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Recurrent High Grade Serous Ovarian Cancer Management

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Abstract : Despite an aggressive treatment strategy for high grade serous ovarian cancer (HGSOC) that incorporates cytoreduction, platinum compounds, anti-angiogenic agents, and poly (ADP-ribose) polymerase (PARP) inhibitors, most patients, especially those who are with stage III-IV HGSOC, will relapse. The management of recurrent HGSOC is a challenging issue faced by gyneco-oncologists and medical oncologists in clinical practice. This chapter provides an overview of the current optimal management of recurrent HGSOC. First, recurrence is classified based on the time of onset. This is followed by a discussion on the place of surgery within the treatment strategy. Finally, the role of systemic treatments (chemotherapy, targeted agents, and immunotherapy) in the management of HGSOC are presented.

Keywords: chemotherapy for high grade serous ovarian cancer; high grade serous ovarian cancer; hyperthermic intraperitoneal chemotherapy; PARP inhibitors for recurrent high grade serous ovarian cancer; surgery for recurrent high grade serous ovarian cancer

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INTRODUCTION

The optimal treatment for high grade serous ovarian cancer (HGSOC) is upfront or intermediate complete cytoreduction to achieve a status of no residual tumor. This is combined with doublet chemotherapy of carboplatin and paclitaxel that can incorporate bevacizumab or Poly (ADP-ribose) polymerase (PARP) inhibitors as concomitant or maintenance therapies (1–3). Even with this aggressive treatment, most patients will relapse, especially those with stages III-IV HGSOC who failed to benefit from an optimal upfront surgery. Despite early responses to chemotherapy, the median progression-free survival (PFS) of these patients is 13.8 months (4). Therefore, gyneco-oncologists and medical oncologists are often confronted with recurrent HGSOC with poor outcome (5). The aim of this chapter is to update clinicians on the current optimal management of recurrent HGSOC. We first classify recurrences based on the time of onset. Then, we discuss the place of surgery within the treatment strategy, and finally, we elaborate on the options of systemic treatments available (chemotherapy, targeted agents, and immunotherapy).

TIME TO RECURRENCE

The time to recurrence (TTR) is a very important parameter for the management of HGSOC because it will determine the treatment strategy optimal for the patients. TTR is defined as the interval between the end of the primary treatment, which is, the last dose of platinum-based chemotherapy, and the recurrence. The detection of the recurrence is highly connected to the type of follow-up that was offered to the patient. Cancer antigen 125 (CA125) is a reliable biomarker to detect recurrences (level IA). After treatment, CA125 levels are considered positive if the detected levels reach twice the normalized baseline value or, in case of pathological levels, twice the nadir (6, 7). Rises in CA125 levels have been observed between 2 to 8 months prior to clinical symptoms of relapse (8). It is noteworthy that a randomized controlled trial led by EORTC showed that early treatment based on the rising CA125 levels fails to improve survival (9). However, to interpret these results meaningfully, it is important to know that this study was performed in 2011, at a time when no efficient targeted therapies were available for HGSOC, and, above all, that no surgery was offered to patients with elevated CA125 levels. The situation in 2022 is completely different as targeted therapies and surgery are now standard of care for recurrences. Of note, the European Group of Tumor Markers (EGTM) recommends including CA125 monitoring in follow-up examinations, especially in patients that could be considered for a second surgery (6).

Elevated CA125 is an independent prognostic factor for survival (10). If CA125 levels rise above the threshold, radiographic imaging (CT scan – PET scan – Diffusion IRM) should be performed to confirm the recurrence (11). Recurrences are defined by symptomatic progression or RECIST progression (Response Evaluation Criteria in Solid Tumors) (12). At the 5th Ovarian Cancer Consensus Conference of the Gynecologic Cancer Intergroup, it was stated that isolated elevations of CA125 without radiologic abnormalities should not be

TABLE 1 Classification of ovarian cancer recurrence

	Old classification	5th OCCCGCI classification
Resistant or refractory	PFI <6 months	TFIp <6 months Added information: TFInp, TFIb
Semi sensitive	PFI 6–12 months	TFIp 6–12 months Added information: TFInp, TFIb
Sensitive	PFI >12 months	TFIp >12 months Added information: TFInp, TFIb

Derived from Wilson et al. (13), 5th OCCCGCI: recurrent disease. For surgical studies, integration of TFI from last cytoreductive surgery could be valuable rather than TFI from the last chemotherapeutic or biological agent. PFI, Platinum free interval; TFI, treatment free interval; TFIp, platinum treatment free interval; TFInp,non-platinum agent treatment free interval; TFIb, biological agent treatment free interval.

