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REVIEW

First-Line Treatment with Olaparib for Early Stage BRCA-Positive Ovarian Cancer: May It Be Possible? Hypothesis Potentially Generating a Line of Research

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Abstract: Olaparib is currently approved in maintenance treatment of advanced ovarian cancer after response to first-line chemotherapy for breast related cancer antigens (BRCA) mutated patients. The use of this agent is based on data from SOLO1 study that observed a decreased risk of disease progression or death and a median progression-free survival about 36 months longer in case of therapy with olaparib. However, this trial recruited only patients with advanced stage ovarian cancer. The aim of this review is to retrace the available data in order to clarify the potential efficacy and feasibility of olaparib administration in newly diagnosed epithelial ovarian cancer also in early stages.

Keywords: newly diagnosed ovarian cancer, early stage ovarian cancer, olaparib, PARPinhibitors, BRCA mutation

Introduction

Early-stage ovarian cancer (ESOC), including the International Federation of Gynecology and Obstetrics (FIGO), stages I and II, represents approximately 30% of the new diagnosis of ovarian cancer every year, with a 5-year overall survival around 50–92%, depending on different prognostic factors.[1,2]

The standard surgical treatment foresees total hysterectomy, bilateral salpingo-oophorectomy, peritoneal sampling and omentectomy.[3] In case of desire to preserve fertility, conservative strategies could be applied, consisting in unilateral salpingo-oophorectomy on the side of the tumor and surgical staging with peritoneal sampling and omentectomy.[4] Currently, according to guidelines, the standard surgical staging of apparently early-stage epithelial ovarian cancer (ESEOC) also includes systematic lymph-node (LN) dissection of the pelvic and the para-aortic regions up to the left renal vessel origin.[5] However, no evidence of benefits of this procedure in ESEOC is strong enough in literature[6] and, on the contrary, retroperitoneal staging is even associated with a higher incidence of morbidity, hospital stay and costs.[7] Therefore, the choice of performing lymph-node (LN) dissection needs to be analyzed and discussed in case of ESOC.[6] After surgery, adjuvant chemotherapy should be offered to patients with ESOC (stage I–IIA) with the exception of fully staged low-grade serous histotype (stage IA), grade 1–2 endometrioid histotype (stage IA) and grade 1 and 2 mucinous tumor (stage IA).[5] Despite

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a better prognosis compared to the advanced setting, up to 40–50% of ESOC patients relapse.[8,9] Such as it concerns molecular characteristics of these tumors about 50% of high-grade serous ovarian carcinomas (HGSOC) are estimated to have a genetic mutation in DNA repair proteins regardless the stage of disease.[10] Defects in breast related cancer antigens (BRCA) 1 and 2 are the most common detected mutations, covering about 20–25% of all HGOC.[11] In the last decades, researchers have been focused on the clinical efficacy of the poly (ADP-ribose) polymerase (PARP) inhibitors (PARPis) in cancer treatment. It has been showed that tumor cells with a defect in the mechanisms of DNA repair, such as homologous recombination repair deficiency (HRD), are more sensitive to PARPi, resulting in tumor cell death.[11]

Olaparib (Lynparza™) was the first PARPi approved in Europe for the treatment of women with a BRCA1 or BRCA2 mutation.[12]

This agent has been approved as maintenance therapy for newly-diagnosed advanced FIGO stage III and IV high-grade serous or endometrioid ovarian cancer, primary peritoneal cancer, or fallopian-tube cancer with a mutation in BRCA1 or BRCA 2 who are in complete or partial response to platinum-based chemotherapy.[13] The SOLO-1 Phase III trial has demonstrated the benefit in terms of progression free survival of olaparib compared to placebo as maintenance therapy after platinum-based chemotherapy in newly diagnosed BRCA-mutated patients with FIGO stage III–IV. More in details, in this international, randomized and double-blind trial, 60% of women treated with olaparib (n=260) remained free from progression at 3 years compared to 27% of patients receiving placebo (n=131).[13]

To date, no studies have been published on the efficacy of olaparib in BRCA-mutated ESOC. Within this context, the aim of our review is to summarize the mechanisms of action of PARPis in BRCA-mutated cells, proposing potential clinical applications in ESOC.

