles. Rucaparib was well tolerated in patients up to doses of 480 mg per day and is a potent inhibitor of PARP, with sustained inhibition 24 h after single doses. The i.v. rucaparib (intermittent dosing schedule)

resulted in an objective response rate (ORR) of only 2% but with 41% (18 out of 44) patients achieved stable disease for 12 weeks and 3 patients maintaining disease stabilization for >52 weeks. The ORR for oral rucaparib (across all six dose levels) was 15%. The key lessons learned from this study is that continuous rucaparib dosing is required for optimal response [89]. Further studies like ARIEL2 and 3 are ongoing to provide us with bigger data.

A Cochrane review also concluded that PARP inhibitors appear to improve PFS in women with recurrent platinum-sensitive disease [90].

A cost effective analysis was done for PARP inhibitor maintenance in ovarian cancer. The cost of olaparib was estimated at $13,440 per month. Rate of germline BRCA1/2 mutation was estimated at 20%. Progression-free survival was determined from published data. The cost of observation in 1110 patients with a BRCA1/2 mutation was $5.5 million (M) versus $169.2 M for maintenance therapy with olaparib. The Incremental cost-effectiveness ratios (ICER) for olaparib maintenance therapy in patients with a BRCA mutation were $258,864 per progression-free life-year saved. If the cost of olaparib was decreased to $2500 per month, the ICER was $49,584. For the 4439 patients with wild-type BRCA, the cost of maintenance therapy was $444.2 M; the ICER was $600,552 per progression-free life-year saved. It was concluded that for both BRCA statuses, olaparib maintenance is not cost effective [91].

HER2 targeting agents

HER2 expression is an important driver in many solid tumors. There is evidence that it is over expressed in ovarian cancer [92]. The epidermal growth factor receptor (EGFR) is over expressed in 30-98% of epithelial ovarian carcinoma (EOC), and the signaling cascades activated are related with cell proliferation, migration and invasion, and angiogenesis, as well as resistance to cell apoptosis [92]. In another study by the GINECO group, HER 2 was found to be amplified in 6.8% of patients [93]. Many preclinical studies have shown the efficacy of HER2 targeting agents in ovarian cell lines [94-96]. In the clinical setting, a phase II trial was undertaken, where the eligible patients had 2/3+ IHC score for HER2. They were given weekly standard dose of trastuzumab (4 mg/kg loading followed by 2 mg /kg weekly). Around 11% of patients had IHC criteria positive, the overall response rate was 7.3%, with one complete and two partial responses. Median treatment duration was 8 weeks (range, 2 to 104 weeks), and median progression-free interval was 2.0 months. So, they concluded that the role of trastuzumab in ovarian cancer is limited because of the low levels of expression of HER2 as well as the low response rates [97]. Trastuzumab emtansine (T-DM1) has also shown to be effective in ovarian cancer cell lines, but there is lack of any meaningful clinical data [95].

Newer targets

The phosphatidylinositol 3-kinase PI3K/PTEN/AKT pathway is a key-signalling pathway in the regulation of cell growth. Dysregulated signalling of this pathway can occur with activating mutations of PI3K-related genes, amplification of Akt signalling or inactivating mutations of PTEN. The phosphatidylinositol 3-kinase (PI3K)/AKT/ mammalian target of rapamycin (mTOR) is activated in approximately 70% of ovarian cancers, resulting in hyperactive signaling cascades that relate to cellular growth, proliferation, survival, metabolism, and angiogenesis. In a phase II study, AGO GYN8, platinum resistant and refractory patients were included. Patients received weekly IV infusions of 25 mg temsirolimus. Primary endpoint was progression

free survival rate after 4 months. Out of 21 evaluable ovarian cancer patients, 10 had disease progression, and the study did not meet its predefined levels during the first stage and thus stopped [98].

The angiogenesis inhibitor dalantercept (formerly ACE-041) is a soluble form of activin receptor-like kinase-1 (ALK1) that prevents activation of endogenous ALK1 by bone morphogenetic protein-9 (BMP9) and BMP10 and exhibits antitumor activity in preclinical models. A phase 2 study of 28 patients with persistent or recurrent disease was undertaken. Patients received 1–12 cycles of dalantercept, and 46% of patients received ≤ 2 cycles. The most common adverse events (AE) were fatigue, anemia, constipation and peripheral edema. Grade 3/4 AEs occurred in 39% and 4% of patients. One grade 5 gastric hemorrhage in a patient with a history of radiation fibrosis/ small bowel obstruction was deemed possibly dalantercept-related. All patients are off study: 86% for PD. Median progression-free and overall survival: 2.1 months (90% CI: 1.4–3.2) and 14.5 months (90% CI: 7.0–17.5), respectively [99,100]. So, its efficacy is questionable.

Cyclin dependant kinase 4 and 6 inhibitors

Deregulation of the cyclin-dependent kinases 4 and 6 (CDK4/6)–p16 – Rb signaling pathway is commonly found in ovarian cancer (OC). Palbociclib is an inhibitor of CDK4/6 and was recently shown to delay disease progression in postmenopausal women with advanced breast cancer in a phase 2 study, patients who failed after chemotherapy were given oral palbociclib 125 mg once daily for 3 weeks followed by 1 week off over 28-day cycles. The primary endpoint was PFS at 6 months. The proportion of patients who were progression-free at 6 months was 9/30 (30%). Using RECIST median PFS was 3.7 months (95%CI, 1.2-6.2). Toxicity was minimal; grade 2 events included anemia (2), nausea (1) abdominal pain (1), grade 3/4 events included neutropenia (5), thrombocytopenia (4), hypokalemia (1) and emesis (1). 1 pt experienced a bowel obstruction and 1 pt died due to disease progression within 30 days of treatment discontinuation [101].

Future Perspectives

The standard of care established by the initial trials with optimal cytoreduction followed by adjuvant chemotherapy with paclitaxel and carboplatin still holds good in the era of targeted therapy. Many strategies have been tried to improve the survival, starting from surgical expertise to addition of triple agent chemo to addition of targeted therapy. However, unlike many other solid tumors like colon and lung, the pace at which targeted therapies are making their mark on ovarian cancer is much slower. The molecular characterization of the tumor has led to its stratification into type 1 and type 2 subtypes with differing gene signatures and clinical behavior. But this classification has still not helped us in identifying the subset of patients who would do well with targeted therapy.

We are yet to discover molecular biomarkers at baseline, which helps us triage patients for molecular therapy. Some studies which evaluated serum VEGF levels at baseline have shown promising results [102]. However, larger data from different subgroup of patients are required before any conclusions can be made.

The discovery of BRCA as a pathogenetic pathway was useful as it led to utilization of PARP inhibitors. They hold promise for the future of this subset of patients. Newer pathways are being targeted, like the programmed death ligand pathway. Epigenetic pathways have also being targeted to improve the platinum sensitivity, however, there are

conflicting results [103,104]. Apoptotic pathways have been found to be dysregulated, and blocking inhibitors of apoptotic pathways with drugs like birinapant have also being tested in phase 1 trials [105, 106].

The optimum usage of targeted (intelligent) delivery of therapeutic agents will emerge from continuing trials. In the next decade, more novel agents will be added in the armamentarium. Individualizing the management strategy and choosing the most appropriate molecule, at the most appropriate phase of disease, on the basis of specific tumor phenotype and evolving genotype, will remain the challenging ultimate goal.

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