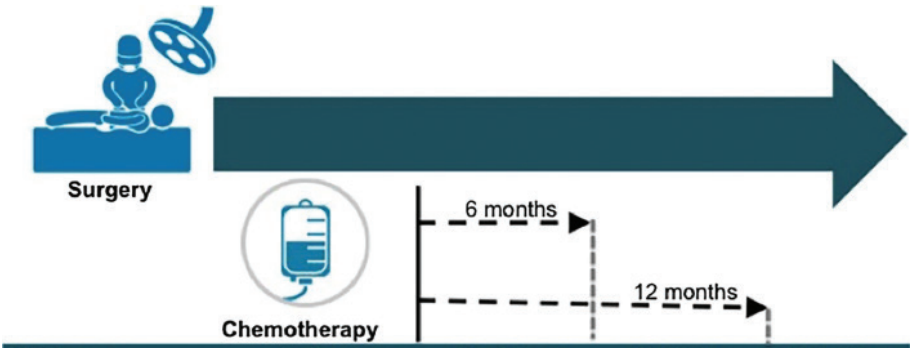
considered as a recurrence and should not trigger renewed administration of chemotherapy or targeted therapy (13). The use of hormone therapy, such as tamoxifen, could be considered in this situation, especially in tumors with high expression of the estrogen receptor. But there is very limited evidence towards its efficacy and only very low response rates have been reported (14, 15). Thus, hormone therapy is not recommended. Therapeutic abstention is considered as the best option in this case.

Historically, recurrences were classified based on the interval between the date of the relapse and the date of the last platinum regiment. The definitions "platinum-resistant" and "platinum-sensitive" were based on three relatively small retrospective studies (16–18), in which, recurrence was diagnosed clinically or radiologically, without the systematic use of CA125 – a situation very different from our present management strategy. The 5th Ovarian Cancer Consensus Conference of the Gynecologic Cancer Intergroup stated that the Platinum-Free Interval (PFI) remains a good tool to stratify the patient. But the method of diagnosing the recurrence needs to be considered and registered systematically.

Furthermore, at in an era of maintenance treatment and targeted therapy, future clinical trials should not only be designed based on last platinum regimen but also on the last treatment regimen, i.e., using the Treatment-Free interval (TFI) rather than PFI (13) (Table 1). Currently, little is known about the influence of these new therapies on tumor biology and the response to subsequent treatment. PFI remains the main criterion to stratify patients and select the treatment for the recurrence. The following sections describe the different therapeutic strategies.

TREATMENT FOR RECURRENCE

Different treatment options must be evaluated when a patient presents with recurrence. Deciding on the course of treatment depends on several factors, such as the platinum interval, (Figure 1) histological subtype, mutational status, Eastern



Platinum sensitivity classification	Refractory	Resistant	Partially sensitive	Sensitive
Probability of second platinum response	0%	<10%	30%	>50%

Figure 1. Platinum resistance definition by GOG. From Oronsky B, et al. Med Oncol. 2017;34(6):103

Cooperative Oncology Group (ECOG) performance status, previous complete cytoreductive surgery, previous type of chemotherapy, number of previous line of chemotherapy and reaction to it, previous other types of therapy, presence and types of symptoms, among others (13). The main categories of treatment, such as, surgery, chemotherapy, biological agents, and radiotherapy are described here. Best supportive care must also always be considered and discussed with the patients and their family.

Surgery for first relapse (secondary cytoreduction surgery)

Surgery for *platinum-resistant* patients (PFI< 6 months), or progressive disease during or soon after the completion of chemotherapy, is generally not recommended (19). Small retrospective studies have shown very short disease-free survival (DFS) and high complication rates (20, 21). This category of patients is usually excluded in clinicals trials that evaluate surgery for recurrent ovarian cancer. The rest of the discussion in this section focuses on platinum-sensitive sensitive recurrent ovarian cancer.