BRCA Role

In human cells there are several pathways of DNA repair:[14,15] direct repair, mismatch repair, base excision repair and nucleotide excision repair act on DNA single strand breaks (SSBs)[16] conversely, non-homologous end-joining (NHEJ) and homologous recombinational (HR) repair act on double-strand breaks (DSBs).[17,18] Any qualitative or quantitative alteration of proteins, enzymes or co-factors involved in the DNA damage response may cause a deficit of DNA repair, leading to mutagenesis. BRCA 1 and 2, located on chromosome 17 and 13, respectively, represent two of the most clinical relevant tumor suppressor genes involved in the HR system.

More in details, DSBs activate the kinases ATM, ATR, and CHEK2, which phosphorylate BRCA1 and regulate its function. Then, BRCA1 and BRCA2 form complexes that repair the DSBs in cooperation with RAD51 protein.[19–22]

Consequently, mutation in BRCA 1 or BRCA 2 leads to a deficient HR, a status known as Homologous Recombination Deficiency (HRD). Additionally, BRCA1/2 mutations in heterozygosis may cause the loss of the non-mutated (wild-type) allele, situation defined as genomic loss of heterozygosity (LOH), and prevent the correct DNA damage response.

Since several proteins interact and cooperate with BRCA1/2 in the DNA repair process and in the maintenance of genomic stability, all the genes implicated in the DNA damage response in the HR system would be alternative candidates for ovarian cancer susceptibility. Patients with a defect in the HR system other than BRCA are defined "BRCAness", being their tumors with features and behaviors similar to BRCA-related ovarian cancers,[23] including higher sensitivity to DNA-damaging agents (eg, platinum compounds), longer disease-free intervals and survival rates, and high-grade serous histology.[24,25]

About 50% of all HGSOC are estimated to have HRD,[10] with about a 20–25% of carcinomas with the detection of a somatic BRCA mutation. Of these, about 15% are confirmed by a germline BRCA mutation, while 5–10% are not and thus arisen during the carcinogenesis process.[11]

Mechanism of Action of Parp Inhibitors

PARP is a large family of 18 proteins[26] that use nicotinamide adenine dinucleotide (NAD+) as a substrate. PARP-1 and PARP-2 represent the best-characterized subtypes: they are activated by DNA damage and facilitate DNA repair in pathways involving SSBs and base excision repair.[27] Upon binding to the damaged DNA, PARP-1 increases its catalytic activity and uses NAD^+ to create polymers of poly (ADP-ribose) (PAR), and then transfers them to acceptor proteins, including PARP itself.[28] This auto-poly ADP-ribosylation recruits various other proteins to the site of the DNA damage (PARP dependent DNA damage repair proteins), forming a repair complex. Ultimately, PARP-1 undergoes a molecular change that leads to a reduced affinity for DNA and, consequently, to the release of the damaged DNA site

that may be accessed by other repair complex proteins.[28] Additionally, over-activation of PARP-1 induces a reduction of NAD^+ and ATP, resulting in cellular dysfunction possibly leading to necrosis or apoptosis.[29] PARPis act as NAD + competitive inhibitors: they bind to the PARP enzymatic catalytic domain, inhibiting the PARP activation and the subsequent DNA repair that involves SSBs.[30,31] In this way, BRCA-mutated cell or with HRD, having already a deficient double-strand breaks (DSBs) repair, cannot correct DNA damage and thus go against death, mechanism called Synthetic Lethality.[32–34]

Moreover, PARPis prevent the molecular change necessary for the release of the PARP itself from the site of the DNA damage. In this way, PARPis impede the access of other repair proteins to the site of DNA damage, mechanism known as PARP trapping, and form toxic PARP-DNA complexes,[35] that are more effective at killing cancer cells than unrepaired SSBs caused by the absence of PARP. The potency to trap PARP–DNA complexes varies across the different PARPis and it is not related with their PARP catalytic inhibition potency. In fact, veliparib is a highly potent catalytic PARPi with a limited trapping of PARP–DNA complexes in comparison with olaparib and niraparib.[36] The high efficiency at trapping PARP–DNA complexes is correlated to clinical potency of PARPis.

