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Review Article

Clinical Conundrums in Ovarian Cancer – A Genetic and Molecular Based Approach – Importance of Personalized Standard-of-care Therapy

PK Prem Ravi Varma*

Head of Department, Department of Medical Oncology, Cochin Cancer Research Centre, Government Medical College Campus, Ernakulam, Kerala State, India

***Corresponding Author:** PK Prem Ravi Varma, Head of Department, Department of Medical Oncology, Cochin Cancer Research Centre, Government Medical College Campus, Ernakulam, Kerala State, India.

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Abstract

Epithelial ovarian cancer is the most lethal gynecological malignancy. It can be divided into five main histological subtypes: high grade serous, endometrioid, clear cell, mucinous and low grade serous. These histological subtypes are distinct disease entities at the clinical and molecular level. There is significant genetic heterogeneity in ovarian cancer, particularly within the high grade serous subtype. This subtype of ovarian cancer has been the focus of much research effort to date, revealing molecular subgroups at both the genomic and transcriptomic level that have clinical implications. Therefore stratifying ovarian cancer patients based on the underlying biology remains in its infancy. This article summarizes the molecular changes that characterize the five main ovarian cancer subtypes and highlight potential opportunities for targeted therapeutic intervention and outline priorities for future research.

Keywords: Ovarian Cancer; Molecular Genetics; Histological Subtypes; Molecular Subgrouping; Ovary

Introduction

Ovarian cancer (OC) is the most lethal gynecological malignancy. Over 21,000 cases are diagnosed every year causing more than 14,000 deaths per year in the United States alone [1]. OCs are mainly of epithelial origin usually diagnosed at an advanced stage. Current management of epithelial ovarian cancer comprises maximal cytoreductive surgical resection alongwith platinum-taxane combination chemotherapy [2].

Clinical parameters that influence outcome in OC patients include age at diagnosis, FIGO stage, disease grade and the presence of ascites are independent factors that affect progression-free-survival (PFS) and overall survival (OS) in OC patients [3-5]. Factors that have a significant impact on patient survival include suboptimal debulking surgery that leaves behind macroscopic residual disease [6].

Epithelial OC is divided into five main histological subtypes: high grade serous (HGS), endometrioid, clear cell (CC), low grade serous (LGS) and mucinous OC [7] (See Table). The five subtypes of epithelial OC have distinct developmental origins: HGS OC arises primarily from the epithelium of the distal fallopian tubes, while CC and endometrioid OC are associated with endometriosis [8-16]. LGS OC progresses in a step-wise fashion from serous cystadenoma or adenofibroma to serous borderline tumor, and finally LGS OC [17]. These histologically different subtypes show distinct molecular landscapes at both the genomic and transcriptomic level [9,18-20]. Following increasing evidence regarding the discrete develop-

mental origins and molecular pathogenesis of OC subtypes, these five histologically-defined groups are now thought to represent separate disease entities but there is a need for stratification in both the clinical and research setting [7,21]. The opinions I express here follow the Gynecologic Oncology tumor board presentation of clinical cases at the Cochin Cancer Research Centre.

	HGS	Endometrioid	Clear cell	Mucinous	LGS
Early stage: FIGO stage I or II; advanced stage: FIGO stage III-IV; amp: amplification					
Approximate proportion of OC cases	70%	10%	10%	<5%	<5%
Overall prognosis	Poor	Favourable	Intermediate	Intermediate	Intermediate
Tissue of origin /precursor lesion	Distal fallopian epithelium	Endometriosis	Endometriosis	Poorly defined	Serous borderline tumor
Intrinsic chemosensitivity	High	High	Low	Low	Low
Associated hereditary syndromes	Germline BRCA1/2	Lynch syndrome	Lynch syndrome	Not determined	Not determined
Typical stage at diagnosis	80% advanced stage	50% early stage	60% early stage	80% early stage	Typically advanced stage
Frequent molecular abnormalities	Chromosome instability BRCA1, BRCA2 TP53, NF1, RB1 CCNE1 amp.	PTEN, PIK3CA, ARID1A, CTNNB1	PTEN, PIK3CA, ARID1A, chr20q13.2, amp	KRAS, HER2 amp	KRAS, BRAF

Table 1: Characteristic of the five main histological subtypes of OC.

Early stage: FIGO stage I or II; advanced stage: FIGO stage III-IV; amp: amplification

Reproduced from: Chan JK, Tian C, Monk BJ, Herzog T, Kapp DS, Bell J, et al. Prognostic factors for high-risk early-stage epithelial ovarian cancer: a Gynecologic Oncology Group study. Cancer. 2008;112:2202–10. [PubMed] [Google Scholar].

Adequate surgery is vital in treating ovarian cancer

Receiving adequate surgery is crucial to achieving the best outcome for a patient with ovarian cancer. Primary cytoreduction can give the best outcomes, with potential for R0. However, the role of lymphadenectomy remains controversial, with some thinking that lymph nodes should also be removed when R0 is achieved. This is because even when the lymph nodes are clinically negative, they may have pathologic evidence of metastatic disease.

When neoadjuvant chemotherapy prior to surgery is chosen, 3 cycles are recommended, followed by interval debulking surgery and a fourth cycle of chemotherapy. This option should be considered primarily for patients who are unlikely to achieve R0 or those who are sick and may not tolerate a radical operation well.

