Chapter 3

Ovarian Cancer Overview: Molecular Biology and Its Potential Clinical Application

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Additional information is available at the end of the chapter

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Abstract

Over the previous two decades, there has been a shift in the ovarian cancer paradigm to consider it as a multiplicity of disease types rather than a single disease, requiring specialized medical management from molecular diagnosis through to treatment. Despite the achieved improvements in diagnosis, surgery, and systemic treatment, ovarian cancer remains the leading cause of death from gynecological tumors in western countries. The study of ovarian cancer at a molecular level could reveal potential biomarkers of disease diagnosis and progression, as well as possible therapeutic targets in areas such as angiogenesis and homologous recombination deficiencies. Although this area of research is proving invaluable concerning newer therapeutic approaches, platinum-based chemotherapy continues to be the core of the first-line treatment. Genomic screening focusing on the identification of prognostic and predictive markers is considered one of the leading areas for future ovarian cancer research.

Keywords: ovarian cancer, epithelial ovarian cancer, clinics, molecular biology, diagnosis, treatment, prognostic biomarkers, predictive biomarkers

1. Introduction

Ovarian cancer (OC) represents almost 4% of all cancer diagnoses among women worldwide. It is the eighth most common cause of death by cancer, resulting in 152,000 deaths (4.3% of all cancer deaths) [1, 2]. Besides its low incidence, OC is associated with a high mortality rate attributable, in part, to the frequent diagnosis at an advanced stage. The late diagnosis of OC is due to several factors including symptomatology absence and/or nonspecificity to the

inexistence of an effective screening method and to the aggressive biology of this tumor with the ability to disseminate.

The geographic variability in OC incidence is considerable, being frankly higher in developed countries with rates surpassing 7.5/100,000 women. The highest continental rate is registered in Europe, where 65,584 new OC cases were observed. In opposite, the lowest continental values were registered in African regions, with incidence rates below 5/100,000 women [1]. Concerning mortality, for women with less than 75 years, the average risk of dying from OC is twice as high in more than less-developed regions. Inclusively, for developed countries, OC stands as the fifth most lethal cancer among women [1]. In Europe, in 2012, 42,749 deaths were observed, which corresponds to more than 25% of all worldwide OC deaths [3, 4]. Among the gynecological tumors, OC is the leading cause of death even being only the third most common, preceded by cervical and endometrial cancers [2–4].

Nevertheless, the numerous attempts to characterize the ovarian carcinogenesis and etiology, age is considered as a major determinant for OC development: there is an increased disease risk after the menopause, being 63 the median age at diagnosis [5].

Beyond age, an important risk factor for OC is the familiar history. Although the germline mutations in genes that predispose to OC are relatively rare in the general population, they are responsible for approximately 10–20% of all cases [6, 7]. The critical genes involved in hereditary OC are *BRCA1* and *BRCA2*, associated with hereditary breast/ovarian cancer syndrome. The risk of spontaneous OC development, throughout life, is around 1.7%, while the heritage of germline mutations that alter *BRCA1* gene function confers a cumulative risk from 40 to 60%, mainly to serous carcinoma. The presence of pathogenic mutations in *BRCA2* gene lowers the risk for about a half (10–30%). OC hereditary women tend to develop the disease nearly 10 years earlier than women with sporadic OC [8–10].

Moreover, reproductive and endocrine factors seem to be important, whereby the nulliparity, early menarche (<12 years), late menopause (>52 years), endometriosis, polycystic ovary syndrome, and the recent exposure to hormone replacement treatment might be associated with a higher risk to develop OC [11–14]. Therefore, some behaviors and lifestyles were associated with a decrease in OC incidence, namely breastfeeding, multiparity, and the oral contraceptives use [11, 13]. Surgical procedures such as tubal ligation, hysterectomy with salpingectomy, and oophorectomy correlate with a lower incidence of this tumor but are mainly reserved for women with higher disease risk, after the completion of familiar planning.

Standard treatment of epithelial ovarian cancer (EOC) is based on cytoreductive surgery, followed by platinum-based first-line chemotherapy. This neoplasia is considered chemosensitive, yielding 40–60% of complete responses rates for advanced disease stages. Despite the apparent efficacy of treatment, up to 75% of patients will relapse and become candidates for second-line chemotherapy. As a result, the high percentage of late-stage diagnosis and the occurrence of tumor recurrence limit the treatment efficacy, and the overall 5-year survival rate remains only around 45%.

In the clinical practice, several pathological factors are considered prognostic for EOC patients, and many efforts are made to identify those that will improve patient's stratification and be

useful tools for therapeutic decisions. Current research is focusing on the identification of both prognostic and predictive biomarkers that would help to optimize EOC treatment strategies and to improve the cost-effective incorporation of emerging biological agents.

2. Clinics and diagnosis

Upon the detection of an adnexal mass suspected of malignancy, the diagnostic approach should be based on a careful clinical history that should include the overall physical examination, as well as gynecological, rectal, and abdominal evaluation. After the clinical evaluation, additional diagnostic and biochemical tests should be requested, judiciously and objectively, to aid in the differential diagnosis of a pelvic mass. Among the complementary diagnostic tests, transvaginal ultrasonography (TVU) and CA125 tumor marker determination are mandatory [8, 12, 15]. Other markers are also used in the diagnostic investigation for suspected EOC cases, such as CEA and CA19.9.