Murai et al demonstrated that talazoparib, olaparib and rucaparib are comparable at inhibiting PARP catalytic activity, but talazoparib is 100-fold more potent at trapping PARP–DNA complexes. They showed that talazoparib is the most potent clinical PARPi in genetically modified chicken and human cancer cell lines (prostate cancer cells, breast cancer cells and Ewing's sarcoma cells) although talazoparib is more cytotoxic than olaparib.[37]

Synthetic lethality and PARP trapping explain either the non-uniform efficacy of PARPis in different patients, or their effect also in non-mutated BRCA patients and HR proficient patients.

A recent metanalysis underlined the role of PARPis in whole ovarian cancer population regardless of BRCA mutational status, as shown by outcomes improvement in wild-type ovarian cancer patients too (HR in wild type: 0.49, 95%, CI: 0.41–0.59, p<0.00001).[38]

Potential Role of Olaparib in Early Stages Ovarian Cancer

Although studies focusing on the use of olaparib in newly diagnosed patients with ESOC are lacking in literature, we may hypothesize that the use of PARPi could be beneficial in this category of patients, justifying the attempt to use them in future clinical trials.

Potential Role in Maintenance Setting

Adjuvant chemotherapy is recommended for patients with grade 2–3 serous histotype and grade 3 endometrioid histotype ovarian cancer, at early stage (FIGO stage I–IIA). Standard chemotherapy consists of 3–6 cycles of platinum-based compounds plus paclitaxel.[5,39] This indication derives from two randomized controlled trials on the use of adjuvant chemotherapy in ESOC. In the ACTION study, 448 women with epithelial ovarian cancer at stages Ia–Ib and grades 2–3 and all stages Ic and IIa and clear cell ovarian cancer at all stages I–IIa were randomized to either adjuvant platinum-based chemotherapy (n = 224) or observation (n = 224) following surgery.

The primary objectives were overall survival (OS) and progression-free survival (PFS). After a median follow-up of 5.5 years, PFS was significantly longer in the adjuvant chemotherapy arm (HR 0.63, 95% CI 0.43 to 0.92; P 0.02) with no difference in OS (HR 0.69, 95% CI 0.44 to 1.08; P 0.10).[40] The benefit in terms of PFS was confirmed by the ICON-1 trial, in which patients treated with chemotherapy had an improvement of both PFS (HR 0.65; 95% CI 0.46 to 0.91; P 0.01) and OS (HR 0.66; 95% CI 0.45 to 0.97; P 0.03).[41] Despite improvements in ovarian cancer survival, up to 40%-50% of women with ESOC develop relapses after the first diagnosis and may die from ovarian cancer.[8,9]

Based on these results, adjuvant chemotherapy is indicated for early stages, regardless of lymph-nodes status, thus lymphadenectomy is not universally performed by expert gynecologic surgeons.

Regarding the advanced disease, the efficacy of PARPis in maintaining after upfront chemotherapy is confirmed in several phase III trials (Niraparib in PRIMA trial, Veliparib in VELIA).[42,43]

Both enrolled wild type patients too, then stratified on the BRCA mutation and HRD status, and showed that PARPi leads to an improved PFS regardless of these characteristics of patients, albeit with some differences between the comparison arms.

VELIA trial assessed the efficacy of veliparib plus first-line chemotherapy with or without the same PARPi in maintenance, while the arm with intravenous chemotherapy alone followed by veliparib in maintenance was not envisaged in the study design.[42] Differently, PRIMA trial treated the same subset of patients with niraparib or placebo only after a response to platinum-based chemotherapy.[43]

On the subject of olaparib, the SOLO-1 trial administered it as maintenance therapy in case of a complete or partial response to platinum-based upfront chemotherapy for only BRCA-mutated OC and has demonstrated the positive effect of maintenance therapy with it in terms of PFS in patients with BRCA mutated advanced ovarian cancer after first-line chemotherapy (HR 0.30; 95% CI 0.23 to 0.41; P <0.001).[13]

Moreover, the phase III PAOLA-1 trial showed an improvement in PFS in case of maintenance therapy with olaparib plus bevacizumab, substantial in patients with HRD-positive tumours, including those without a BRCA mutation: 537 patients with a response after first-line platinum–taxane chemotherapy and bevacizumab were assigned to receive olaparib and 269 to receive placebo while bevacizumab continued to be administered in both arms. The median PFS resulted of 22.1 months with olaparib plus bevacizumab versus 16.6 months with bevacizumab and placebo (HR for disease progression or death, 0.59; 95% confidence interval [CI], 0.49 to 0.72; P<0.001).[44]

Given the efficacy of olaparib in the advanced setting, it is reasonable that this PARPi may have a positive effect also on earlier stages, even if it has not yet been tested in this context.