What is the standard systemic treatment for newly diagnosed advanced epithelial ovarian cancer?

Once a surgical plan is confirmed, the next treatment consideration to tackle is the optimal standard systemic therapy for patients with newly diagnosed advanced ovarian cancer. This choice is not one size fits all and depends on several factors. The age and fitness of the patients may determine the type of regimen they

can tolerate. Considering histologic subtype, 85% of patients with ovarian cancer have high-grade serous carcinomas. However, other less common tumor types such as low-grade serous, mucinous, clear cell, and possibly endometroid carcinomas may also be seen in the clinic. The volume of disease may affect treatment outcomes; we will consider some data that bevacizumab may be most active in large-volume residual disease. The setting is another important factor; for example, intraperitoneal chemotherapy would not be appropriate in the neoadjuvant setting. Finally, guidelines can provide some order and standardization of treatment.

My opinions on ovarian cancer management

Acknowledging the argument that they are different diseases, these subtypes exhibit different levels of chemosensitivity. While CC, mucinous and LGS OC are highly platinum resistant, HGS OC is often platinum sensitive in the first-line setting [22-24]. Despite the tendency to display therapy resistance, LGS OC is associated with superior clinical outcome compared to HGS, exhibiting a more indolent disease course even when diagnosed at advanced stage [25]. Endometrioid and CC OC also exhibit superior clinical outcome when compared to HGS, which is likely due to their propensity for diagnosis at earlier stage [22,26-30].

Histological subtype alone does not account for the significant clinical heterogeneity seen in OC. In fact, HGS OC patients matched for disease grade and stage show differential therapy sensitivity, PFS and OS, strongly implying a molecular basis for the clinical heterogeneity occurring within these histologically-defined groups [31]. Almost one fifth of OC is associated with inherited pathogenic variants in the germline, commonly in *BRCA1 or BRCA2* accounting for around 75% of hereditary disease. *BRCA*-associated disease is the most common form of hereditary OC, defects in other DNA repair associated genes have also been identified. These include genes that, like *BRCA1 and BRCA2*, are involved with double stranded DNA repair, such as *BARD1, CHEK2, RAD51, PALB2 and BRIP1* [33-36].

Initiating systemic therapy after primary surgical resection

For any patient with newly diagnosed ovarian cancer, there is no one-size-fits-all approach. Carboplatin with paclitaxel every 3 weeks is one of the most common treatment approaches, and many people would consider this the standard of care. However, there are emerging data that support other options. Some patient subgroups have shown better outcomes with dose-dense weekly paclitaxel in combination with carboplatin every 3 weeks, including in the phase III Japanese Gynecologic Oncology Group trial and a subset of patients in the GOG-0262 trial [37,38].

The addition of bevacizumab is also appealing due to its clinical activity when added to chemotherapy. However, it is an expensive medication and not yet approved by the FDA in this setting. If Karunya Arogya Suraksha Padhathi (KASP) or Pradhan Mantri Jan Arogya Yojana (PM-JAY) package were available for bevacizumab, this would likely be my choice for the patient. Otherwise, I would opt to treat this patient with carboplatin and weekly paclitaxel.

Let's look at the data behind some of these treatment options. In higher-risk patients, such as those with stage IV or large-volume residual disease, the addition of bevacizumab to chemotherapy may be preferred. Data on stage IV patients in the GOG-0218 trial [39] and high-risk patients in ICON7 [40] suggest that carboplatin/paclitaxel every 3 weeks with bevacizumab is the preferred regimen. Emerging biomarkers, such as ascites, angiogenesis phenotype, and tumor *VEGF-A*, may help predict treatment benefit with bevacizumab. But again, the fact that bevacizumab is not approved for ovarian cancer can lead to challenges associated with cost and reimbursement.

An alternative for patients for whom bevacizumab is not available or appropriate is carboplatin with dose-dense weekly paclitaxel. The weekly schedule can use a dose-intense regimen of 80 mg/week [38,41]. Alternatively, the MITO-7 trial used fractionated paclitaxel at 60 mg along with weekly carboplatin at AUC 2 every week for unfit patients who may not be able to tolerate more aggressive therapy [42].

Angiogenesis as a target: 9 positive ovarian phase III studies

Targeting angiogenesis remains an important strategy in treating advanced ovarian cancer. Several phase III antiangiogenesis trials have shown improvement in PFS: GOG 218 [38] and ICON7 [43] in frontline treatment, AURELIA in recurrent platinum-resistant disease, [44] and OCEANS [45] and GOG 213 [46] in recurrent platinum-sensitive disease. Other phase III studies, such as OVAR12, [47] OVAR16, [48] and ICON6, [49] used oral tyrosine kinase inhibitors or, in the case of TRINOVA-1, [50] an agent that targets angiopoietin rather than *VEGF*. All of these trials showed positive effects of targeting angiogenesis and suggest that patients should have an-

tiangiogenesis therapy integrated into their treatment, whether as part of first-line therapy or at the time of relapse.

