

Updates of Ovarian Cancer Therapy

Literature Review

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Abstract – Epithelial ovarian disease is often diagnosed in the advanced stage. The current state of the art of surgical and chemotherapy brings high incidence of complete remission; in any case, the recurrence rate is also high. In many patients, the disease eventually turns into a continuation of the symptoms of free time and recurrence episodes. Differential treatment-based approaches to adjacent therapies, now in use, provide assurance that we will turn ovarian malignancy into a manageable, chronic disease. In this review, we examine the prevalence of ovarian cancer treatment, the apparent late-term research into new forms of traditional medicine, and new approaches to rehabilitation, such as late investigations and early treatment issues. The latter include angiogenic therapies, polyADP-ribose polymerase (PARP) inhibitors, growth factor signaling inhibitors, or folate receptor inhibitors, immunotherapeutic methods. We are also talking about the low cost of alternative therapies and the issue of better patient care options.

Keywords – Ovarian cancer, biological drugs, targeted treatment, clinical trials.

I. INTRODUCTION

Ovarian cancer is the second most common and deadly gynecologic disease in the western world. To date, there are no suggested strategies for early detection and diagnosis of the disease. As a result, and moreover due to the invisibility of the first notice, about 70% of cases are diagnosed at an advanced stage and have bad prognosis, late-stage ovarian malignancy in most cases, but will usually turn into chronic disease, (Table 1).

Table 1. 2014 FIGO ovarian, fallopian tube, and peritoneal cancer stage system and NM corresponding.

I	Tumour confined to ovaries or fallopian tube(s)	T1
IA	Tumour limited to one ovary (capsule intact) or fallopian tube. No tumour on ovarian or fallopian tube surface. No malignant cells in the ascites or peritoneal washings.	T1a
IB	Tumour limited to both ovaries (capsules intact) or fallopian tubes. No tumour on ovarian or fallopian tube surface. No malignant cells in the ascites or peritoneal washings	T1b
IC IC1 IC2 IC3	Tumour limited to one or both ovaries or fallopian tubes, with any of the following: Surgical spill intraoperatively Capsule ruptured before surgery or tumour on ovarian or fallopian tube surface Malignant cells present in the ascites or peritoneal washings	T1c
II	Tumour involves one or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or peritoneal cancer (Tp)	T2
IIA IIB	Extension and/or implants on the uterus and/or fallopian tubes/and/or ovaries Extension to other pelvic intraperitoneal tissues	T2a T2b
III	Tumour involves one or both ovaries, or fallopian tubes, or primary peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes	T3
IIIA IIIA1 IIIA1(i) IIIA1(ii) IIIA 2 IIIB III C	Metastasis to the retroperitoneal lymph nodes with or without microscopic peritoneal involvement beyond the pelvis Positive retroperitoneal lymph nodes only (cytologically or histologically proven) Metastasis ≤ 10 mm in greatest dimension (note this is tumour dimension and not lymph node dimension) Metastasis ≥ 10 mm in greatest dimension Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes Macroscopic peritoneal metastases beyond the pelvic brim ≤ 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes Macroscopic peritoneal metastases beyond the pelvic brim ≥ 2 cm in greatest dimension, with or without metastases to the retroperitoneal nodes (Note 1)	T1, T2, T3aN1 T3a/T3aN1 T3a/T3aN1 T3b/T3bN1 T3c/T3cN1
IV	Distant metastasis excluding peritoneal metastases	Any T, Any N, M1
Stage IV A Stage IV B	Pleural effusion with positive cytology Metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of abdominal cavity) (Note 2)	Any T, Any N, M1

Based on 'DG Mutch and J Prat. 2014 FIGO staging for ovarian, fallopian tube and peritoneal cancer. Gynecologic Oncology 2014;133:401-04'

Notes:

1. Includes extension of tumour to the capsule of liver and spleen without parenchymal involvement of either organ.

2. Parenchymal metastases are Stage IV B.

Currently, there are many new complementary therapies underway and have tried out the first clinics designed to test their adequacy in the treatment of ovarian cancer. New drugs are often combined against cell targets and pathways that are important for cell growth, tumor growth and escape from the body's immune system and mortality. This is, for example, anti- angiogenic agents, factor signaling inhibitors, poly ADP-ribose polymerase (PARP) inhibitors, or folate receptor inhibitors. Similarly, there are many protective mechanisms in place in the body. To date, these new agents and recovery methods have not been shown to treat ovarian malignancy, however they can improve treatment and lead to delayed recurrence or intensification of the disease.