In addition, the safety profile of olaparib appeared to be generally acceptable in patients receiving maintenance treatment, after a first-line chemotherapy.

In fact, grade 3–4 haematological toxicity in the SOLO-1 trial was observed as follows: leucopenia in 3% of cases, thrombocytopenia in 1% of cases, neutropenia in 6% of cases.

Anemia was more frequent, and occurred in 22% of patients. Gastrointestinal toxicity was found with a frequency of 3%. Although nausea and fatigue were the adverse effects most frequently associated with olaparib (77% and 63%, respectively), they occurred in a severe grade (grade 3–4) only in 1% and 4% of cases, respectively.[13]

Potential Role as Monotherapy

As mentioned above, the use of adjuvant chemotherapy should be considered in ESOC, except for cases indicated in Table 1. Carboplatin alone (six cycles) or carboplatin plus paclitaxel (3–6 cycles) are both considered acceptable regimens, since literature data did not show a benefit in survival for the use of one schedule in comparison with the other one.[5]

However, the administration of carboplatin plus paclitaxel is not free from complications or contraindications. In these cases, olaparib could be an alternative therapeutic strategy to be tested in clinical trial.

The Phase II 42 trial explored the use of olaparib (capsules) monotherapy in 193 patients affected by platinum-resistant recurrent ovarian cancer with BRCA-deficiency (germline only). The response rate was 31.1% (60 of 193; 95% CI, 24.6 to 38.1).[45] In a subgroup of patients who had received ≥3 prior lines of chemotherapy (n=154 out of the 193 patients), 89% of patients (n=137) had measurable disease at baseline and among them, objective response rate was 34% (46/137; 95% CI 26–42) and the duration of response was 7.9 (95% CI 5.6–9.6) months.[46] Consequently, based on this analysis, on December 19, 2014, the FDA granted the accelerated

Table 1 Ovarian Cancers in Which the Benefit of Adjuvant Chemotherapy Is Absent or Unclear

Benefit of Adjuvant Chemotherapy	Figo Stage	Histology	Grade	Level of Evidence	Strength of Recommendation
NO	IA	SEROUS	LOW GRADE	II	A
	IA	ENDOMETRIOID	I–II		
	IA (expansile invasion)	MUCINOUS	I–II		
UNCERTAIN	IB-IC	SEROUS	LOW GRADE	III	C
	IB-IC	ENDOMETRIOID	I–II		
	IC	MUCINOUS (expansile invasion)	I–II		
	IA	MUCINOUS (infiltrative)			
	IA-IB-IC1	CLEAR CELL			

Abbreviation: FIGO, International Federation of Gynecology and Obstetrics.

approval to olaparib as fourth-line therapy for women with BRCA-deficient (germline only) ovarian carcinoma. Following these positive results, the SOLO-3 phase III trial was designed. SOLO-3 is a randomized, open-label, controlled and multicentre trial, in which the efficacy and safety of olaparib (tablets) mono-therapy were tested, compared with a standard mono-chemotherapy, in a total of 266 patients with platinum-sensitive relapsed high-grade serous or endometrioid ovarian cancer. The hazard ratio for PFS evaluated by independent central review was 0.62 (95% CI 0.43–0.91; P 0.013), with a median of 13.4 months in the olaparib arm versus 9.2 months in the standard mono-chemotherapy arm. The PFS evaluated by investigator's assessment was 0.49 (95% CI 0.35–0.70; P < 0.001), with a median of 13.2 months versus 8.5 months, respectively.[47]

Anyway, it should be considered that it is true that these data refer to patients with recurrence of OC and evident disease and thus different from subset of patients of our interest but, exactly for this, even greater should be the benefit for the latters due to a reduced tumor load after surgery or, as hopefully, absent.

Assuming that, even if the efficacy of monotherapy with olaparib is proved for recurrent disease, there are some conditions in which it could be used instead of chemotherapy, also in newly-diagnosed patients, and thus, in our opinion, it is worthy of evaluation in future clinical studies.