Phase III GOG 218: addition of bevacizumab for primary therapy in stage III/IV ovarian cancer

The phase III GOG 218 study investigated the use of bevacizumab in the front-line setting [38]. Patients with newly diagnosed stage III/IV ovarian cancer (N = 1873) received chemotherapy plus placebo, chemotherapy plus bevacizumab with placebo maintenance, or chemotherapy plus bevacizumab with bevacizumab maintenance. Chemotherapy with paclitaxel and carboplatin was administered every 3 weeks. Treatment duration was chosen to be 15 months because that was the estimated median time to recurrence in this group. This group did not include R0 patients. The primary endpoint was PFS.

GOG 218: investigator-assessed PFS

Adding bevacizumab to chemotherapy and as maintenance led to a nearly 4-month improvement in PFS compared with the control arm (14.1 vs 10.3 months, respectively; HR: 0.717; P < .001) [38]. The PFS events included radiographic, RECIST-defined, or CA-125–defined progression as well as global deterioration of health or death from any cause per study protocol.

However, a retrospective analysis from the GOG 170-D [62], a phase II trial of single-agent bevacizumab in patients with persistent or recurrent ovarian or peritoneal carcinoma, suggested that approximately 10% of patients demonstrate progression earlier by CA-125 vs RECIST-defined criteria [51]. When you censor patients with CA-125–defined progression in the GOG 218 trial, the PFS improvement with bevacizumab becomes exaggerated to 6 months, 18 months with bevacizumab compared with 12 months with placebo (HR: 0.645; P < .0001) [38]. It is not necessarily appropriate to exclude these patients from the overall analysis because patients who have an elevated CA-125 are at higher risk of recurrence radiologically. However, I think looking at this subset helps add context to the clinical benefit of adding bevacizumab.

Ascites predicts treatment benefit of bevacizumab in GOG 218

The presence of ascites also appears to predict for treatment benefit of bevacizumab [52]. A total of 80% of the patients in this trial had ascites (defined as peritoneal fluid > 50 cm3). Among these patients, both PFS and OS were significantly prolonged with bevacizumab compared with chemotherapy alone. The ascites appear to be a phenotype for a high degree of angiogenesis; new blood vessels are leaky. This hypothesis would support the observed benefit with bevacizumab.

Angiogenesis phenotype (MVD/CD31 and Tumor VEGF-A) treatment benefit

A recently published biomarker substudy from GOG 218 provides additional evidence for a predictive role of angiogenesis [53]. Higher microvessel density, assessed by CD31 level, predicted a larger PFS benefit with bevacizumab (HR: 0.40 vs 0.80 with high vs low CD31 expression; P = .003). Although it is not shown here, higher expression of another angiogenesis marker, tumor *VEGF-A*, showed potential predictive value for an OS improvement with bevacizumab (HR: 0.72 vs 1.06 with high vs low VEGF-A expression; P = .75) [52]. Together, these results show that phenotypic and clinical manifestations of uncontrolled angiogenesis predict clinical benefit with bevacizumab.

Considerations for genetic mutations in patients with ovarian cancer

BRCA1/2 mutations: basic concepts

When considering the various treatment approaches available for ovarian cancer, it is useful to understand the basic concepts behind the genetics of the disease. Genetic mutations can arise via different mechanisms; defects can either be inherited (germline mutations) or develop sporadically in the tumor (somatic mutations). Many mutations of interest occur in the *BRCA*, or breast cancer–associated genes but *non-BRCA1/2* mutations that similarly impair DNA repair can also arise.

What these mutations have in common is that they impair the homologous recombination pathway that repairs double-stranded breaks in DNA. These defects offer a mechanism by which to target the cancer. For example, both platinum agents and *PARP* inhibitors cause apoptosis through double-stranded breaks and interference with DNA repair.

Overview of BRCA1 and BRCA2

The *BRCA1 and BRCA2* genes code for enzymes that repair double-stranded DNA breaks. Mutations in these genes are associated with an increased risk of developing breast or ovarian cancer [54]. A *BRCA1* mutation imparts a 39% increased risk of ovarian cancer

over normal *BRCA1*, whereas a *BRCA2* mutation increases risk by 11% to 17%. However, *BRCA1/2* mutations are also a prognostic marker for how a patient is likely to respond to treatment. *BRCA*-mutant tumors are less able to repair a double-stranded break induced by platinum-based chemotherapy or a *PARP* inhibitor, so the cancer cells die and the patient's prognosis is better. Patients with *BRCA1/2* mutations have improved outcomes and longer survival compared with patients without these mutations, even though these patients are at high risk of developing cancer.

The ASCO and the SGO guidelines currently recommend that all patients with ovarian cancer, including fallopian tube and peritoneal cancer, undergo germline *BRCA1/2* testing to screen for mutations. As awareness is growing of other *BRCA*-like genes, there is now movement toward using next-generation sequencing to test for mutations in multiple genes that, like *BRCA*, may be associated with improved outcomes as well as increased cancer risk.

Genetic testing: timing recommendations

Germline testing should be done at the time of cancer diagnosis. It can be beneficial to engage family members at that time and look at the patient's family history.

The tumor itself can also be tested for somatic mutations, including *BRCA1/2* and other homologous recombination pathway markers, as well as microsatellite instability (MSI). Patients with MSI, as demonstrated through a deficiency in DNA mismatch repair, may be sensitive to on-label treatment with pembrolizumab, a checkpoint inhibitor. Ideally, somatic testing would be done just before initiating therapy for recurrent disease. Evolving technology, such as the development of liquid biopsy testing, may improve the feasibility of timely somatic testing.