In addition, the area of improved ovarian treatment is compromised by the heterogeneity of these tissues. Different types of histology of epithelial ovarian malignancy have a specific cell origin, a range of variables, and accordingly, abnormal detection [1, 2]. Indeed, even within a single histological species, certain subtypes of molecules with different prognosis can be found [3, 4]. To address these issues, it is necessary to easily explain these differences, to find reliable biomarkers and to build appropriate medical-focused constructions. Apart from the fact that most research focuses on biomarker creation, and many putative biomarkers are published, not many end up in clinics [5].

In this review, we talk about current trends in the treatment of ovarian cancer and new treatments, and their current status.

II. STANDARD THERAPY FOR OVARIAN DISEASE

The most common treatment for malignant ovarian growth is maximal cytoreductive surgery debulking followed by platinum-based chemotherapy. Confirmation of the diagnosis, and staging of the disease was made during the surgical procedure.

Regardless, efforts should be made to determine the histological nature of the tumor, including grading [6]. A high grade/ low grade is now used, with the exception of endometrioid ovarian disease where a three-grade scale (G1, G2 or G3) is used [7]. stage measurement by pathologic degrees carefully should be performed with current FIGO recommendations [8].

According to the Gynecologic Oncology (GOG) team, optimal cytoreduction has recently been identified as particles of each remaining lump measuring 1 cm or less in size. In addition, large multivariate studies have shown improved progression- free and normal survival of a group of patients with complete resection compared with well-known bunches (somewhere in the range of 0.1 and 1 cm) and lower cytoreduction ($p < 0.0001$) [9]. In line with these lines, according to the 2017 ESGO ovarian cancer guidelines, the point of advanced surgery to achieve complete transplantation of the visible remnants of the disease (complete cytoreduction) [10].

After the surgical procedure, patients were treated with platinum / taxi procedures inserted into the veins, intermittently, in six cycles (the first line was chemically treated). In patients with phase IA / IB and G1 / G2 tissues, chemotherapy may be discontinued [6].

In advanced stages (III / IV), complete cytoreduction is often irrational. The most well-known explanation is seizure of small bowel mesentery and the lesions in the liver hilum. Patients with ulcers that do not work or due to poor working conditions are first treated with registered chemotherapy (neoadjuvant). After three chemotherapy patterns, if there is a response to treatment, interval debulking surgery (IDS) procedure can be performed, during which time, chemotherapy is continued, up to six cycles [6].

The treatment effect was evaluated after the end of first-line chemotherapy. Therapeutic response testing is performed according to the imaging results and as indicated by RECIST 1.1 (Responsive Tests for Responding to Hard Boils) [11]. Most patients respond well to primary line therapy, achieving complete response (CR), no matter how possible, many will grow back. In patients with residual disease < 1 cm, the risk of recurrence was assessed at 60-70%; in women with a large number of remaining diseases, the risk was assessed by 80-85% [12]. In this way, patients with CR should be exposed to internal controls. The increased level of CA125 may be the first manifestation of recurrence, however, if it is not combined with clinical symptoms, it is not recommended to perform second-line treatment. Referral of treatment, until adverse clinical outcomes, is not significantly worse for survival [13]. There is agreement that patients with recurrent CA125-based disease are eligible for clinical trials [14].

III. NEW WAYS TO DEAL WITH FIRST-LINE TREATMENT

Phase III clinical trials show that the introduction of anti-angiogenic therapy with bevacizumab and weekly dose-dense paclitaxel in the first line of ovarian board can improve survival. In this way, both approaches can be viewed as new guidelines for care. However, they have a wide variety of finances in particular and detect undoubted weight in patients (high toxicity and drug resistance).

In 2011, thanks to information from the Gynecologic Oncology Group Convention 0218 (GOG0218 / NCT00262847) and the International Collaboration for Ovarian Neoplasia 7 (ICON7 / NCT00483782) preliminaries, bevacizumab has recommended the European Medicines Agency (EMA) recommendation. main line and this with standard chemotherapy (carboplatin and paclitaxel) in women with epithelial advanced ovarian malignancy, fallopian tube disease or primary peritoneal cancer (OFPC) [15]. However, the FDA has not approved bevacizumab for first-line treatment.