In the suspicion of ovarian neoplasia, abdominal-pelvic computed tomography (CT) should be requested to confirm and characterize the presence of lesions, to evaluate the tumor extension, to identify unresectable disease, and to exclude nonovarian metastatic disease. Nevertheless, the EOC diagnosis is surgical as only the anatomopathological exam confirms the definitive diagnosis. Diagnostic radiologically guided aspiration/biopsy or laparoscopy should be requested, whenever neoadjuvant chemotherapy is being considered [8, 16].

Late disease diagnosis explains, in part, the high mortality rate of these patients [12, 17]. Over the past 25 years, there has been little improvement in the survival rate, being around 37% in the early 1970 and 44% in 2000, despite the advances in the medical treatment [18]. However, the currently available tests lack adequate sensitivity and specificity, promoting a noneffective screening strategy. Prospective studies have shown that the combined use of serum CA125 and TVU improved the specificity of the tests and allowed the detection of a number of OC cases in the preclinical phase (this is discussed in detail in another chapter).

3. Histopathology

Ovarian tumors are classified according to the World Health Organization (WHO) proposal for gynecological tumors. Ovarian cancer has high cellular heterogeneity, and most of the primary ovarian tumors can be integrated into three major groups, namely epithelial, sex cord and ovarian stroma, and germ cell tumors [2].

Although the ovarian epithelial surface represents only a small fraction of all ovarian cell types, EOC is the most common, corresponding to almost 60% of all ovarian tumors [19, 20]. According to the criteria proposed by the WHO in 2014, EOC can be divided into seven histological subcategories, namely serous, mucinous, endometrioid, clear cell, Brenner, seromucinous, and undifferentiated [2]. All the mentioned histological subtypes, except for the undifferentiated type, are further subdivided into benign, borderline, and malignant neoplasia, depending on the optical microscopy characteristics.

Sex cord and stroma tumors arise from the ovarian connective tissue, often responsible for hormone secretion. These tumors encompass a vast group of tumors, for which the subgroup of "pure" ovarian stromal tumor is the most frequent (9% of all OC), usually with benign behavior. Also in this group of tumors, granulosa cell tumors are associated with aggressive behavior and represent 1% of all OC. Regarding the germ subgroup, a mature cystic teratoma is very common (32% of all OC), although the remaining germ cell tumors, both benign and malignant, are rare, representing 3–5% of all OC cases [2, 21].

4. Staging

Ovarian cancer staging is surgical, being performed according to the International Federation of Gynecology and Obstetrics (FIGO) criteria [22]. CT or magnetic resonance imaging scans, although of limited impact for OC early diagnosis, allow to establish a surgery plan and to determine tumor irresectability criteria for 70–90% of all patients. The ability to detect peritoneal implants in both exams depends upon their location, size, and the presence of ascites. However, CT is the imaging modality of choice for OC staging, since it is indispensable for the preoperative evaluation to optimize maximal cytoreduction surgery or to help in the decision of neoadjuvant chemotherapy.

Ovarian cancer dissemination can occur through all known propagation routes, i.e., lymphatic, hematogenic, transcavitary, and contiguous. The transcavitary course is undoubtedly the most clinically relevant and, in the vast majority of cases, has an impact on the patient prognosis [23, 24]. The dissemination to the peritoneal cavity is an early phenomenon in the natural history of the disease, since the malignant cells follow the peritoneal fluid, flow concerning intra-abdominal pressure variations. Ovarian cells are characterized as anchorage-dependent cells, meaning that they could only survive when adherent to the extracellular matrix or in contact with neighbor cells. However, when OC cells exfoliate into the peritoneal cavity, they can avoid anoikis (apoptosis process triggered by the loss of binding to the extracellular matrix) and survive even when isolated. Cancer cells in this state can survive and disseminate into the peritoneum, depositing accordingly to the passive flow distribution of peritoneal fluid, predominantly into the paracolic gutters, diaphragmatic surfaces, liver capsule, intestine surface, and omentum. The adhesion of malignant cells to the peritoneum precedes the local invasion and the secondary metastasis, namely to the pleural cavity by the transdiaphragmatic pores (Stage IV) [25]. The transcavitary route seems to be related to the OC cells predilection for the abdominal cavity (homing) rather than the deposition in other organs such as liver, lungs, brain, or bone (rarely in these latter two locations). The dissemination by contiguity is also important and of particular interest for organs like fallopian tubes, uterus, contralateral appendix and bladder, rectum, and pouch of Douglas. The iatrogenic route by contiguity, for example, to the abdominal wall is less frequent. Lymphatic dissemination is frequently observed when the disease is confined to the ovary, being found in almost 15% of FIGO I–II cases [26]. In fact, for a proper FIGO staging, lymphadenectomy is required, and the removal of bulky lymph nodes should be performed to achieve complete macroscopic resection. Although the systematic lymphadenectomy in advanced OC surgical management

is still discussed, it has an impact in early disease stages not only to define FIGO staging but also to establish the need for adjuvant treatment, with a significant impact in survival [27, 28]. Blood dissemination is less frequent and usually occurs in advanced disease stages [23, 24].

5. Prognostic factors

A considerable number of clinical-pathological factors have been implicated in OC prognosis. Disease stage, tumor size, histological subtype, differentiation degree, and residual tumor after surgery are considered as the classic prognostic factors. More specifically, the extent of residual disease after surgery is regarded as a major prognostic factor, shown to influence the chemotherapy response and survival [29–33]. Inclusively, a recent meta-analysis has shown that residual tumor is a more powerful prognostic determinant than FIGO stage [31]. The correct histological classification of EOC is also crucial, since it is an independent prognostic factor and provides a guideline for therapeutic management [8, 27]. Performance status (PS) and age are also important factors having an impact on the prognosis and, ultimately, in the decision of medical treatment [27].