However, awareness and access to genetic testing are critical issues for the cancer community. Many patients still do not have germline testing, much less somatic testing. Currently, there is an FDA-approved somatic test for *BRCA*, called the Foundation Focus CDx BRCA test, which is a companion diagnostic for rucaparib. There is also an FDA approved test for deleterious germline *BRCA* mutations, BRAC Analysis CDx, which was approved as a companion diagnostic test with olaparib. There is also a FDA-approved homologous recombination deficiency (HRD) test, called my Choice HRD. This test was used in the phase III NOVA trial of the *PARP* inhibitor niraparib.

Bevacizumab for recurrent ovarian cancer: clinical data summary

First, let's consider the current data on the use of bevacizumab in recurrent ovarian cancer. Two phase III trials, GOG 213 and OCEANS, explored the potential benefit of bevacizumab in the platinum-sensitive relapse setting. GOG 213 used carboplatin/paclitaxel as the chemotherapy backbone with or without bevacizumab; OCEANS used carboplatin/gemcitabine with or without bevacizumab. A third phase III trial, the AURELIA trial, included 3 chemotherapy options for platinum-resistant disease: weekly paclitaxel, pegylated liposomal doxorubicin, or topotecan with or without bevacizumab.

This summary of all 3 trials shows that adding bevacizumab improved the response rate and PFS in all 3 studies. However, of the 5 chemotherapy regimens, only 1 showed a statistically significant OS advantage with the addition of bevacizumab: carboplatin/paclitaxel in the GOG 213 trial. This is why I would choose carboplatin, paclitaxel, and bevacizumab for my patient.

The phase III OCEANS trial compared carboplatin and gemcitabine plus either bevacizumab or placebo as second-line treatment for patients with platinum-sensitive, recurrent ovarian cancer and an Eastern Cooperative Oncology Group performance status of 0/1 (N = 484). It is important to notice the attenuation of the doses of chemotherapy relative to first-line dosing: carboplatin AUC 4 rather than AUC 5 or AUC 6, and gemcitabine 1000 mg/m^2 rather than 1250 mg/m^2 on Days 1 and 8. These patients had been previously treated with platinum and, often, taxanes. The primary endpoint was PFS, and secondary endpoints included OS, ORR, and duration of response.

Adding bevacizumab improved median PFS by approximately 4 months, from 8.4 months to 12.4 months (by investigator assessment). The ORR increased by approximately 20% and the median response duration increased by 3 months. These results supported FDA approval of this regimen. However, the final OS analysis showed no advantage with the inclusion of bevacizumab.

ASCO 2017: My top clinically relevant ovarian cancer abstracts

The 2017 ASCO Annual Meeting featured multiple important phase II and phase III gynecologic cancer studies. In this commentary, I discuss my top abstract picks in ovarian cancer that I feel

have the most potential to influence clinical practice at the Cochin Cancer Research Centre.

Surgery in ovarian cancer

Bulk-reducing surgery remains a backbone of ovarian cancer treatment despite advances in neoadjuvant chemotherapy. Three abstracts selected for oral presentation focused on this setting for ovarian cancer. The decision to perform systemic lymphadenectomy at the time of primary surgical debulking after achieving complete resection (R0) is controversial. The Lymphadenectomy in Ovarian Neoplasms (LION) study was a prospective, randomized phase III trial of lymph node dissection (LND) in patients with advanced (stage IIB-IV), resectable ovarian cancer. Intraoperatively, the patients had to have a complete resection and clinically negative nodes (N = 647) [55]. These patients were randomized to systematic pelvic and periaortic LND vs no further surgery. The study showed longer operative time and significantly more blood loss, transfusions, ICU care, postoperative antibiotics, and repeat laparotomies for complications in the LND group. The primary endpoint of OS showed no significant difference in the median OS which was 65.5 months with LND vs 69.2 months without LND (P = .65). Likewise, median PFS was 25.5 months in both arms. The study data demonstrate the lack of benefit of systematic LND in patients with complete cytoreduction for ovarian cancer. Therefore the authors suggest that this procedure be omitted to spare patients the increased morbidity.

Another surgical conundrum in ovarian cancer questions the clinical benefit of secondary cytoreduction for patients who have experienced a significant disease-free interval after initial treatment. Du Bois and colleagues conducted the phase III AGO DESKTOP III/EnGOT ov20 study [56], which was designed to provide a clearer answer to this clinical challenge. This study was the third DESKTOP trial and used the AGO score developed in DESKTOP I [57] and validated as a predictive marker of complete resection in DESKTOP II [58]. Patients enrolled for the study (N = 408) had platinum-sensitive recurrent ovarian cancer, defined as recurrence 6 months or longer after completion of platinum therapy, and a positive AGO score (ECOG PS 0, R0 at the time of first debulking surgery, and ascites ≤ 500 mL). Patients were randomized to receive cytoreduction with maximal effort or no cytoreduction prior to platinum-based chemotherapy. Results showed complete macroscopic resection in 72.5% of patients in the surgery arm. Data for the primary endpoint, OS showed that median PFS was prolonged by 5.6 months with the addition of surgery to chemotherapy (19.6 *vs* 14.0 months for chemotherapy alone; P < .001). And longer PFS was only seen in those patients who had complete resection of macroscopic disease. It is worth noting that there was no significant difference in mortality rates at 30, 60, 90, or 180 days and that cytoreductive surgery is safe for the selected patient population. One caveat for this study is that as RECIST 1.1 is used to assess progression, it systematically biased the median PFS in favor of the surgery cohort (as target lesions were presumably removed during cytoreduction). This illustrates the fact that primary endpoint of OS is needed to truly evaluate the clinical efficacy. Presenting the secondary endpoint of PFS prior to maturity of the primary endpoint of OS is unusual. Thus, level 1 evidence for secondary cytoreduction looms large.