Previous Japanese GOG 3016 results (NCT00226915) suggested that dose-dense weekly paclitaxel with the addition of carboplatin improve survival compared to traditional practice. Survival of free Median progression (PFS) was significantly higher in intensive treatment collections (28.0 months, 95% CI 22.3-35.4) than in traditional treatment cohorts (17.2 months, 15.7–21.1; HR 0.71; 95% CI 0.58–0.88; $p = 0.0015$). In normal tolerance over 3 years, it was significantly higher in dosage doses (72.1%) than in the standard treatment regimen (65.1%; HR 0.75, 0.57-0.98; $p = 0.03$) [16, 17]. In fact, the previous GOG 0262 (NCT01167712) showed that weekly paclitaxel, as a standard and traditional procedure, did not release PFS among patients with ovarian malignant growth (14.7 versus 14.0 months; HR = 0.89; 95% CI 0.74-1.06; $p = 0.18$). However, it should be noted that 84% of the analyzed patients received bevacizumab. Among patients who did not receive bevacizumab, the weekly paclitaxel was associated with PFS 3.9 months longer than that observed at the standard treatment meeting (14.2 compared with 10.3 months; HR = 0.62; 95% CI 0.40-0.95; $p = 0.03$). These results support the weekly paclitaxel benefit over carboplatin, but without the administration of bevacizumab [18]. Global Ovarian Neoplasia 8 preliminary co-operation (ICON8 / NCT01654146) is a randomized, third-phase, phase III trial aimed at testing and whether weekly chemotherapy is more compelling than conventional

chemotherapy. ICON8B is testing a combination of dense chemotherapy and bevacizumab in a subgroup of high-risk patients with stage III-IV ovarian malignancy [19].

There is also an ongoing debate over whether neoadjuvant chemotherapy and IDS could be better than undergoing primary surgery (PDS) in advanced ovarian malignancy. The second method is associated with high mortality and morbidity while the first can cause relapse and limited survival. The results of the European Organization for Research and Treatment of Cancer (EORTC) 55971 preliminary (NCT00003636) suggested that patients with stage IIIC and small metastatic tissue had higher tolerance for basic surgery, whereas patients with stage IV and larger metastatic tissue would do well tolerated with neoadjuvant chemotherapy. In patients who did not meet these criteria, both alternative therapies produced similar levels of motivation [20].

Most ovarian cancers have chemosensitivity and are confined on the surface of the peritoneal cavity for a long time. This outstanding conclusion concludes that ovarian cancer is a good basis for intraperitoneal (IP) chemotherapy. A new meta-analysis investigated results from nine randomized clinical trials, examining 2119 women with primary epithelial ovarian malignancy, of any FIGO stage, after PDS [21]. General intravenous (IV) chemotherapy was compared with chemotherapy involving part of IP management. Women were less likely to die if they received the IP component in chemotherapy (8 studies, 2026 females; HR = 0.81; 95% CI 0.72-0.90). IP part chemotherapy delayed the free course of the disease (5 studies, 1311 women; HR = 0.78; 95% CI 0.70-0.86). There has been a very prominent real toxin that affects intestinal effects, pain, fever and infection but ototoxicity and IP are less than IV. However, the last IP study, GOG 252, was overlooked to show less IP in the IV organization [22]. In this way, it is currently unsatisfactory whether IP chemotherapy builds OS and PFS. In addition, the potential for catheter-related complications and risk should be considered.

IV. TREATMENT OF RECURRENCE

Without a high rate of response to critical treatment, a significant proportion of patients will develop recurrence [23]. A notable option for the treatment of ovarian cancer from time to time is chemotherapy.

An important predictive factor is the time from the end of previous treatment (free treatment interval, TFI). The chance of recurrence is further used as a determinant of platinum exposure to platinum. Tumors are classified as:

- a. Platinum resistance - when the tumor persists during first line treatment
- b. platinum resistance - recurrence within 6 months after completing first line treatment
- c. slow recovery - recurrence at 6 to 12 months.
- d. excellent recurrence - after more than 12 months.