Secondary cytoreductive surgery must be proposed to patients with *platinum-sensitive* (PFI > 6 months) recurrent ovarian cancer. Three clinical trials (22–24) showed an improvement of the DFS for these patients if the surgery resulted in complete cytoreduction. One of the studies also demonstrated, for the first time, an overall survival (OS) benefit in this scenario (Table 2). The only study showing an OS benefit is the DESKTOP III trial. The difference in the observed OS benefits between the DESKTOP III trial and the GOG213 trials might be explained by the different proportion of patients that received bevacizumab, and the selection criteria for patients that were applied.

TABLE 2 **Three major randomized clinical trials for secondary cytoreduction in recurrent platinum-sensitive ovarian cancer**

Variables	DESKTOP III	GOG213	SOC-1
Total number of patients	407	485	357
Age	60.5	57	54.1
Secondary cytoreduction (SC)/ chemo alone (CA)	206/201	240/245	182/175
Selection criteria	AGO score	By investigator	iMODEL score
Rate of CR	74.5%	67%	76.7%
PFS SC/CA (months)	18.4/14	18.9/16.2	17.4/11.9
OS SC/CA (months)	53.7/46	50.6/64.7	58.1/53.9 *(not mature)*
Platinum-based chemotherapy	89%	100%	97%
2nd line Bevacizumab	23.1%	84%	1%
2nd line PARPi maintenance	11%	0%	4.9%

DESKTOP: Descriptive Evaluation of pre operative Selection KriTeria for Operability; GOG, Gynecologic Oncology Group; SOC, Surgery or chemotherapy in recurrent Ovarian Cancer; CR, complete resection; PFS, progression free survival; PARPi, Poly(ADP-ribose) polymerase inhibitor

The DESKTOP III trial is the result of a long and rational work with a validated scoring system for patients who will benefit from second cytoreductive surgery. The Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) first retrospectively validated criteria (Table 3) that correctly predicted complete resection in 80% of patients (Descriptive Evaluation of perioperative Selection KriTeria for OPerability in recurrent OVARian cancer – DESKTOP OVAR). In this retrospective DESKTOP I trial was also confirmed that only complete surgery resulted in survival benefits for the patients (25). In DESKTOP II, the scoring system the AGO developed was used to prospectively predict resectability. The group showed that complete resections were achieved in 76% of patients with a positive AGO score (26).

Finally, the DESKTOP III aimed at evaluating the efficacy of the AGO score as a criterion that identifies patients that would benefit from secondary cytoreductive surgery. In the trial, patients with a positive AGO score (=0) were randomized in 2 groups that either received only chemotherapy or cytoreductive surgery followed by chemotherapy. The study showed that cytoreductive surgery offered to patients who met the strict AGO selection criteria resulted in prolonged OS and PFS. These results were even more pronounced in patients in whom complete resection was achieved. Finally, the trial determined that the patient's quality of life was not worsened by second cytoreductive surgery.

In the SOC-1 trial, the iMODEL score (based on complete resection at first surgery, residual disease after primary cytoreduction, progression-free interval, Eastern Cooperative Oncology Group (ECOG) performance status, CA125 and ascites at the recurrence) was used to select patients that might benefit from surgery. Similar to the AGO score of the DESKTOPIII trial, a high complete

TABLE 3 **AGO score to predict resectability in recurrent ovarian cancer**

AGO score
Complete resection at the first surgery
Good performance status (OMS 0-1)
Ascites < 500 ml

resection rate (77%) was achieved in patients selected by the iMODEL score. The GOG 213 trial did not randomize patients. Instead, patients were selected at the surgeon's discretion without predefined criteria. This study observed lower complete resection rate than the two other trials. In the whole study cohort, there was no statistically significant benefit from the surgery compared to chemotherapy alone. A recent meta-analysis of the three trials concluded that surgery is beneficial at first recurrence in platinum-sensitive ovarian cancer (27).

All three trials observed clear benefits for patients offered secondary complete cytoreduction surgery. However, selecting patients who might benefit pre-operatively using validated criteria is crucial (28).