Bevacizumab has also been studied as part of primary ovarian cancer therapy in the phase III GOG 218 trial. However its use in the neoadjuvant setting and the potential effect on surgical outcomes at the time of interval debulking surgery has not been adequately studied.

Targeted therapy in relapsed ovarian cancer

Targeting defective DNA damage repair using *PARP* inhibitors has demonstrated clinical benefits in the treatment of ovarian cancer . The results of the phase III SOLO2 study [59] of maintenance therapy with the *PARP* inhibitor olaparib in platinum-sensitive, relapsed ovarian cancer were presented at the Society of Gynecologic Oncology Annual Meeting on Women's Cancer in March 2017. The study enrolled 295 patients with germline *BRCA1/2* mutations who had a CR to platinum-based chemotherapy after at least 2 lines of treatment. The median PFS with olaparib was 19.1 months vs 5.5 months for placebo. There are clearly outstanding results with olaparib. It must be taken orally every day, often for many months or years. This may affect health-related quality-of-life (HRQoL).

Friedlander and colleagues reported the preplanned HRQoL assessment from SOLO2 using the change in the Trial Outcome Index [59], an established and validated single-targeted index derived from the Functional Assessment of Cancer Therapy—Ovarian (FACT-O), a patient-reported questionnaire specific to ovarian cancer–related symptoms. There was no significant detrimental effect of olaparib *vs* placebo on HRQoL. Patients felt "relatively well"

when followed up for more than 12 months. Despite the relative toxicity of olaparib, the quality-adjusted PFS remained significant: 13.96 months with olaparib *vs* 7.28 months with placebo (P < .0001). The use of maintenance olaparib delayed the onset of disease-related symptoms associated with recurrent ovarian cancer compared with those receiving placebo: 13.5 months *vs* 7.21 months (P < .0001). These study data provide mounting evidence as an important step forward in understanding and quantifying the tradeoffs patients experience during maintenance therapy with olaparib. (NOTE: On August 17, 2017, the FDA approved olaparib tablets for maintenance treatment of patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, in those patients who are in CR or PR to platinum-based chemotherapy.

Angiogenesis inhibitors is an emerging area of tumor targeting in ovarian cancer. Ledermann and colleagues presented the final analysis of ICON6 [49], a randomized, controlled phase III study of upfront chemotherapy with or without the pan-*VEGF* inhibitor cediranib in platinum-sensitive, relapsed ovarian cancer after primary cytoreduction and adjuvant platinum-based chemotherapy. Participants (planned N = 2000) were randomized to chemotherapy plus either placebo continued through the maintenance phase, cediranib 20 mg daily followed by placebo maintenance, or cediranib followed by cediranib maintenance.

My thoughts on the expanding roles of bevacizumab and *PARP* inhibitors in ovarian cancer treatment

Recent new approvals and indications are transforming management strategies and improving outcomes for patients with ovarian cancer. Bevacizumab is commonly used for recurrent disease, but *PARP* inhibitors are becoming increasingly important. However planning the optimal treatment sequence can be a challenge. In this commentary I discuss recent clinical data and explain how to optimize the use of both bevacizumab and *PARP* inhibitors in treating patients with ovarian cancer.

Bevacizumab

Bevacizumab has been approved by the FDA in the treatment of recurrent ovarian cancer - both in the platinum-resistant and platinum-sensitive settings. In Europe, bevacizumab is more broadly approved for treating advanced high-risk ovarian cancer i.e, FIGO stage III/IV disease. For women with newly diagnosed ovarian cancer I do not prefer to use bevacizumab because it is not approved by FDA in this setting although I prefer to use bevacizumab for recurrent disease. Let's discuss the different scenarios.

- **Front Line therapy:** In the phase III GOG-0218 trial of women with newly diagnosed stage III/IV ovarian cancer [63], median PFS was improved by approximately 4 months with the addition of bevacizumab 15.0 mg/kg to every-3-week carboplatin/paclitaxel followed by bevacizumab maintenance vs chemotherapy alone. In the phase III ICON7 trial [60], a European study used a reduced dose of bevacizumab at 7.5 mg/kg in combination with carboplatin/paclitaxel followed by bevacizumab maintenance for patients with stage I-IV disease. The PFS improvement in this study vs carboplatin/paclitaxel was a 2.4-months which was statistically significant. Improvement in OS was not seen in either trial.
- **Platinum-Resistant Recurrence:** In the phase III AURELIA trial that assessed single-agent chemotherapy with or without bevacizumab in patients with platinum-resistant ovarian cancer - a doubling in median PFS, from 3.4 months with chemotherapy alone to 6.8 months with addition of bevacizumab (P < .0001) was observed [44]. The median OS improved from 13.3 months to 16.6 months. In this trial both chemotherapy and bevacizumab were continued until progression or unacceptable toxicity.