This collection is commonly used, except that it is currently commonly reported that platinum exposure is a continuous, rather identifiable focus on autonomous period, and cannot be precisely determined by a free period of progress (PFI) only [14].

The determination of the second phase chemical assembly depends on the tumor's sensitivity to the presence of platinum. Patients with partially or deeply sensitive tumors can be treated with platinum in combination with other drugs. These patients benefit from a variety of drug regimens. Typically, carboplatin or cisplatin is used in combination with paclitaxel or pegylated liposomal doxorubicin (PLD) or gemcitabine (with or without bevacizumab). Treatment of mild sensitivity, in which platinum is not an option (anaphylaxis in platinum compounds), trabectedin PLD may be used [24]. As evidenced by the OVA-301 phase III study (NCT00113607), patients with mutations in the BRCA type have PFS and OS longer in this way [25]. Trabectedin alone was tested in MITO15 phase II (NCT01772979) for the treatment of patients with ovarian malignancy introducing BRCA mutations and the BRCA-less phenotype (≥ 2 previous platinum reactions). It has been hypothesized that the 'recurrent platinum sensitivity' mark separates patients who are deeply receptive to trabectedin which may be an important alternative for patients presenting resistance to platinum [26].

The prediction of patients who are refractory or resistant to platinum treatment is poor. In this combination of patients, there was no benefit to the combined treatment that appeared in addition to monotherapy with PLD, topotecan, gemcitabine or paclitaxel. The combination of chemotherapy and bevacizumab completely increases the survival rate of free radicals (PFS), however, patients with good functional status are eligible for this treatment.

In some cases of recurrent ovarian disease, resection can be considered, it is suitable for patients with complete reduction and in any case an illness period of one year after first line treatment, and the possibility of major surgery [14]. The Arbeitsgemeinschaft Gynecological Oncology (AGO) Group DESKTOP OVARI I preceded, by looking at the review, showed three things that are freely linked to complete resection: complete apparent recovery in initial surgery, good performance status, and no more than 500 ml of ascites. These three items were combined with an "AGO-score" which was considered positive if the three models were satisfied. Survival analysis showed a median OS of 45.2 months in fully discharged patients, as compared to 19.7 months in patients with insufficient compensation (HR = 3.71; 95% 2.27-6.05; $p < 0.0001$) [27, 28]. The previous points are confirmed in the following preliminary - AGO DESKTOP OVARI II (NCT00368420).

The total resection rate was 76%, although bad points probably do not protect the chances of achieving a full resection. Before DESKTOP OVARI III (ENGOT ov20 / NCT01166737) was randomized, phase III looked at second-line chemotherapy compared with a voluntary treatment option followed by chemotherapy, in patients with platinum-sensitive recurrence ovarian malignancy with good AGO-score. Application information is not yet available, but the central PFS was significantly improved in the experimental arm (14 months out of 20 months by medical procedure; [29]. In synopsis, DESKTOP initiatives have shown that it is possible to select patients who may benefit from optional cytoreductive surgery.

There are a few early and clinically advanced therapies aimed at exploring new therapies for recurrent ovarian disease, for example bevacizumab re-treatment [30,31].

V. HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY (HIPEC)

At the end of the term, a combination of cytoreductive surgical and hyperthermic intraperitoneal chemotherapy (HIPEC) was used to further the treatment of peritoneal metastases. This method is currently accepted as a standard treatment for pseudomyxoma peritonei, peritoneal mesothelioma and peritoneal metastases of critical disease. In some clinical settings, HIPEC is increasingly used in the treatment of patients with ovarian cancer.

In ovarian cancer patients, HIPEC is used in combination with systemic treatment that begins approximately three weeks after surgery. Cisplatin (as well as doxorubicin) and taxanes are used as often as possible in HIPEC. Good results are being achieved in the treatment of sensitive platinum tissues, although it is recommended that qualified individuals are patients who recover later and after a several lines of chemotherapy. This therapy could also apply for the patients with large residual disease after the primary surgery and for those who have inoperable lesions. In the latter case, neoadjuvant chemotherapy is given, and patients, who will respond, are ready for cytoreductive surgery combined with HIPEC. Another relevant circle may remember patients who have undergone laparoscopy revealed malignancy, rather than an apparently benign tumor. HIPEC is not prescribed when the disease has spread to inaccessible organs outside the peritoneum [32].