Potential Role Considering Toxicity, Safety and Compliance to Standard Chemotherapy

Several adverse events have been observed during the administration of carboplatin and paclitaxel. Haematological toxicity develops quite frequently: grade 3–4 leukopenia, thrombocytopenia or granulocytopenia are associated with this chemotherapy regimen in about 60%, 40% and 90% of cases, respectively.[48] Moreover, 40–70% of patients develop severe anemia (grade 3–4) during this chemotherapy treatment.[49] Other adverse effects include: neurotoxicity (grade 3, 7%), gastrointestinal toxicity (grade 3–4, 10%), cardiovascular and renal toxicity, and hypersensitivity reactions.[50] Recently we showed that first-line platinum-based chemotherapy in BRCA-mutated ovarian cancer patients is associated with worse hematological toxicity profile. Higher frequency of thrombocytopenia (24% vs 5%; P < 0.001), anemia (21% vs 7%; P 0.006) and neutropenia (62% vs 27%; P ≤0.001) is observed in BRCA-mutated patients compared to wild-type patients.[51]

Hence, it could be useful to assess mono-therapy with olaparib in BRCA-mutated patients and to compare toxicity profiles and clinical benefit, thus avoiding platinum-based chemotherapy. Liu and colleagues explored the adverse events associated with olaparib mono-therapy, comparing with olaparib plus cediranib. They found grade 1–2 neutropenia in 11% of patients and grade 1 thrombocytopenia in 7% of patients in the olaparib group. According to the previous results, anemia, nausea and fatigue were the most frequent adverse events and occurred with a grade 2 severity in 4%, 26% and 15% of cases, respectively. However, there was not grade 3–4 haematological or non-hematological toxicity, except for 11% of patients with grade 3 fatigue.[52] In conclusion, despite the absence of studies directly comparing the toxicity of olaparib versus chemotherapy, these data suggest that this PARPi could be more tolerated, showing a more acceptable safety profile than carboplatin and paclitaxel doublet chemotherapy.

Moreover, intravenous administration of chemotherapy requires a greater compliance of patients with necessity to access to the hospital every 3 weeks, or even more frequently in case of dose-dense chemotherapy schedule. Preservation of health-related quality of life (HR QoL) is important for cancer patients during treatment, especially in patients affected by ovarian cancer in which the treatment is often palliative. There are few studies that investigated the impact of chemotherapy on quality of life (QoL) in ovarian cancer patients. The majority of them have demonstrated that the QoL is strongly compromised in these patients.[53] As an example, in the MITO-8 study, it has been shown that there is a worsening of the QoL in 30.6% of recurrent ovarian cancer patients treated with platinum-based chemotherapy. Peripheral neuropathy and other chemotherapy side effects were more frequently severe in the platinum-based chemotherapy arm, and consequently, the higher rate of toxicity negatively affected the QoL.[54]

The role of the QoL is more prominent in the maintenance setting, given that patients previously responded to chemotherapy, showing no disease-related symptoms.

Ledermann and colleagues have demonstrated with the results of the Study 19, that adverse events of olaparib were manageable, with a discontinuation rate of 4.4% for the olaparib group versus 1.6% for the patients who received placebo. In this study, the HR QoL was evaluated as a secondary objective, and the results confirm that the

maintenance treatment with olaparib did not have an adverse impact on HRQoL in patients with relapsed ovarian cancer, who showed a high compliance to the treatment.[55,56]

Furthermore, data from a recently published meta-analysis suggest that there is no appreciable difference in the QoL for patients receiving olaparib compared with placebo or PLD (P 0.058) and that olaparib maintenance therapy is well tolerated by patients affected by platinum-sensitive BRCA-mutated ovarian cancer.[57]

Results from the phase III SOLO-1 trial showed that two-year maintenance therapy with olaparib led to an improvement in PFS in newly diagnosed patients with advanced ovarian cancer and a BRCA1/2 mutation without detriment to quality of life.[13]

Although data on quality of life of recurrence ovarian cancer patients in maintenance setting suggest a good tolerability of olaparib, no studies have been conducted to compare the quality of life of patients receiving chemotherapy and patients treated with olaparib monotherapy.

It has been demonstrated that the quality of life in ovarian cancer patients treated with standard chemotherapy could be compromised. However, prolonged therapies with fairly tolerable drugs could affect the quality of life of the patients more than treatments with greater toxicity administered for a shorter period of time.