Thereafter in a subsequent analysis by chemotherapy cohort, of the 3 chemotherapy regimens included in this trial, the most pronounced benefit was seen with weekly paclitaxel plus bevacizumab. This led to an improvement in median PFS by 5.7 months vs paclitaxel alone, from 3.9 months to 10.4 months (HR: 0.47). Lesser benefit was noted with pegylated liposomal doxorubicin (median PFS: 3.5 vs 5.1 months) and topotecan (median PFS: 2.1 vs 6.2 months). No significant difference in OS were observed between treatment arms in any of the chemotherapy cohorts. However, this showed a trend toward improvement in the weekly paclitaxel cohort (unadjusted HR: 0.65; median 22.4 vs 13.2 months).

In a patient with platinum-resistant ovarian cancer, development of symptoms, rapid growth, or potential for near-future progression - adding bevacizumab to single agent chemotherapy is beneficial. The treating clinician should weigh the potential benefit against the adverse events associated with this agent, mostly hypertension, proteinuria, and risk of perforation. The most common

adverse event is hypertension which can be controlled with medication but must also be closely monitored. Another concern is proteinuria which must be monitored with kidney function using the UPC ratio. Although gastrointestinal perforation is uncommon it is a significant risk with bevacizumab therapy. In platinum –resistant disease, a phase II study of single-agent bevacizumab resulted in a higher incidence of gastrointestinal perforations in patients with 3 or more lines of chemotherapy, thickening of the bowel on CT, and/or evidence of bowel obstruction. Bevacizumab should therefore be avoided in patients with a current diagnosis of a bowel obstruction, signs and symptoms possibly related to bowel dysfunction, or an impending small bowel obstruction.

Platinum-sensitive recurrence

Two trials examined the combination of bevacizumab with platinum-based chemotherapy for the treatment of platinum-sensitive, recurrent ovarian cancer. A phase III OCEANS study examined the addition of bevacizumab to carboplatin/gemcitabine followed by bevacizumab maintenance as second-line therapy for patients with epithelial ovarian, primary peritoneal, or fallopian tube cancer. This study showed that the addition of bevacizumab provided a 4-month median PFS improvement vs chemotherapy alone (12.4 vs 8.4 months), although with no OS improvement.

The phase III GOG-0213 study [46] evaluated the addition of bevacizumab to carboplatin/paclitaxel followed Although patients with platinum-sensitive recurrence respond well with carboplatin/paclitaxel, carboplatin/gemcitabine, or carboplatin/pegylated liposomal doxorubicin and consideration of a *PARP* inhibitor for maintenance therapy. Moreover, Bevacizumab combined with paclitaxel in the platinum-resistant setting can extend efficacy.

PARP Inhibitors

Another exciting new treatment option are the *PARP* inhibitors for patients with ovarian cancer. Mutated *BRCA* proteins rely mainly on the *PARP* pathway to repair DNA damage. *PARP* inhibitors induce apoptosis through double-stranded breaks and interferes with DNA by a process named "synthetic lethality." Many *PARP* inhibitors have now been approved for use in ovarian cancer. The first *PARP* inhibitor approved in this setting was olaparib in 2015 and rucaparib in 2016 for the treatment of *BRCA1/2*-mutated ovarian cancer after multiple lines of chemotherapy. FDA approved Olaparib for germline *BRCA1/2* ovarian cancer after 3 or more lines of previous therapy, and, rucaparib was approved for germline or somatic *BRCA1/2* ovarian cancer after 2 or more lines of previous therapy. The FDA in 2017 approved niraparib and then olaparib as maintenance therapy for patients with platinum-sensitive recurrent ovarian cancer for those patients who completed and are responding to platinum chemotherapy. Considering these indications, the best way to sequence treatment with bevacizumab and the *PARP* inhibitors for recurrent disease is unclear.

It should be noted that although the initial approvals for olaparib and rucaparib included only patients with *BRCA1/2* mutations (whether germline or somatic), the indications for maintenance *PARP* inhibitors have been extended to all patients with platinum-sensitive recurrence. *PARP* inhibitors demonstrate the greatest efficacy in patients with mutations in *BRCA* genes depending on the level of underlying DNA repair deficiency possessed by the cancer cell. The efficacy of *PARP* inhibitors extends to patients with platinum sensitivity and certain histologies, such as high grade serous cancers. A patient with a prolonged platinum-free interval may benefit greatly from maintenance therapy with a *PARP* inhibitor.

PARP inhibitors : current indications

Olaparib was the first FDA-approved *PARP* inhibitor and was originally approved for treatment of patients with deleterious germline *BRCA1/2* mutations after ≥ 3 previous lines of chemotherapy. Following the phase III SOLO-2 trial results, the FDA approved olaparib as a maintenance therapy for patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, and, in those patients who achieve a CR or PR to platinum-based chemotherapy. It should be noted that olaparib also comes with the introduction of a new tablet formulation that can be used for both indications. The dosing recommended for tablets is different than the older capsules due to differences in bioavailability. Hence direct mg-to-mg substitution is inappropriate. The recommended dose of the tablet form is 300 mg (2 tablets) which is taken orally twice daily with or without food. Whereas 8 capsules twice daily are needed with the old capsule formulation.