Numerous studies have been conducted to assess the clinical significance of molecular alterations in OC. However, so far, the obtained results do not allow a prognostic biomarker to be universally accepted, although the determination of *BRCA* germline mutations has been recently approved as a predictive biomarker for OC. Recently, the development and the application of new genomic technologies have allowed the description of molecular signatures integrated into prognostic and predictive models. In particular, the Cancer Genome Atlas Project (TCGA) has been critical in adding to our knowledge, as it has been used to confirm the importance of *BRCA* genes to serous OC patients survival, as well as being able to help to describe a transcriptional signature with prognostic relevance [34] (this will be investigated further in a separate chapter).

6. Treatment

6.1. First-line treatment

The therapeutic strategy for EOC is based on cytoreductive surgery and staging, followed by adjuvant chemotherapy with the duplet platinum/taxane [8, 20]. As mentioned above, the extent of surgery is a determinant for survival and response to chemotherapy, since these parameters vary significantly depending on the success (optimal or suboptimal) of the surgical procedure [33]. Systemic therapy with cytotoxic agents plays a fundamental role in the treatment of this neoplasia. Chemotherapy is generally recommended in the EOC, including early stages with histopathological criteria of poor prognosis (FIGOIA/IB G3, FIGO IC, FIGO II, or clear cell histology at any stage). However, stage IA or IB G1 or G2 tumor patients, if adequately staged (i.e., with peritoneal washings, assessment of the contralateral ovary and fallopian tube, pelvic and para-aortic node assessment and omentectomy), have a better prognosis and can be treated with surgery alone without the need for adjuvant chemotherapy [35–37] (**Figure 1**).

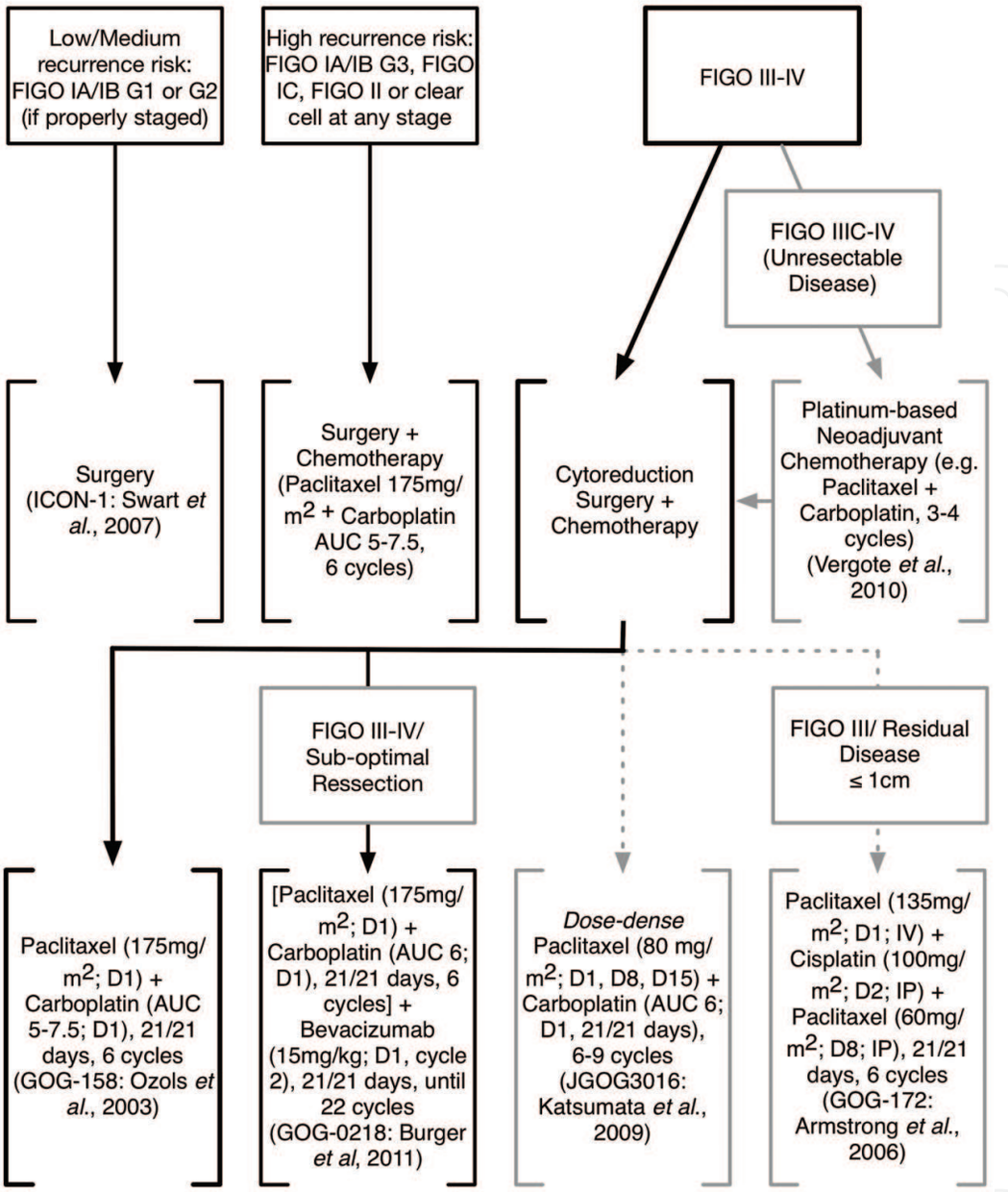

Figure 1. EOC first-line treatment algorithm according to the clinical trial that determines their approval.