Therefore, comparative studies of quality of life of these patients are needed.

Concerning the drug hypersensitivity reactions, literature data report that the incidence of allergic reactions to carboplatin, ranges from 8% to 16% but can reach 44% in second- and third-line settings. In patients who develop moderate or severe allergic reactions, platinum-based chemotherapy is discontinued, despite its potential clinical benefit. For this reason, many efforts have been made to identify risk factors that may predict hypersensitivity reactions. Medical data of patients enrolled in two clinical trials of combined therapy (olaparib plus carboplatin) were reviewed by Moon and colleagues. The authors showed that the incidence of carboplatin-related hypersensitivity reactions was 21%, and the majority of the patients who developed allergic reactions had a deleterious BRCA1/2 mutation (93%) ($p<0.0001$). They concluded that BRCA1/2 mutation carriers have an increased susceptibility and a shortened time to carboplatin hypersensitivity reactions. The development of an allergic reaction to carboplatin did not adversely affect clinical benefit despite delays or treatment discontinuation, probably due to the activity of olaparib in BRCA mutation carriers.[58]

Regarding the allergic reactions to olaparib, they have been reported in several patients worldwide. Hives, dyspnea and dizziness may be signs and symptoms of hypersensitivity reactions, however these are uncommon side effects (<1%). A case report by colleagues of Charité European Competence Center for Ovarian Cancer of Berlin, describes a specific 2-day desensitization protocol used after an allergic reaction of angioedema and cutaneous wheals, developed by a patient. The protocol required subsequent oral applications of incremental doses of specifically prepared olaparib capsules, with a starting dose of 12.5 mg and a final dose of 800 mg. No additional drugs such as antihistamines or glucocorticoids were used and no adverse effects have been reported.[59]

Given the effectiveness of olaparib for the treatment of BRCA-mutated ovarian cancer patients, desensitization can be a promising option in patients who develop this category of side effects.

Elderly women, the so-called “frail patients”, represent another category of patients that may have difficulty receiving intravenous chemotherapy.

There are a few data on elderly patients affected by ovarian cancer in the literature. This is due to poor recruitment of these patients in clinical trials. Interestingly, the AGO-OVAR group showed that more severe adverse events occurred in elderly patients (febrile neutropenia 5% in patients >70 years old versus <1% in younger ones, P 0.005).[50]

However, most recently, the results of the EWOC-1 trial have been presented. The aim of the study was to identify vulnerable elderly ovarian cancer patients and evaluate the best first-line treatment regimen in terms of feasibility and clinical benefit. One hundred twenty patients (>70 years old) with FIGO stage III–IV OC were randomized to receive carboplatin AUC5-6 + paclitaxel 175mg/m2 3weekly or carboplatin AUC5-6 3weekly or carboplatin AUC2 + paclitaxel 60mg/m2 weekly. This study proved that carboplatin plus paclitaxel is more active than carboplatin alone, but it was prematurely closed due to significantly worse survival in carboplatin alone arm. Anyway, among patients treated in this trial the main reason for end of treatment was toxicity, which occurred in percentage from 15% to 22.5%.[60]

Dockery and colleagues have conducted the first study that reports data on toxicity and tolerability of olaparib in older women. Patients >65 years old were stratified into age groups by 5-year increments (ages 65–69, 70–74, ≥75 years old) and compared to those <65 years old. They

demonstrated that there were no significant differences in toxicities across the different age groups (Grade 3/4 nausea in 2% of patients <65 years compared to 3% of patients aged 65–69 years, 4% of patients aged 70–74 years, and 0% of those ≥75 years (p = 0.69), grade 3/4 anemia in 13% of patients <65 years compared to 13%, 9%, and 24% of patients aged 65–69 years, 70–74 years, and ≥75 years, respectively (p = 0.70) and that the tolerability was similar between elderly and younger patients.[61]

In conclusion, for patients who really need the adjuvant treatment but cannot tolerate it, eg, in case of toxicity, scarce compliance, known allergic reactions to platinum or paclitaxel or advanced age, alternative strategies should be investigated and olaparib could represent a concrete possibility.

Potential Role in Case of Fertility-Sparing Desire

Young women with a desire for pregnancy and undergoing a fertility-sparing surgery represent a group of patients who could benefit from the use of olaparib instead of chemotherapy and should be included in potential studies evaluating the effectiveness of this alternative approach.