In March 2017, Niraparib as approved by the FDA as a maintenance treatment for patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in CR or PR following platinum-based therapy after ≥ 2 previous lines of therapy.

Earlier in December 2016, Rucaparib was approved by the FDA for patients with deleterious *BRCA1/2* mutations (germline or somatic) after ≥ 2 previous lines of chemotherapy. Emerging data from the ARIEL3 trial showed clinical benefit for rucaparib as a maintenance therapy for patients with platinum-sensitive recurrence.

Optimal selection between multiple *PARP* inhibitors

Again, optimal selection between the different *PARP* inhibitors is currently driven mostly by indication but other considerations, such as AE profile and administration concerns, should also be considered. Olaparib and niraparib are now both approved choices for maintenance after a response to second-line therapy, and rucaparib is an option as next therapy for patients with a somatic *BRCA1/2* mutation who have progressed after ≥ 2 previous lines of treatment. Olaparib is also indicated for patients with germline *BRCA1/2* mutations after 3 previous lines of therapy.

When considering maintenance therapy for patients with platinum-sensitive recurrent ovarian cancer, either a *PARP* inhibitor or bevacizumab are reasonable options. Based on the GOG 213 and OCEANS trials, patients with platinum-sensitive recurrent ovarian cancer who begin therapy with chemotherapy plus bevacizumab should also receive bevacizumab maintenance. Alternatively, patients with platinum-sensitive, recurrent disease who receive second-line chemotherapy without bevacizumab should receive either niraparib or olaparib as a maintenance therapy.

The recommended dosing for olaparib tablets is different than the older olaparib capsules, due to differences in bioavailability, so direct mg-to-mg substitution is not appropriate. The recommended tablet dose is 300 mg (2 tablets) taken orally twice daily with or without food. This replaces the 8 capsules twice daily needed with the old capsule formulation.

For recurrent disease in later lines of therapy, rucaparib can be used for patients with deleterious *BRCA1/2* mutations (germline or somatic) after ≥ 2 previous lines of chemotherapy. Olaparib is also indicated for patients with germline *BRCA1/2* mutations after 3 previous lines of therapy.

Clinicians need to balance treatment sequencing, possible cumulative toxicity, reimbursement or KASP approval, guidelines, and patient preference to select the best therapy for individual patients. For patients with recurrent platinum-sensitive disease who achieve a response with chemotherapy plus bevacizumab, bevacizumab maintenance is optimal based on the current data from the GOG 213 and OCEANS trials. However, for patients who are treated with chemotherapy without bevacizumab, maintenance therapy with either olaparib or niraparib would likely be optimal based on data from the NOVA and SOLO-2 trials, particularly for patients with germline *BRCA1/2* mutations.

How intend to use bevacizumab and *PARP* inhibitors in my clinical practice

There are multiple treatment approaches clinicians can consider for recurrent OC. In my clinical practice, I use bevacizumab with platinum-based chemotherapy for patients with platinum-resistant disease. Although not available in the hospital formulary, maintenance therapy with a *PARP* inhibitor for platinum-sensitive recurrence will give significant clinical benefit. Many clinical trials are also in the pipeline evaluating combinations of anti-angiogenic agents, like bevacizumab, with *PARP* inhibition as well as with immunotherapy agents. I am waiting on the data to mature before considering this combination approach. It still remains unclear on which patients benefit most from which maintenance therapy approaches - either *PARP* inhibition after chemotherapy or chemotherapy plus bevacizumab followed by bevacizumab maintenance.

The results of the phase II QUADRA trial led to the recent FDA expanded approval of niraparib in patients with ovarian cancer, especially heavily pretreated patients with ≥ 3 previous lines of chemotherapy whose cancer is homologous recombination deficiency (HRD) positive as detected by a companion diagnostic test. HRD is defined by the presence of a *BRCA* mutation or genomic instability in patients who have platinum sensitive disease. This is the first indication of a *PARP* inhibitor in ovarian cancer requiring a companion diagnostic HRD test.

QUADRA study – important findings

The most important findings from the QUADRA study [61] showed that the primary endpoint of ORR in HRD-positive, platinum-sensitive patients who received 3-4 previous lines of chemotherapy was 28% with a significant median duration of more than 9 months. In patients harbouring a *BRCA* mutation, the ORR was remarkably higher at 39%. It should be remembered that in retrospective historical data the expected ORR in this setting was < 10%.

A subset of patients achieved stable disease. This clinical benefit can be meaningful over many months until the next line of therapy and is important and relevant from a clinical standpoint when making decisions for patients especially in later lines of therapy. Furthermore almost 60% of the *BRCA*-mutated, platinum-sensitive patients achieved clinical benefit at 24 weeks. The clinical benefit rate for platinum-sensitive patients who were HRD positive without a *BRCA* mutation was 40% at 24 weeks. Clinicians need to know real-world endpoints when making decisions for their patients because clinical benefit at 6 months or more is meaningful to patients.

A clinically relevant endpoint from QUADRA was OS of approximately 17 months from enrollment compared with historical controls of 5-9 months.

Clinical implications

Niraparib provides an active, tolerable, oral regimen that has efficacy in heavily pretreated patients with ovarian cancer who are HRD positive. The earlier you use a *PARP* inhibitor, the better the outcomes are. Many patients living with ovarian cancer who have received 3 or more lines of previous chemotherapy regimens but not a *PARP* inhibitor, niraparib provides expectations for clinical benefit. This patient population will continue to exist for the next several years, and, access to niraparib will allow us to not leave any patient behind which I feel is incredibly important and is an exciting advance for our patients with ovarian cancer.