The last decades have brought significant advances in the medical treatment of EOC. The association of paclitaxel with platinum has been shown to prolong both progression-free survival (PFS) and overall survival (OAS) of advanced stage patients when compared to the previous nontaxane treatment regimens. Globally, the inclusion of paclitaxel in the adjuvant chemotherapy scheme resulted in a 30% reduction in the risk of death [38–40]. Thus, the intravenous combination of paclitaxel (175 mg/m^2) and carboplatin (AUC 5–7.5), every 3 weeks, for six cycles, was established as the standard primary adjuvant chemotherapy for advanced stage disease, after cytoreductive surgery (**Figure 1**) [8, 38, 39, 41–43].

This treatment regimen has been the standard for more than 15 years, and the clinical trials conducted in the last decades for the introduction of a third agent, as in the ICON-5/GOG182

clinical trial, have not shown any improvement in the survival [44]. For patients that develop allergy or toxicity to paclitaxel, namely hypersensitivity or neurotoxicity, the combination of docetaxel/carboplatin or pegylated liposomal doxorubicin (PLD)/carboplatin can be considered as an alternative [42, 45]. The cisplatin/paclitaxel duplet is equally valid but associated with increased toxicity and less convenience in the administration, being currently reserved for patients who have developed hypersensitivity to carboplatin [8, 41].

The inclusion of bevacizumab, an anti-VEGF (Vascular Endothelial Growth Factor) monoclonal antibody, is recommended for advanced OC patients with poor prognostic characteristics (Stage IV or suboptimal resection). This targeted therapy should be administrated concomitantly with paclitaxel/carboplatin (after the first cycle) and be maintained after the six cycles of chemotherapy. Regarding the dose and duration of maintenance, the results are not clear, although a similar benefit is obtained with the administration of 7.5 mg/kg and 15 mg/kg for 12 and 15 months, respectively [46, 47]. Although not licensed in the United States of America and not consistently used in Europe, bevacizumab was approved by the European Medicines Agency (EMA) at a dose of 15 mg/kg for 22 cycles (15 months) [8, 46].

To improve the efficacy of the primary treatment, several clinical trials have evaluated the addition of a third cytotoxic agent (such as epirubicin, topotecan, gemcitabine, or PLD) to the first-line regimen, but none have demonstrated a benefit for triplets [8]. In addition, the Japanese JGOG-3016 trial evaluated the impact of a dose-dense therapeutic regimen (paclitaxel, weekly, 80 mg/m^2) on the chemotherapy effectiveness for OC patients. The results were promising for the benefits in PFS and OAS although associated with higher toxicity, especially myelotoxicity. Although it was a trial with potential impact on the clinical practice, because of the pharmacogenetic differences between the Japanese and Caucasian populations, further study was required to confirm these results. The European MITO-7 study did not confirm these findings in Caucasian patients, showing no benefit in the PFS and OAS with the weekly carboplatin (AUC 2) and paclitaxel (60 mg/m^2) regimen [48]. In the absence of new data, paclitaxel dose-dense administration can only be considered as an option [8].

Clinical data demonstrate that, despite the high response rate to the first-line treatment, a significant proportion of OC patients will develop disease recurrence, which in most cases is confined to the abdominal cavity. Based on this particular feature, intraperitoneal chemotherapy administration was associated with an improvement in PFS and OAS in phase III randomized studies (GOG 104, 114 and 172), in combination with intravenous chemotherapy [49, 50]. However, this strategy is not widely used in clinical practice due to its high toxicity [8]. Chemotherapy administered directly in the abdominal cavity might also be performed in the surgical setting using hyperthermal intraperitoneal chemotherapy (HIPEC). The justification for the use of the last therapeutic approach is based on studies that demonstrated that high temperatures help to overcome the resistance to cisplatin, as a result of increased penetration and cellular accumulation of this drug when administrated intraperitoneally in association with hyperthermia [51]. Although it represents a promising strategy, the use of HIPEC remains controversial.

Numerous studies have shown that neoadjuvant chemotherapy is feasible in advanced disease (Stage IIIC–IV), for which the disease is considered unresectable or when optimal

primary cytoreduction is not possible due to the disease extension and/or comorbidities that increase the surgical risk [30, 52]. Neoadjuvant chemotherapy is associated with some advantages, including tumor size and disease extension reduction, improvement of optimal cytoreduction rate, less extensive surgery with lower morbidity/mortality, improvement of patients' PS before surgery, and evaluation of tumor chemosensitivity. The chemotherapy scheme to be applied should be based on platinum (often a paclitaxel/carboplatin combination), and it is not recommended to perform more than 3–4 cycles to avoid the emergence of resistant clones [8, 30]. Consequently, the use of primary chemotherapy with interval surgery has become widely accepted, whereas the role of secondary interval debulking surgery after primary surgery (suboptimal cytoreduction and three cycles of chemotherapy) is less clear, as improved survival was reported by the European Organization for Research and Treatment of Cancer (EORTC) trial [32] but not confirmed by the Gynecological Oncology Group (GOG) [53]. Also, the "second look" diagnostic laparoscopy or laparotomy to evaluate the intraperitoneal condition is obsolete and should not be considered an option [8].

6.2. Recurrent disease treatment

The maximal surgery resection strategy combined with adjuvant chemotherapy achieves complete clinical remission in about 75% of EOC patients. However, after 12–18 months, approximately 75% of these patients will develop recurrent disease and be subjected to further treatment. The OC recurrence is defined according to the progression-free interval (PFI) after the end of the initial treatment (**Figure 2**) [8, 21, 41, 54–56].