HIPEC is being investigated for high morbidity and mortality. Significant confusion includes anastomotic rupture, intestinal congestion, intraperitoneal bleeding and wound dehiscence. The reported illnesses ranged from 0 to 31.3% (Illnesses in Grades 3 and 4 as indicated by Clavien-Dindo's order) and mortality rates ranged from 0 to 4.2%. A several authors argue that these numbers are similar to those seen in surgical patients only [33].

To date, a large proportion of several effects on ovarian cancer come from phase I-II or review reviews, e.g., case studies (246 patients with ovarian cancer with recurrent intraperitoneal injury or with persistent lesions after systemic treatment) it has been shown that median survival overall was 49 months after the most severe cytoreductive surgery with HIPEC [34, 35].

VI. THE NEW TREATMENT FOCUSES ON THE TREATMENT OF OVARIAN CANCER

6.1-Angiogenesis inhibitors

Angiogenesis is a tightly controlled cycle that occurs first in fetal growth, during wound healing and due to ovulation. In any case, it is commonly performed in the midst of many irritating conditions, for example, trauma, recurrence of diabetes such as various ischemic, infectious, and physiological disorders. Among the well-known regulators of angiogenesis are growth factors, matrix metalloproteinases, cytokines, and integrated. A key contributor to the development of vascular tumor association is the Vascular Endothelial Growth Factor (VEGF) and its signaling pathway. It was initially expected that blocking VEGF signaling in malignancy would inhibit angiogenesis and cause reduction, due to anemia. In addition, a detailed investigation suggested the possibility that anti-angiogenic agents could "mimic" the abnormal structure and function of the tumor vasculature to make it more effective in oxygen transfer and medication [36].

In epithelial ovarian cancer, increased VEGF extension has a predictive value: it is related to tumor level, stage of disease, and patient survival. Since VEGF receptors are found outside the cells of ovarian disease, it seems that VEGF may play a significant role in the development of this malignant disease. By increasing vascular penetration into the peritoneum, VEGF is also responsible for ascitic regulation in ovarian cancer patients. Thus, the barrier to disease angiogenesis found one of the most widely sought-after therapies in the treatment of ovarian cancer; promising results appear with bevacizumab, cediranib and pazopanib, just as flibcept.

a. VEGF inhibition: bevacizumab

Bevacizumab is a modified anti-monoclonal antibody that opposes VEGF. Prevents VEGF from binding to its receptor; it has been shown that bevacizumab promotes tumor vasculature balance and decreased internal tumor pressure, improving the adequacy of conventional treatment. In 2004, it became the leading clinical angiogenesis inhibitor in the US (allowing for treatment, integration with conventional chemotherapy, for harmful colon growth) [37]. In 2011, based on data from GOG0218 and ICON7 preliminaries, bevacizumab received European Commission approval for primary line therapy and standard chemotherapy for women with advanced OFPC [38]. In 2014, the Food and Drug Administration (FDA) approved bevacizumab, in combination with paclitaxel, topotecan or pegylated liposomal doxorubicin (PLD) for the treatment of patients with platinum-resistant recurrent epithelial ovarian, fallopian tube and primary peritoneal cancer [37]. The first phase of a Phase III clinical trial examining bevacizumab in ovarian diseases, which have been completed and are still being evaluated extensively in [39, 40].

GOG 218 was a blind-placebo-controlled, three-arm intervention aimed at determining whether the combination of bevacizumab in standard chemotherapy (cisplatin and paclitaxel) in first-line treatment improves continuous free survival (PFS) in phase III and IV epithelial ovarian risk patients undergoing surgery. The study examined bevacizumab added to standard chemotherapy followed by bevacizumab maintenance for 22 cycles (months PFS 14.1) compared with conventional chemotherapy (median PFS = 10.3 months). Patients in the third arm received bevacizumab only with chemotherapy and did not have selective clinical effects than those treated with standard chemotherapy alone (PFS = 11.2 months). Compared with the control collection, HR mortality was 0.908 (95% CI 0.795-1.040; $p = 0.16$) and bevacizumab-inception and 0.717 (95% CI 0.625-0.824; $p < 0.001$) and bevacizumab ubiquitous. The absence of a significant difference in PFS between the control group and bevacizumab-initiated meant that bevacizumab should be administered in addition to chemotherapy to delay the progression of the disease [41, 42].