Surgery after the first recurrence (tertiary cytoreductive surgery)

Most patients who achieve a complete response to their first relapse nevertheless carry significant risks to further subsequent recurrences. The management for further recurrences is less well established than for first- and second-line treatment strategies. Currently, only chemotherapy is proposed. However, complete cytoreductive surgery may be achieved once more in very well selected patients. A recent meta-analysis pooled the results of 10 studies (Data from 759 patient) that evaluated the role of tertiary surgery, excluding patients with platinum-resistant disease. It confirmed that patients with complete tertiary resections (TCR) had longer disease specific survival (DSS) (HR= 0,35) and OS (HR= 0,34) than patients with sub-optimal resections (29). The authors of this meta-analysis analyzed the rate of complete cytoreductive surgery in the studies included as well as any major impact on survival. Further, the authors also considered other factors that influence survival after TCR, such as TFI, amount of abdominal disease, distant or mesenteric nodes, and platinum-sensitivity. Despite its limitations, the study shows that patients benefit from complete cytoreduction even during their second relapse. The authors concluded that all effort must be exerted to achieve complete cytoreduction in very well selected patients with second relapse.

Hyperthermic Intraperitoneal chemotherapy (HIPEC)

ESGO-ESMO's most recent recommendations (9) for managing ovarian cancer did not recommend HIPEC for recurrent ovarian cancer because well-designed studies to assess its efficacy are still lacking. However, a recent meta-analysis showed that combining secondary cytoreductive surgery with HIPEC results in

OS benefits without DFS advantages (30). It is noteworthy that the studies included in the meta-analysis were very heavily criticized because of their methodology, variability in the HIPEC protocol, the selection of patient, among others. It is highly likely that the benefits in OS without prolonged DFS are due to bias rather than the treatment itself. Thus, HIPEC remains excluded from the standard of care for recurrent ovarian cancer. We await the results of ongoing prospective randomized trials on HIPEC in recurrent OC (clinicaltrial.gov).

Chemotherapy and new therapeutic agents

For decades, chemotherapy has been the only treatment proposed for recurrent ovarian cancer. Recent progress in biological agents and targeted therapies has led to a dramatic change in the standard of care. BRCA-mutated HGSOC patients usually respond very well to chemotherapy and benefit from Olaparib in the first-line with a median PFS of 56 months (31). Interestingly, 88% of these patients will remain relapse-free after one year. These women will in all probability fit all the AGO criteria and thus a secondary maximal cytoreductive surgery must be proposed to them when they present with a recurrence (see above).

Non-BRCA-mutated patients, who underwent a cytoreductive surgery without residue, could not be offered maintenance therapy with PARP inhibitors in the vast majority of countries because they were not included in the PRIMA trial. Most non-BRCA-mutated patients are expected to relapse after 12 months (4). Considering that most of these women will fit the AGO criteria, second cytoreductive surgery must be discussed at relapse. Non-BRCA-mutated patients who receive maintenance treatment with niraparib after surgery and chemotherapy has a median PFS increased from 8.2 months to 13.8 months (4). Half of these patients will relapse after one year and should be considered for second surgery based on the AGO criteria. With PARP inhibitors as new first-line maintenance treatment, the proportion of platinum-resistant disease has decreased significantly. The efficacy of rechallenging with carboplatin in patients progressing under PARP inhibitors is presently unknown. With that caveat, the choice of chemotherapeutic agent is still based on the platinum-free interval.

PLATINUM-RESISTANT DISEASE

As discussed above, the manner in which the recurrence is discovered strongly impacts the management of platinum-resistant disease and has to be considered in clinical trials. Old studies used to only include symptomatic patients or used older generations of scanners to diagnose RECIST progression. Today, it is very different. Systematic evaluation of CA125 levels, high-definition CT scanners, and PET scans will detect recurrences earlier. Clearly, patients who have received early diagnosis of recurrence through modern techniques cannot be compared to patients who display symptoms within 6 months post first-line treatment. Furthermore, studies that include patients who are resistant after first-line therapy have to be considered separately to studies concerning patients who acquired resistance after several lines of chemotherapy. Finally, we now collect genetic and biological information on the initial tumor and the recurrence that may also

influence subsequent treatment strategies. This aspect also must ideally be considered, and patients stratified accordingly in future clinical trials (as recommended by the OCCCGCI). For example, platinum-resistant patients with BRCA mutation respond much better to platinum-based chemotherapy than non-BRCA mutated patients and should thus receive platinum even during early relapses (32).