Fertility-sparing surgery (FSS) in ovarian cancer is based on unilateral salpingo-oophorectomy and complete surgical staging (peritoneal washing, omentectomy, peritoneal and retroperitoneal biopsies).[5] According to NCCN guidelines, this approach can be considered for patients with apparent early-stage disease (FIGO stage IA-IC) and/or low-risk tumors (early-stage invasive epithelial tumors, LMP lesions, malignant germ cell tumors, mucinous, or malignant sex cord-stromal tumors) who wish to preserve fertility.[39] In the recent ESMO and ESGO guidelines, a conservative approach is indicated for low grade IA and IC1 EOC with unilateral involvement, in case of mucinous, serous, endometrioid or mixed histotype.[5] However, the role of FSS is still debated for high-risk patients (clear cell, stage> or equal IA G3).[62,63] More in details, Fruscio et al, in a retrospective study of 240 patients with malignant ESOC treated with fertility-sparing surgery, confirmed that a high grade of nuclear differentiation (G3) was the only predictor for survival, associated with a significant higher rate of distant recurrence (RFS: HR 4.2, 95% CI 1.5–11.7; P 0.0067; OS: HR: 7.6, 95% CI: 2.0–29.3, P 0.0032).[63] However, patients with G3 tumors included in this study, had a comparable prognosis in terms of disease-free and overall survival compared to patients with G3 neoplasia included in the ICON1/ACTION trial where all women underwent radical surgery.[40,64] Recently, Bentivegna and colleagues have showed that the majority of the relapses occurring after a conservative surgical approach are extra ovarian, suggesting that the preservation of one ovary is not necessarily the cause of the recurrence.[65] Moreover, the adjuvant therapy in early-stage epithelial ovarian cancer ESEOC improves survival and delays recurrence in patients with IC stage, as demonstrated by the ICON 1, an open-randomized trial. More in details, the group who received adjuvant chemotherapy immediately following surgery had better overall survival (HR 0.66, 95% CI 0.45–0.97; P 0.03) and recurrence-free survival compared to patients who did not receive any post-operative treatment (HR 0.65; 95% CI 0.46–0.91; P 0.01).[41] However, the role of postoperative chemotherapy after FSS is controversial. Fruscio et al evaluated the safety of FSS for ESEOC without confirming the independent positive role of FSS neither on relapse-free interval (RFI) (HR 0.83, 95% CI 0.52–1.34; P 0.450) nor on cancer-specific survival (CSS) (HR 0.81; 95% CI 0.54–1.20; P 0.300). Clinical practice suggests that patients treated with FSS should receive adjuvant chemotherapy in case of high-risk factors (eg, high-grade clear cell histology, tumor growth through the capsule, surface excrescences, malignant cells in ascitic fluid or peritoneal washings, preoperative rupture and dense adhesion).[40,41,66–69]

In these cases, the fertility of the patients is negatively affected also by the gonadotoxic effect of the subsequent chemotherapy.[70] Platinum-based compounds and taxanes are the most used drugs in ovarian cancer. The impact on fertility of these drugs is variable, with a risk of 30–70% of amenorrhea, whereas protocols containing antimetabolites and anthracyclines are characterized by a lower risk (less than 30%). Germ cells are the most sensitive cells in the body to radiation and chemotherapy.[71] The reason for this high sensitivity to genotoxic and carcinogenic agents related to the presence of TAp63, a crucial molecule of the apoptotic pathway. TAp63, as a guardian of germ cells, decides the fate of the cells depending on the intensity of DNA damage.[72] Platinum based compounds and taxanes are female-specific mutagens.[73–75] They are classified in the medium-risk category of gonadotoxicity and may cause chromosomal aberrations leading to dyskarriosis, such as deletions, ring formations and DNA rearrangements, leading to embryotoxicity and embryonic demise.[74,76] In 168 cancer patients, the odds ratio of ovarian failure after platinum exposure was

1.77, second only to an odds ratio of 3.98 for the alkylating agents.[77]

On the other hand, the effect of paclitaxel on fertility has not been fully evaluated. However, in accordance with the available scientific data, it is assumed that paclitaxel might affect the ovarian reserve through the primordial follicles, while the most destructive effect on primary follicle count is attributed to platinum. The result is that combination of both the antiblastic agents causes a more prominent follicle loss.[78]