Another first study of the adequacy of standard chemotherapy and bevacizumab supplementation in patients with OFPC was the ICON7 study (NCT00483782). This phase III was randomly performed, preceded by two arms indicating that simultaneous use of bevacizumab with 5 or 6 cycles of platinum-based chemotherapy and 12 additional cycles continued to improve PFS by 2 months and extended the response by 20%. The benefits of PFS and OS were particularly significant among patients at high risk of progression [3.6 months development (confinement) and 7.8 months (median) respectively], bevacizumab increased the range of toxic effects, for example, blood pressure, and bowel perforation [43, 44].

Thus, the findings of GOG-0218 and ICON7 have shown that the use of bevacizumab maintenance after conventional chemotherapy increases median PFS in patients with advanced epithelial ovarian cancer [39].

Various studies recommend that patients with recurrent ovarian cancer may benefit from bevacizumab, regardless of sensitivity to platinum treatment [45]. A The first randomized, open-label, open-label, phase III first combination of bevacizumab and standard chemotherapy in patients with common platinum-resistant ovarian injury given single-agent chemotherapy alone or with bevacizumab until the progression of the disease was AURELIA (NCT00976911). Median PFS was 3.4 months chemically only compared to 6.7 months of treatment containing bevacizumab (HR = 0.48, 95% CI 0.38-0.60; excluded log-rank $p < 0.001$). The Median OS was 3.3 months longer in the treatment circle; however possible, it was not overly important. Safety analyzes have shown that high blood pressure and proteinuria are more common in patients treated with chemotherapy and bevacizumab than in the control group. Therefore, this study showed that adding bevacizumab to chemotherapy significantly improved PFS and objective response rate (ORR) [46].

Another final outcome study was OCEANS (NCT00434642), a randomized, placebo-controlled, phase III trial, evaluating the adequacy and safety of bevacizumab support after gemcitabine and carboplatin. Patients with recurrent platinum-sensitive recurrent cancer were treated with 6-10 chemotherapy cycles after which bevacizumab or placebo was administered until the disease progressed. Median PFS was 4 in the treatment group (HR = 0.484; 95% CI 0.388-0.605; log-rank $p < 0.0001$). Middle OS was the same between the arms. No new safety indicators were identified after prolonged exposure to bevacizumab, in any case, in the

control of the case at the time of contradictory events that appeared more frequently than in the control group [47]. Preliminary AGOOVAR17 (NCT01462890) is designed to test the duration of treatment as maintenance.

Three clinical trials of phase III bevacizumab in the treatment of acute ovarian cerebral palsy (AURELIA, OCEANS and GOG0213 / NCT00565851) which examined a total of 1502 patients, were included in two meta-analyses [48, 49]. Both of these meta-analysis studies have shown that the addition of bevacizumab to standard chemotherapy improved ORR, PFS and OS, and had higher, but more manageable toxic effects (tested 3-4).

A similar experiment was made to include bevacizumab in neoadjuvant carboplatin-paclitaxel achieve to complete IDS rehabilitation in patients with early low-grade ovarian cancer (ATHALYA / NCT01739218). Complete resection rate was significantly higher in the bevacizumab additional group. A well-known trial of 3 adverse treatment responses occurred in 62% of patients in the bevacizumab circle and 63% of patients in the control group. Postoperative complications occurred in 28 patients and 36%, respectively [50].

It was noted that bevacizumab may initiate macrophage / monocyte infiltration [51] which has been classified as an independent predictive factor in several types of cancer [52]. The main survival factor for these cells is granulocyte - macrophage colony-stimulating factor 1 (GM-CSF1). The first NCT02923739 was developed to test the efficacy of emactuzumab, a GM-CSF receptor inhibitor [53], followed by paclitaxel and bevacizumab, of OFPC's anti-platinum antagonist.

Then again, bevacizumab can cause hypoxia in tumors that can increase genomic instability, which is thought to create cell sensitivity to PARP inhibitors [54].