The prognosis and the likelihood of response to second-line therapy (and subsequent lines) are dependent on the PFI after the last cycle of the previous chemotherapy line. This categorization defines "platinum-refractory," when disease progresses during therapy or within 4 weeks after the last cycle; "platinum-resistant," whose progression occurs within 6 months after platinum therapy completion; "partially platinum-sensitive," for disease which progression occurs between the 6 and 12 months; and "platinum-sensitive," whose progression occurs in a period superior to 12 months [57]. The biological behavior of tumors in these groups is quite variable, with distinct response rates and variable symptoms with different treatment needs. If relapse occurs 6 months after the completion of first-line chemotherapy, a platinum-based regimen should be performed, since the disease is considered platinum sensitive. For patients with platinum-sensitive relapses, there are several therapeutic strategies available which, since this phenomenon can occur repeatedly, allows the selection of different therapeutic combinations [8]. However, the time to subsequent relapse will be progressively shorter until the tumor becomes virtually resistant to these agents [21].

The platinum re-administration is associated with a response rate around 30%, similar to the improvement seen in the PFI. Available treatment options for OC platinum-sensitive relapse are ideally based on the association of platinum with paclitaxel, gemcitabine (with or without bevacizumab), or with PLD [58–62] (**Figure 2**). The therapeutic scheme selection should consider the toxicity profile of each regimen, the residual toxicities of the previous regimens, and the patients' preferences.

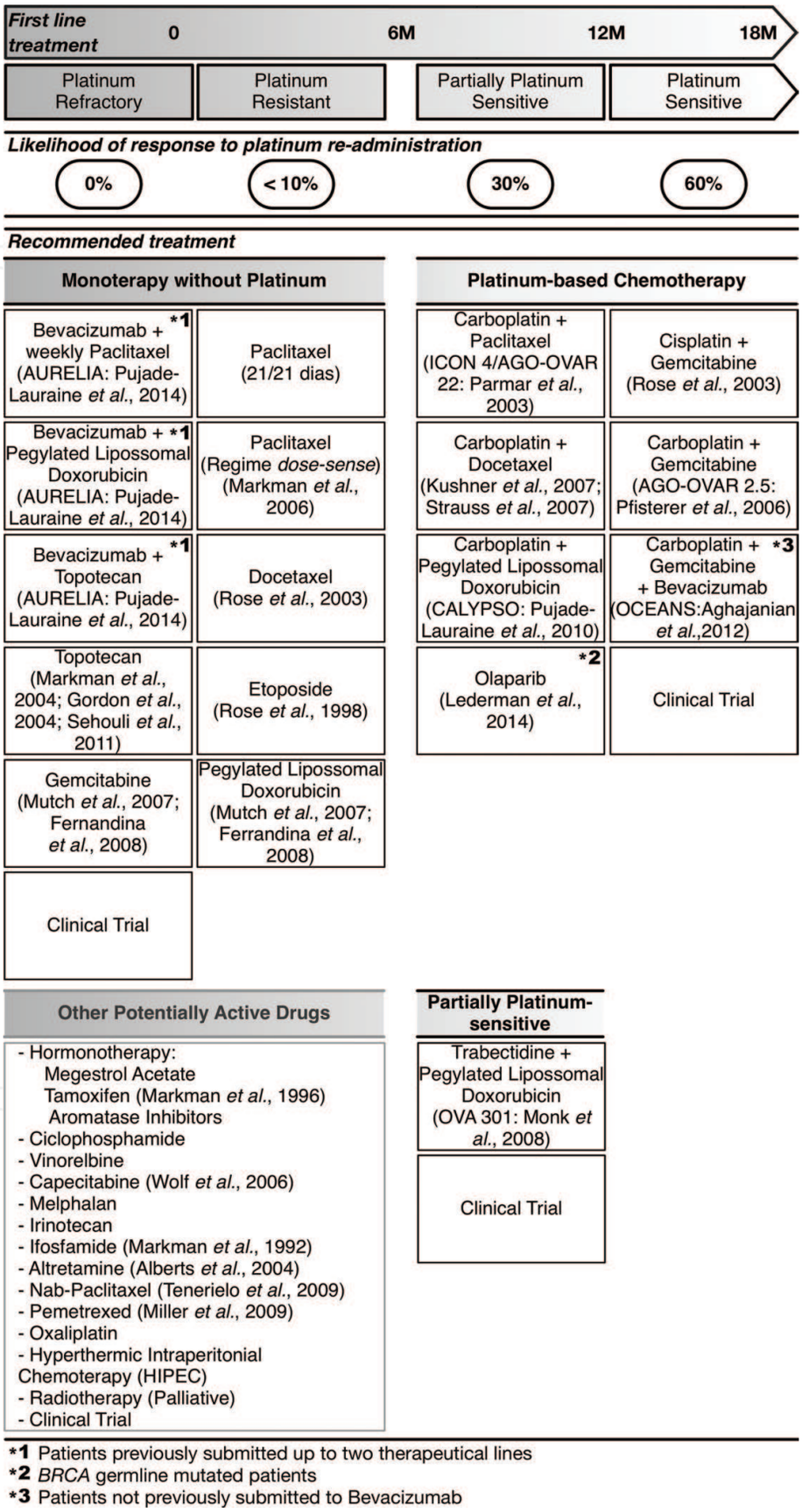

Figure 2. EOC recurrence treatment algorithm based on platinum-free interval, according to the clinical trial that determines its approval.