A study on animals revealed that paclitaxel and carboplatin can interfere with the ovarian function also by lowering the level of pituitary gonadotropin secretion (LH IU/mL 1.35 ± 0.92 vs 0.78± 0.36 paclitaxel, 0.40 ± 0.18 carboplatin, 0.10 ±0.01 in combination, FSH IU/mL 1.41 ± 0.48 vs 1.08 ±0.23 paclitaxel, 0.93 ± 0.48 carboplatin, 0.62 ± 0.27 in combination P <0.05) and increasing the production of oxygen-free radicals, causing a decreased number of healthy follicles and an increased number of atretic follicles.[79] Consequently, for patients treated with FSS and candidate to adjuvant therapy, some authors advise to cryopreserve oocytes, acquired during unilateral ovariectomy.[70]

While the gonadotoxic effect of intravenous chemotherapy is established, little is known about the damage to fertility due to olaparib. Studies about the reproductive and developmental toxicity and assessing male and female fertility were conducted in rats. Twenty-two female rats were treated with 0, 0.05, 0.5 or 15 mg/kg/day, from 14d prior to pairing (with undosed males) and continuing up to 6 days post-coitum inclusive. There was no effect of olaparib on mating performance or fertility (ovulation and pregnancy rates) at any dose level despite an increased incidence of extended oestrus during dosing. Moreover, olaparib leads to a reduced embryofetal survival at the higher dose of 15 mg/kg/day that was no longer present after a recovery period of 4 weeks.[80] Similarly, in male mice treated with olaparib for at least 70 consecutive days prior to pairing with undosed females and until fertility was proven, there were no test article-related effects on sperm counts, motility, or progressiveness, mating and fertility rates at doses up to 40 mg/kg/day of olaparib compared to controls.[81] On the other side, olaparib seemed to have a negative impact on embryo-fetal development with intrauterine death, major fetal malformations (eye, vertebra/ribs, skull and diaphragm) and minor skeletal and visceral abnormalities.[82,83] To sum up, after investigation in a clinical trial, olaparib could be administrated as adjuvant therapy to young women with the desire of future maternity, avoiding the period of the pregnancy or breastfeeding.

Conclusion

First-line treatment in ESOC is not universally established and studies focusing on olaparib and ESOC are lacking. Certainly, all mentioned above constitutes evidence to support our hypothesis prompting the design of future studies for this setting of patients.

In this regard, some points of reflection occur spontaneously:

-Researches of olaparib as monotherapy might start precisely from patients with new diagnosis of ESOC who cannot undergo chemotherapy (due to toxicity, allergy, bad performance status, scarce compliance, fertility sparing, difficult access to cancer care facilities) for which olaparib could be a valid alternative.

-Based on evidence of efficacy of PARPis with other indication not only in BRCA-mutated patients,[38,43,44,84] it would be better not to deprive wild-type patients of the possibility of receiving olaparib and, therefore, also of being involved in these initial evaluation/trials. The evaluation of HRD status could be useful. Anyway, testing BRCA-mutated patients in the first place could pave the way for subsequent enlargement of the study population.

- Studies including patients affected by ESOC and treated with olaparib monotherapy should be designed, also with a single arm, in order to test the efficacy of this agent and compare it with data already present in literature regarding upfront platinum-based chemotherapy. In fact, to our knowledge, previous comparative studies on the matter are lacking.

- Since the use of PARPis currently prevents receiving it at a later time, the studies should evaluate the real benefit of this first-line administration and in these stages with favourable prognosis. Long-term endpoints like OS would be more significant to be studied.

-Olaparib is not free from adverse events, clinical trials should be conceived paying particular attention to quality of life, especially for the prolonged administration.

-The major limit for the realization of potential trials is the restricted number of patients diagnosed with OC at an early stage that might affect the study recruitment.

Nevertheless, it is worthwhile carrying out eventual trials on olaparib and ESOC, even if with a big international effort, in order to provide patients with this promising therapeutic chance.

Disclosure

Drs Nicoletta Colombo reports personal fees from Roche, Pharmamar, Astra Zeneca, Clovis, Tesaro, GSK, Pfizer, Amgen, Immunogen, and Biocad, outside the submitted work. The authors report no other conflicts of interest in this work.

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