Treatment options

The standard chemotherapeutic agents used in platinum-resistant ovarian cancer (PROC) are non-platinum mono-chemotherapy, including paclitaxel, topotecan, gemcitabine, and pegylated liposomal doxorubicin (PLD). None of these agents shows superiority over the other (33). The median response rate remains very poor (10–35%) with a high risk of rapid progression after the initiation of treatment (34). Combining cytotoxic drugs leads to higher toxicities with no clear added benefits to response rates and survival. Over the decades, numerous phase 2 and 3 trials observed a progressive improvement of the DFS and OS, probably due to a better selection of patients, and including patients with early diagnosis of the recurrence (as discussed above) (35).

Anti-angiogenic agents have shown improvements in DFS. Bevacizumab , an antibody directed against VEGF (vascular endothelial growth factor), blocks the interaction of VEGF with its cognate receptor and inhibits angiogenesis (36). A randomized phase III trial in patients with recurrent platinum-resistant ovarian cancer demonstrated that bevacizumab increased PFS (three months) and the response rate, but not OS (37). Therefore, bevacizumab is a standard of care applicable to recurrent ovarian cancer. Trebananib, an angiopoietin 1 and 2 inhibitor, also improved PFS in the TRINOVA trial (paclitaxel plus trebananib versus placebo) (38). A recent phase II trial showed some added efficacy of using an immunomodulator of the glucocorticoid receptor, relacorilant, in combination with nab-paclitaxel (39). This result must be confirmed in a randomized phase III trial. A randomized phase III trial that compared trabectedin (ET-743, a marine-derived antitumor agent) against other chemotherapeutic agents of the investigator's choice in PROC patients failed to demonstrate any superior activity of ET-743 but reported higher toxicity (40). Considering the lack of any efficient standard of care and that the combination of chemotherapy and bevacizumab results in only minimal long-term responses, we propose that those patients with resistant ovarian cancer should be included in clinical trials

PLATINUM-SENSITIVE DISEASE

The role of chemotherapy, antiangiogenic agents, PARP inhibitors, immunotherapy, and radiotherapy for platinum-sensitive disease (PSOC) is discussed in this section.

Chemotherapy

Carboplatin alone and combinations of platinum-based chemotherapy combination have been tested for platinum-sensitive recurrent ovarian cancer (PSOC) (Table 3). A meta-analysis confirmed that platinum-based chemotherapy

combinations result in better outcomes than carboplatin alone (41). Rechallenging with carboplatin and paclitaxel has been shown to be more effective than carboplatin alone or in combination with other agents in a randomized trial (42). It has to be noted that only 34% of patients received the same combination in the first-line. Currently, the usual clinical practice is that nearly all patients receive carboplatin and paclitaxel in the first-line.

The combination of carboplatin and gemcitabine was compared against carboplatin alone in a randomized controlled trial in which 70% of the patients had already received carboplatin-paclitaxel in the first-line. Very high response rates and a significant improvement in PFS but not in OS were observed (43). Interestingly, the benefit was noted in both early sensitive relapse (6–12 month after last platinum base regiment) and late sensitive relapse (> 12 months). Finally, the CALYPSO trial (Caelyx in Platinum Sensitive Ovarian patients) tested the combination of carboplatin and PLD. It is noteworthy that more than 95% of patients received carboplatin and taxane in the first-line and the standard arm in this study was carboplatin and paclitaxel (44). This trial showed a statically significant improvement of DFS (HR:0,82 – p = 0,005) with carboplatin and PLD. The combination performed best in patients with late recurrent disease (TFIp > 12 months), and in recurrence with no measurables disease and low CA125. In conclusion, the platinum-based combinations result in better outcomes than carboplatin alone. But there is no combination regimen that has been shown to be clearly superior to another. Considering the high proportion of patients that receive carboplatin-paclitaxel in first-line treatment, rechallenging with paclitaxel is clearly less efficient than combinations with, e.g., PLD in this population.