The administration of bevacizumab in combination with carboplatin/gemcitabine, followed by maintenance until progression or toxicity, was approved by EMA as the first-line treatment for platinum-sensitive relapse (for bevacizumab-naïve patients), being associated with an improvement in PFS despite no impact on OAS [8, 63]. In December 2016, US Food and Drug Administration (FDA) also approved bevacizumab administration to platinum-sensitive recurrent patients, either in combination with carboplatin/paclitaxel or carboplatin/gemcitabine, followed by bevacizumab alone.

Patients with PFI between 6 and 12 months, considered as partially sensitive, also benefit from platinum-based second-line therapy, although with a lower therapeutic effect (**Figure 2**). For these patients, the administration of trabectedin associated with PLD might also be an option, according to the results of the OVA301 trial, probably by restoring platinum sensitivity due to the artificial prolongation of the platinum-free interval [8, 64].

For relapses linked to a disease-free interval less than 6 months, the tumor is defined as platinum resistant and another treatment strategy should be instituted, with monotherapy regimens being recommended [8, 40, 65]. The treatment of platinum-resistant/refractory patients is mostly directed toward improvement in the quality of life and symptom control, as these patients are usually associated with a reduced prognosis with a reduced OAS (generally less than 12 months) [8]. Surgery as a therapeutic alternative in these cases might be considered only in need of symptom palliation. Monotherapy regimens with paclitaxel (preferably weekly), PLD, gemcitabine, and topotecan, among others, have shown similar response rates (not exceeding 15%) and PFS between 3 and 4 months [8, 66–73]. Thus, the choice for one of these agents should be based on previously performed therapies, toxicity profiles, administration convenience, cost, and patient opinion. Combination therapy regimens did not significantly improve response rates or survival for platinum-resistant disease, when compared to monotherapy regimens, even when considering toxicity [8, 40].

Recently, promising results have been achieved with biological maintenance treatments, in particular with anti-angiogenic agents (bevacizumab, pazopanib, and trebananib) and PARP (poly(ADP-ribose) polymerase) inhibitors (olaparib, niraparib, and rucaparib) [74]. Bevacizumab was the first antiangiogenic agent to demonstrate clinical benefit in platinum sensitive and resistant relapse, concomitantly with chemotherapy and as maintenance therapy. As previously mentioned, according to the results published in the OCEANS trial, EMA approved the combination of bevacizumab with carboplatin/gemcitabine for patients with platinum-sensitive OC relapse, if there was no previous exposure to this antiangiogenic drug [63]. According to the AURELIA results, the addition of bevacizumab to the chemotherapy (weekly paclitaxel, PLD or topotecan) in patients with platinum-resistant OC (previously treated with up to two therapeutic lines) has been shown to be associated with an improvement in PFS, response rates, and quality of life, although without impact on OAS [75]. Therefore, this regimen could be an alternative in this subgroup until the development of toxicity or progression (**Figure 2**).

In addition to bevacizumab, olaparib is also considered as a target therapy option in OC recurrence. This drug was the first PARP inhibitor to be authorized by EMA as maintenance treatment of *BRCA*-mutated patients, with partial or complete responses to platinum-based chemotherapy. The results have shown almost a 7-month extension in PFS for patients with

BRCA mutations exposed to Olaparib (11.2 versus 4.3 months; HR, 0.18), although the impact on OAS was not observed [76]. Response rates to this drug correlate with the platinum-free interval, being 69.2, 45.8 and 23.1% for the sensitive, resistant, and platinum-refractory disease, respectively [77]. Furthermore, olaparib administration allows for a time extension for a subsequent therapy which suggests that its administration did not adversely affect the treatment recurrence.

With the existence of several treatment alternatives that allow for sequential approaches and the emergence of new targeted therapies, most of which are well tolerated, it is possible to administrate extended therapeutic regimens concomitantly with significant symptomatic control and a positive impact in the quality of life.

6.3. Emergent therapeutic approaches

The duplet platinum/taxane is considered the standard first-line therapy for advanced OC treatment. Nevertheless, chemotherapy response rates remain disappointing, and the introduction of newer treatment strategies at recurrence is essential to increase the long-term survival. The recent adoption of molecular therapies targeting the inhibition of angiogenesis and DNA repair is a step forward in the OC medical treatment, aiming to delay disease progression and the re-treatment with chemotherapy [33]. The encouraging study results with bevacizumab, in first-line treatment and both platinum sensitive and resistant recurrence, illustrate the importance of angiogenesis inhibition in the success of OC treatment [46, 63, 75].

PARP is an enzyme involved in the response to DNA single-strand breaks, and so it was initially suggested that its inhibition could be used to enhance the effects of chemotherapy [78]. However, the finding that the survival of tumor cells carrying *BRCA* homozygous deletions is significantly lower with the administration of PARP inhibitors prompted the development of a new therapeutic strategy for OC [79, 80]. The molecular rationale for this association is based on the fact that cells with BRCA defective proteins are not able to repair DNA double-strand breaks by homologous recombination (HR), depending on other pathways to repair the damage, namely the base excision repair (BER) pathway, in which PARP is involved. In the BER pathway, PARP is responsible to detect single-strand breaks and to activate effector proteins to repair the damage. Thus, homologous recombination deficiencies (HRD), as in the presence of *BRCA* mutations, in concomitance with PARP inhibition lead to cell death due to the excessive accumulation of unrepaired damage. This phenomenon is designated as synthetic lethality and occurs when two nonlethal defects are combined to culminate in cell death. This strategy is also of benefit in that toxicity is reduced for normal tissues, as nontumor cells can repair DNA by the HR pathway [80, 81].