The cost of bevacizumab costs was investigated according to the results of ICON7 preliminary (NCT00483782), which showed that the inclusion of bevacizumab (7.5 mg / kg) in first-line chemotherapy improves PFS and OS in a group of women previously shown to be at greater risk of progression. for post hoc subset of 465 high-risk patients, i.e., phase IIIC and residual disease > 1 cm or stage IV, the OS after standard chemotherapy was 28.8 months compared to 36.6 months in the treatment group; HR = 0.64; 95% CI 0.48-0.85; p = 0.002). There were three studies, one directed at the U.S. Government's health care system. [55], one according to U.K. guidelines. Public Health Service [56] and one of the Canadian medical care programs [57]. It has been estimated that patients with ovarian cancer who are at high risk of progression receive bevacizumab in addition to standard chemotherapy that has a 0.374-year-old systemic health benefit (QALY) benefit. The equivalent cost (ICER) of bevacizumab was around \$ 167,771 in a year of saved life (Medicare). In a Canadian study, ICER was \$ 95,942 per QALY, while in Britain it was £ 48,975, which was considered above the average cost limit (£ 20,000- £ 30,000 per QALY) accredited by the British National Institute for Health and Care Excellence (NICE).

All in all, bevacizumab has been shown to improve PFS for 2-4 months and in other settings similar to OS, although it is associated with other side effects. Reducing the cost may be necessary in order for this item to cost effectively for most of the national health services. Up to this point, there were no biomarker clinics available that could help select patients, who could get greater benefit from bevacizumab.

b. Inhibitors of VEGF receptors

i. Cediranib

Cediranib is an anti-angiogenic multikinase inhibitor with anti-VEGF receptors (VEGFR1-3) activity. phase III primers with cediranib have tried to combat various types of cancer with disappointing results; however, a stimulating action has been observed with cediranib in ovarian cancer. The start of ICON6 (NCT00532194) was a randomized double-blind placebo-controlled study, a placebo-controlled study, that enrolled women with platinum-sensitive relapses in ovarian cancer. It provided evidence of activity and manageable toxicity of cediranib added to platinum-based chemotherapy and continued as a maintenance treatment for up to 18 months. The 11.0-month median PFS was found in the cediranib treatment group combined with chemotherapy and subsequently cediranib as well as daily maintenance, while the 8.7-month PFS was found in a placebo-tolerant combination during treatment and maintenance (HR = 0.56; 95% CI 0.44-0.72; p < 0.0001). In the cediranib treatment group in combination with chemotherapy where placebo is kept, median PFS was 9.9 months. Cediranib adverse effects were the most significant after-exposure effect: the most common were diarrhea, neutropenia, high blood pressure, and voice changes [58, 59].

In hindsight, the choice of cediranib has shown a marked improvement in free survival, but there are additional toxic effects.

ii. Pazopanib

Pazopanib is a multikinase inhibitor of VEGFR1-3, a platelet-determinate development factor receptor α and β (PDGFRA and PDGFRB) and c-Kit. Mito-based randomized MITO-11 (NCT01644825) assessed the efficacy and safety of pazopanib in combination with paclitaxel in patients with platinum-resistant ovarian cancer. The PFS was significantly longer in the experimental circle (PFS-6.35 center compared to 3.49 months in the placebo treatment circle; HR = 0.42; 95% CI 0.25-0.69; p = 0.0002). adverse events include neutropenia, fatigue, leucopenia, high blood pressure and anemia [60].

A phase III study AGO-OVAR16 (NCT00866697) was proposed to evaluate the efficacy and safety of pazopanib monotherapy compared with placebo treatment of women with OFPC who did not progress after the first line of chemotherapy, showed better PFS in patients receiving pazopanib (median PFS = 17.9 months) rather than a collection of placebo treatment (median PFS = 12.3 months). The PFR HR was 0.77 (p = 0.0021). First among the OS time tests did not raise a profit. Tests of 3 or 4 adverse events of hypertension (30.8%), neutropenia (9.9%), liver-related destruction (9.4%), and diarrhea (8.2%) were critical outcomes [61, 62].