The MITO-8 trial demonstrated that using a non-platinum single-agent at first recurrence followed by platinum-based combination therapy at the next progression is inferior to platinum combination therapy at first recurrence (45). HGSOC patients that present with relapse between 6 and 12 months are often called semi-sensitive patients. In these patients, a combination therapy with platinum-salt has been tested and approved. The combination of trabectedin and PLD is an alternative to classic platinum-based chemotherapy, according to the Phase III OVA-301 trial (46), which showed an improved PFS in platinum-sensitive patients. An exploratory analysis of this trial showed that treating patients with "early" sensitive relapse (beyond 6–12 months) first with carboplatin and PLD and then with platinum at next progression resulted in an improvement in OS for the combination versus PLD alone. This leads to the hypothesis that treating patients who are semi-sensitive to platinum with a non-platinum-based combination artificially prolongs the time without platinum and could restore platinum sensitivity (47). Another exploratory analysis of this trial revealed longer DFS and OS for BRCA1-mutated patients offered the trabectidine-PLD combination, in comparison with PLD alone (48).

The recently presented INOVATYON trial compared trabectidin and PLD versus carboplatin and PLD. It failed to demonstrate superiority of the non-platinum chemotherapy (49). Therefore, it is recommend using platinum-based chemotherapy in all PSOC patients. The response to this chemotherapy is an excellent surrogate marker for the efficacy of PARP inhibitors (as maintenance). The combination of platinum-based regimens with Bev recently showed very good results even as a re-challenge (see anti angiogenic agents section). In patients for whom platinum-based regimens are not an option (allergy, residual toxicity), the combination of PLD and trabectedin remains a valuable option.

Antiangiogenic agents

Three prospective randomized trials (OCEANS, GOG-213 and ICON-6) (50–52) (Table 4) that tested the addition of anti-angiogenic agents to platinum-based combination chemotherapy in platinum-sensitive recurrent OC showed statistical improvement in DFS. Thus, there is evidence that guides adding bevacizumab or cediranib (an oral anti-angiogenic VEGFR 1–3 inhibitor) to chemotherapy. A poster at ESMO meeting 2018 presented data that carboplatin-PLD with bevacizumab outperformed the standard treatment for platinum-sensitive recurring ovarian cancer, carboplatin-gemcitabine plus bevacizumab, in terms of PFS in patients without previous bevacizumab treatment (53). Thus, carboplatin-PLD with bevacizumab should be the preferred combination. The ENGOT-OV17/MITO-16 trial studied adding bevacizumab concomitantly to chemotherapy and using bevacizumab a maintenance treatment in 400 ovarian cancer patients who were platinum-sensitive and had already been exposed to bevacizumab in first-line treatment (54). The median PFS increased from 8.8 months to 11.8 months (HR = 0,51 (0,41–0,65)) and interestingly, subgroup of patients progressing while under bevacizumab also benefited.

PARP inhibitors

Using olaparib (a PARP inhibitor) as maintenance for patients with platinum-sensitive recurrent ovarian cancer who responded to platinum-based chemotherapy showed a significant improvement of DFS compared to the placebo. Since the publication of the phase II randomized trial (55) that showed this effect, most

TABLE 4 **Various randomized clinical trials testing chemotherapy regiment in cisplatin-sensitive recurrent disease**

Study	ICON4/AGO-OVAR-2.2 (34)	AGO-OVAR 2,5 (35)	CALYPSO (36)
Regimen tested	Carboplatin + paclitaxel	Carboplatin + Gemcitabine	Carbotplatin + PLD
Standard arm	Carboplatin	Carboplatin	Carboplatin + paclitaxel
DFS **OS**	12 vs. 9 months (HR: 0.76) 7% more 2 year surviving patient (HR:0.82)	8.6 vs 5.6 months (HR: 0.72) No diff	12 vs 9.4 months (HR: 0.82) Not assessed
Toxicities	Alopecia Neuropathy Arthralgia	Myelotoxicity	Palma-plantar erythodysesthesia Mucositis thrombopenia
% Patient paclitaxel first line	34%	70%	96%

countries registered olaparib for this indication. A sub group analysis demonstrated that BRCA (germline or somatic) mutated patients achieved the greatest benefit of olaparib (56). A retrospective analysis of the same phase II trial revealed additional positive effects of the olaparib maintenance (57)—time to first and second subsequent treatment or death was significantly delayed with olaparib (56). Later, the phase III SOLO-2 trial confirmed this dramatic efficacy of olaparib in BRCA-mutated patients (58).