As molecular and genetic knowledge of OC is increasing, studies with PARP inhibitors are indicating that more patients with OC may benefit. According to data published by the TCGA project, the presence of *BRCA* mutations is identified in about 20% of high-grade serous ovarian cancer (HGSOC), and about 50% of these tumors have a positive HRD phenotype, even in the absence of a familial history of breast/ovarian cancer [34, 78]. In addition to the excellent results obtained with olaparib for the subgroup of patients with *BRCA* mutations, the study published by Ledermann et al. also demonstrated that PARP inhibition is also useful for *BRCA* wild-type patients, although to a less extent [76].

The promising results achieved with olaparib encouraged the development of new PARP inhibitors, including niraparib and rucaparib [82, 83]. Maintenance clinical trials ongoing with both agents include *BRCA* wild-type patients to test the effect of PARP inhibitors in this major group, incorporating additional molecular tests for HDR. Namely, for patients with platinum-sensitive recurrence, the PFS mean duration is significantly higher for patients receiving niraparib when compared to placebo, regardless of the presence/absence of *BRCA* germline mutations or HRD status [83]. Thus, clinical trials are being developed to evaluate not only the impact of PARP inhibitors on limiting recurrence, as in the SOLO2 trial [84], but also as a maintenance strategy for first-line treatment, as in SOLO1 [85]. In addition, the GOG3005 trial evaluates the addition of the PARP inhibitor veliparib to first-line therapy (carboplatin/paclitaxel), as well as its role in subsequent maintenance [78].

A possible synergy between PARP inhibitors and other pathways inhibitors, such as anti-angiogenic, has also been hypothesized. In fact, preclinical studies have demonstrated an additive effect on the association of inhibitors of these two pathways, since hypoxia leads to a decreased expression of DNA repair proteins, thereby increasing the sensitivity for PARP inhibitors [86, 87]. Thus, a recent phase I clinical trial, which combined a tyrosine kinase inhibitor of VEGF receptor, cediranib, with olaparib, achieved an objective response rate of 44% in recurrent disease [88]. The results of this study prompted the development of a randomized phase II trial, demonstrating an improvement in PFS and in the objective response rate for the cediranib/olaparib combination when compared to olaparib alone (17.7 versus 9.0 months; HR, 0.42; 95% CI, 0.23–0.76; $P = 0.005$ and 79.6% versus 47.8%; OR, 4.24; 95% CI, 1.53–12.22; $P = 0.002$) in patients with platinum-sensitive recurrence [89]. Although the results must be interpreted carefully, due to the low number of recruited patients, they are of high interest as it suggests a synergistic action for the combined use of angiogenesis/DNA repair inhibitors. Thus, numerous clinical trials exploring these pathways are under development, either isolated or in combination, for first-line therapy or maintenance, with the prospect of increasing the treatment opportunities for OC patients.

6.4. Monitoring treatment response

The treatment response evaluation in OC is based on CT, following RECIST criteria, complemented by the CA125 serum measurement following Gynecologic Cancer InterGroup (GCIG) criteria [90]. In fact, despite the limitations as a diagnostic biomarker, CA125 is a good predictor of relapse as it proved to be a useful biomarker for monitoring treatment response in more than 80% of OC patients [91]. Normalization of CA125 serum levels following first-line therapy does have clinical implications, especially when considering maintenance treatment in OC. However, even the systemic therapy in early recurrence stages had the potential to improve survival, studies have demonstrated that the premature treatment in asymptomatic patients with single elevation of CA125 levels (without clinical or radiological evidence) had no positive impact [92].

In Medical Oncology clinical practice, high heterogeneity in the response and toxicity to cytotoxic agents are observed. There are subgroups of patients who, despite being at an early disease stage, have a higher risk of tumor progression. In these cases, surgery and classic prognostic factors do not allow to predict the biological behavior of these tumors correctly. In

the current era of individualized therapy, and according to the OC heterogeneity, biomarkers need to be developed to identify patients at an early disease stage but with the potential to progress and disseminate [93].

6.5. Predictive factors

Several biomarkers are considered to have prognostic relevance, independent of the therapeutic approach. In OC, as previously mentioned, FIGO staging, histological subtype, or the extent of residual disease are considered as key prognostic factors. The identification and characterization of predictive biomarkers for OC have proven to be a challenge, and none of the molecular determinants that underlie platinum-sensitivity/resistant phenotypes have reached the clinical setting [91].

Additionally, the inability to select those patients that will benefit from bevacizumab to maximize survival and minimize toxicity and costs complicates treatment planning. Several studies have been performed to unravel the role of the VEGF signaling pathway and the key drivers of response to antiangiogenic agents in OC. VEGF serum levels are thought to be representative of the VEGF-mediated OC angiogenesis, but the results were not systematically concordant [94]. Also, VEGFR-2 plasma levels were not predictive for patients treated with bevacizumab in the GOG-218 trial [95]. Translational research conducted within the ICON7 trial identified three candidate biomarkers (mesothelin, VEGFR-3, and alpha-1-acid glycoprotein) for patients treated concomitantly with this antiangiogenic agent and first-line chemotherapy. Each of these biomarkers was considered as an independent factor and, in combination with CA125 measurement, was included in a predictive nomogram for bevacizumab [96]. However, though several promising candidate angiogenesis biomarkers for OC were identified, it was neither possible to achieve meaningful results for their use in routine clinical practice nor possible to select patients for this targeted therapy [97, 98].