HRD testing in ovarian cancer

I think for patients in later lines of therapy who have not had the opportunity to access a *PARP* inhibitor, HRD testing becomes urgent if it has not been done before. It is imperative to find out which of our patients are HRD positive in order to determine if they are eligible for niraparib using a companion diagnostic test. I expect that in the times ahead the rate of HRD testing will likely increase for that reason alone.

Many oncologists do not test for HRD because it is not mandatory for prescribing *PARP* inhibitors for their OC patients. Multiple phase III studies of *PARP* inhibitors as first-line maintenance therapy in ovarian cancer (ESMO 2019) were positive regardless of HRD status. Therefore HRD may or may not be a required companion diagnostic test if and when they are approved by the FDA in this setting. Regardless of the labels that do not require HRD testing, clinicians may still use an HRD assay prior to prescribing on whether to use a *PARP* inhibitor or bevacizumab.

The main disadvantage is that a robust assay that detects homologous recombination deficiency in ovarian cancer is not available. The HRD assay used currently is inadequate according to experts in DNA repair. These tests should include so called 'HRR' genes that are associated with olaparib response. The 'DNA damage response' (DDR)' genes are not necessarily classical HR genes, and there is ongoing preclinical work to refine this. I think it would be also be worth trying out (in addition to the Myriad test) the *RAD51* foci assay. The lack of a robust assay that will predict sensitivity to *PARPi* is probably the reason that patients with tumors that are not HR deficient also respond. Finally, as with all other new approaches such drugs have to be evaluated first line so that recurrences are reduced.

Conclusions

OC is a significant cause of morbidity and mortality. Disease stage, grade and surgical outcome are known to affect PFS and OS rates in OC. The five histologically-defined subtypes of OC are recognized as separate diseases and exhibit differences in stage at diagnosis, responses to platinum-based chemotherapies as well as OS.

Significant clinical heterogeneity occurs within these histological groups, particularly within HGS which represents the majority of OC. The majority of the research has focused on this subtype, evaluating clinically meaningful subgroups at both the genomic and transcriptomic level, although displaying extreme genomic heterogeneity. These subgroups are a challenge to be taken forward from the bench to the bedside. A consensus awaits clinically meaningful transcriptomic subgroups for validating a wealth of publicly available HGS OC gene expression data. Currently only *BRCA* status is routinely used clinically. Germline *BRCA1 and BRCA2* genetic testing is used as a biomarker for the use of *PARPi* therapy. Genomic defects in HRR pathway which occur rarely are an area of great interest. This field awaits data on whether those patients who are truly HRR deficient will benefit from *PARP* inhibition.

To summarize, the data I have discussed here show that cytotoxic chemotherapy still has a role in ovarian cancer. However, there are multiple choices of agents, differences in dose, and differ-

ences in schedule that are important considerations when selecting the best regimen for an individual patient. Meanwhile, I believe the role of IP chemotherapy has become clearer as the GOG 252 trial showed no survival advantage benefit over IV treatment [64].

Angiogenesis is an established target in treating ovarian cancer, and use of bevacizumab can help improve patient outcomes and should be incorporated into chemotherapy regimens, either first line or during initial disease recurrence for both platinum-sensitive or platinum-resistant disease.

PARP inhibitors are also an important therapeutic option. Olaparib, rucaparib, and niraparib are all currently FDA approved for specific indications. I expect that the indications for these agents will continue to expand based on recently reported positive trials. Finally, the emerging role of immunotherapy is promising in ovarian cancer.

The clinical implications of genomic defects viz., *NF1* and *RB1* loss, are yet to be established. Recurrent HGS OS with acquired chemoresistance is the ultimate cause of the majority of patient mortality. Hence investigating its molecular drivers and the acquisition and molecular characterization of matched primary and recurrent samples for using novel therapeutic strategies and re-sensitizing to cytotoxic agents are urgent research priorities.

More classical oncogenic mutations characterize non-HGS OC, and, subtype-specific studies of endometrioid, CC, LGS and mucinous OC to further stratify these subtypes at both the transcriptomic and genomic level is the need of the hour. Acquiring sufficiently large cohorts for these investigations to make meaningful conclusions is a real challenge. However this can pave the way for stratification of therapy, which will undoubtedly require international collaborative efforts.

Future Directions

Relationship between MSI and tumor-associated inflammatory response

The relationship between MSI and the tumor-associated inflammatory response in ovarian cancer is important [52]. An increased risk for ovarian cancer is seen in patients with Lynch syndrome, which is caused by a mutation in a DNA mismatch repair (MMR) gene. In addition to germline mutations in MMR genes, patients can also have somatic mutations and/or epigenetic silencing, which is generally caused by hypermethylation of the promoter.

In May 2017, pembrolizumab received accelerated FDA approval for treatment of patients with high-MSI or MMR-deficient colorectal cancer that progressed following chemotherapy in the phase II KEYNOTE-100 study [65]. The approval of pembrolizumab was also expanded to include all patients with solid tumors with high MSI or MMR deficiency who progressed and have no satisfactory treatment options.

Disclosure

No conflicts of interest.

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