Another PARP inhibitor with efficacy in recurrent platinum-sensitive ovarian cancer with or without BRCA mutation is niraparib (59). Interestingly, responses to niraparib in the non-BRCA mutated cohort occurred regardless of the homologous repair deficiency (HRD) signature score, leading us to question the value of the HRD signature.

Since the recent SOLO-1 (31) and PRIMA (4) trials showed the dramatic efficacy on DFS and OS of olaparib in BRCA-mutated patients and of niraparib in all patients, PARP inhibitors are administered to nearly all patients in first-line treatment for two years as maintenance. Thus, we are now facing recurrent ovarian cancer in patients already treated with PARP inhibitors. The OreO trial presented statistically significant improvements in PFS following the administration of olaparib as maintenance in patients with heavily pre-treated platinum sensitive recurrent ovarian cancer that previously responded to platinum-based chemotherapy (60). It has to be noted that the amplitude of benefit is not very large (few months) but in those heavily pre-treated patients, it represents an improvement.

Immunotherapy

Immunotherapy is very efficient in some types of cancer such as melanoma and lung cancer, which are known to have very high mutational burdens. This leads to the production of neoantigens that are recognized by T-cells, inducing antitumor immunity (61). The immune checkpoint inhibitors CTLA4 (Cytotoxic T-lymphocyte-associated protein 4) and programmed death-ligand 1 (PDL-1) are used and studied the most. Ovarian cancer is potentially a good candidate for immunotherapy. Although the mutational burden in ovarian cancer is lower than in melanoma and lung cancer (62), many ovarian tumors are infiltrated by T-cells (Tumor infiltrating lymphocytes [TILs]). The proportion of TILs in ovarian tumors is positively correlated with the prognosis of the patient (63).

Unfortunately, trials that used immune checkpoint inhibitors as monotherapy showed low response rates around 10–15% (64–66). Currently, neither the FDA nor EMA approved immunotherapy for ovarian cancer. Ongoing studies are testing different combinations (with bevacizumab, PARP inhibitors, and chemotherapy). Furthermore, new strategies of immunotherapies are being developed and studied. These target other aspects of the immune reaction, such as innate immunity, the tumor microenvironment, regulatory and immunosuppressive cells, among others (67).

Radiotherapy

Radiotherapy was previously used as palliation therapy for local control (68). It was replaced by palliative chemotherapy because radiotherapy failed to control

upper abdominal disease, indeed whole abdominal irradiation causes toxicities for a moderate effect. However, in case of oligometastasis (especially vaginal/perirectal lesions and/or in lymph nodes) in heavily pre-treated patients, intensity-modulated radiation therapy (IMRT) with additional high-dose brachytherapy could be proposed. A small retrospective study series showed that this approach is safe and provides long-term control of the irradiated region (69, 70).

CONCLUSION

We are facing multiple challenges in the treatment of recurrent HGSOC. First, all patients will develop resistance to chemotherapy—first to platinum and later to other chemotherapeutic agents. Nowadays, we should also expect resistances to targeted agents, e.g., PARP inhibitors. We cannot exclude a link between resistance to PARP inhibitors and platinum-resistance, because platinum sensitivity seems to be the best marker for efficacy of PARP inhibitors in recurrent ovarian cancer. Furthermore, we are limited in our choice of available agents due to prior treatment-related toxicity. Lastly, ovarian cancer seems to be immunogenic, but the efficacy of immune checkpoints inhibitors is modest. To move forward, we will have to combine chemotherapy with targeted agents and/or immunotherapies. We will have to develop strategies to cope with prior toxicities. Access to the treatments depends on the authorization in each country, and this will limit our choice regarding available first- and second-line treatments. The access to hardware such as scanners also depends on individual countries and resources and impacts the delay of diagnosing relapses. We must develop biomarkers to predict the benefit of new therapies to avoid exposing patients to unnecessary toxicity. Ultimately, we should think not only in terms of increasing of PFS but more on the increasing "time at home". As with increasing lines of therapy in HGSOC, we observe a decrease in PFS and an increase in toxicity. Quality of life should be a marker that also guides treatment choice.

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