Failure to improve the therapeutic strategies in OC has resulted in studies focusing on genomic features, such as the TCGA project. This project aims to determine the impact of OC genomic and epigenomic changes and, thus, to identify molecular markers influencing clinical outcome and possible therapeutic targets for OC. One of the most interesting findings obtained from this study is the presence of HRD in about 50% of HGSOC, which could represent a patient subgroup which could benefit from PARP inhibitor treatment [34]. In fact, the presence of *BRCA* mutations and an HRD positive phenotype is both positive predictive factors for PARP inhibition, thus indicating personalized OC therapy defined by a genetic biomarker [76, 83]. The impact of *BRCA* mutations as predictive biomarkers has been published for other agents such as PLD and trabectedin [99, 100]. The implications of these advances are still being investigated, and as a result, genetic testing for *BRCA* mutations should be offered for all patients with nonmucinous tumors, regardless of age or familial history. The test should be performed at diagnosis, as it provides information on the likelihood of response to chemotherapy and can then be systematically incorporated into clinical practice to promote an individualized therapeutic strategy [33]. The TCGA project also provided the opportunity to identify four OC subtypes based on the expression of marker genes (differentiated, immunoreactive, mesenchymal, and proliferative), and several retrospective subanalyses have already demonstrated that is possible to correlate distinct outcomes between the subgroups [101, 102].

Based on the TCGA data, other studies have also proposed molecular signatures, namely the prognostic model "Classification of Ovarian Cancer" (CLOVAR), for which 23 genes involved in the platinum-induced DNA damage repair are predictive of treatment response among HGSOC patients [103]. Recently, the ARIEL2 clinical trial showed that the combination of *BRCA* mutational status with the degree of genome-wide loss of heterozygosity (LOH) in the tumor could predict the rucaparib treatment response. *BRCA*-mutated patients (germline or somatic) or *BRCA* wild-type with high LOH had longer PFS and clinical response to rucaparib, when compared with *BRCA* wild-type and low LOH patients [104].

The concept of *BRCA*ness must be promptly clarified, as the associated phenotypes define a clinical subpopulation of EOC patients with common characteristics. These include high response rates to both first-line platinum-based treatment and to relapse therapies (including platinum based), long treatment-free intervals (even in recurrent disease), and improved OAS and include mainly serous tumors. The HRD phenotype (somatic or germline) might be complemented with other molecular defects, beyond *BRCA* deficiencies, which lead to an analogous clinical profile and be targeted for PARP inhibition [34, 105]. Commercial tests are already available, and multiple clinical trials (as ARIEL3 and NOVA) are ongoing to investigate PARP inhibition in *BRCA* wild-type patients and to identify a putative predictive signature.

7. Pharmacogenomics for future predictive marker definition

Although *BRCA*ness signature definition can provide valuable information regarding the magnitude of the benefit of targeted therapy, these biomarkers may not be unique for the determination of the likelihood of treatment sensitivity/resistance. To date, besides *BRCA* mutations and HRD status, platinum sensitivity remains the best biomarker of PARP inhibitor response. Platinum sensitivity correlates with HRD, and platinum-sensitive tumors are more responsive to PARP inhibitors than platinum-resistant tumors, whatever the genetic background [33, 78]. Therefore, perhaps the PARP inhibitors administration should be offered to all OC patients that respond to platinum-based treatment.

Platinum-based compounds are among the most active and used cytotoxic agents in the clinical practice. They exert their biological effect by acting as alkylating agents by the ability to covalently bind to DNA, leading to the formation of intrastrand and interstrand DNA adducts that promote cell-cycle arrest and tumor cell apoptosis. The mechanisms underlying the development of chemoresistant phenotypes in OC are not fully recognized. Interindividual variation in platinum-drug response might be a major determinant for OC. This is suggested from the wide variability in the PFI and its direct association with a platinum response, as well as the finding that intrinsic resistance to these compounds, occur in up to a fifth of OC patients [106–109]. Mechanisms involved in platinum resistance are likely to be multifactorial although seems to be greatly determined by the platinum detoxification pathway and DNA damage repair ability [54, 108, 110–113].

While platinum therapy is prescribed to achieve a target exposure based on renal function, the dose of taxanes is based on body surface area. Taxanes are microtubule-stabilizing drugs,

inducing cell cycle arrest and activating proapoptotic signaling. The cellular toxicity to taxanes is controlled by the action of multiple mediators, namely those involved in transport (i.e., ABCB1, ABCC1, and ABCC2), metabolism, and metabolism-associated proteins (cytochrome P450s and nuclear receptors), as well as pharmacodynamics (i.e., TP53 and CDKN1A), which appear to play a role in taxane efficacy [54, 108, 114–116]. However, to date, no reliable biomarker or signature exists to predict the sensitivity or resistance to paclitaxel. Although the duplet platinum/taxane is associated with better outcome, rather than platinum alone, the results of the GOG132 trial showed that only 42% of patients are likely to benefit from paclitaxel administration [117], and thus, further study into the mechanisms of resistance is needed.

8. Conclusion

Achieving an individualized therapeutic strategy will only be possible through the identification of feasible, validated, and reproducible biomarkers in the clinical practice that will allow the prediction of the likelihood of response to a given treatment. Biomarker validation is crucial, both in respect of predictive ability and sensitivity/specificity, and should be stated previously in the definition of treatment subgroups [106, 107, 118, 119].

Research in OC treatment evolution and improvement needs to focus on the identification of interindividual determinants, which is often associated with genetic polymorphisms to identify potential biomarkers and/or treatment targets. Circulating tumor cells or tumor nanovesicles (as exosomes) may help to identify the molecular targets. Consequently, the incorporation of molecular and genetic information into integrated clinical models may be a potential approach in order to define predictive nomograms. Pharmacogenomics will be important in clinical practice to improve efficacy, reduce toxicity, and predict nonresponders to several therapies, thus allowing for individualized treatment strategies.

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