All in all, pazopanib shows benefits in long-term PFS, in the treatment of platinum-resistant/refractory ovarian cancer and support affecting platinum; no matter, other tests are important to note patient clips where improved performance can measure the balance to that treatment.

iii. Nintedanib

Nintedanib (BIBF1120) is a future, triple-acting angiokinase inhibitor of VEGFR1 / 2/3, FGFR1 / 2/3 and PDGFR α / β , with less activity against RET, Flt-3 and Src. It has shown a critical anti-tumor action in several types of tumors in pre-surgical investigation and treatment [63]. In 2014, the FDA approved nintedanib for the treatment of idiopathic pneumonic fibrosis. Nintedanib in combination with docetaxel was confirmed, in 2014, by the European Commission for the treatment of elderly patients with local, recurrent, or recurrent cell cancer [64].

LUME-OVAR 1 (AGO-OVAR 12 / NCT01015118) was a randomized, blind study, phase III trial where nintedanib was added to standard first-line chemistry, followed by nintedanib maintenance for 120 weeks, in patients with advanced epithelial cancer ovary. This study showed a significant improvement in the median PFS of the treatment group comparing and controlling the combination (17.2 months compared to 16.6 months; HR = 0.84; 95% CI 0.72-0.98; p = 0.0239). The most significant benefit of PFS was found in small group studies in patients with < 1 cm extra tumor (21.1 compared with 20.8 months; HR = 0.75; 95% CI 0.61-0.92; p = 0.005). The most common adverse events were intestinal (open bowel) and hematological (neutropenia, thrombocytopenia, paleness). Negative treatment-related adverse events occurred in three patients in the nintedanib cycle and in one patient in the placebo treatment group [65].

Randomized treatment, placebo treatment, phase II NCT00710762 trial tested maintenance treatment with nintedanib following chemotherapy in patients with ovarian disease that recurred. It showed an increase in PFS at 36 weeks compared with placebo (HR = 0.68; 95% CI 0.44-1.07; p = 0.07). There was a high level of diarrhea, nausea, vomiting and in the nintedanibgroup [66].

Nintedanib has a shorter half-life (7-19 h) than bevacizumab (14-21 days). GINECO-OV119 (CHIVA /

NCT01583322) was II study phase of nintedanib randomized, double-blind, placebo treatment in spite of neoadjuvant chemotherapy and IDS in patients with OFPC. No significant differences were observed between placebo treatment and the nintedanib group in terms of duration of surgery similar to the pre-operative and postoperative IDS combination [67].

There are currently phase II beginners starting nintedanib. METRO-BIBF (NCT01610869) is a randomized, placebo-administered trial that aims to assess the adequacy and safety of the combined oral combination of nintedanib and metronomic cyclophosphamide in patients with multiple relapsed advanced ovarian cancer, which eliminated any previous two lines of chemotherapy who under any circumstances should not receive additional standard chemotherapy instructions [68]. A second continuous second phase is NCT01669798 which is important to test whether nintedanib can produce a number of women with resistant, persistent, or recurrent ovarian malignant malignant tumors that do not occur in any event for six months [69].

The combination of Nintedanib with carboplatin and paclitaxel as a first-line treatment is greatly enhanced by PFS for women with advanced ovarian cancer, with severe gastrointestinal events.

iv. Angiopoietin inhibitor

Apart from VEGF, various mechanisms related to angiogenesis are further aggravated. Angiopoietin 1 and 2 (Ang1 / 2) bind to the Tie-2 receptor, which serves to promote endothelial cell proliferation, motility and survival. Trebananib (AMG386) is a protein compound that binds to Ang1 / 2, apparently inhibiting Tie-2. The results obtained from two clinical primers: NCT00479817 [70] and TRINOVA-1 (NCT01204749) [71] were associated with meta-analyses [49] that showed PFS reversal (HR = 0.67; 95% CI 0.58-0.77; $p < 0.00001$) and OS (HR = 0.81, 95% CI 0.67-0.99, $p = 0.04$) of trebananib combined with weekly paclitaxel in women with recurrent OFPC, in part platinum-sensitive or incompatible.

Several anti-angiogenic therapies have been shown to be effective in improving PFS of recurrent ovarian disease with a potential benefit of 2-6 months, regardless of the toxic effects. angiogenic antidepressants are given to unselected patients as no predictable marks have been obtained as recently as possible. Other data suggest that patients with tumor blood perfusion or oxygenation increments after the start of anti-angiogenic treatment, live longer than those with tumor perfusion that do not change or decrease [36]. In particular, with the detection of angiogenic drugs (bevacizumab, VEGFR inhibitors and trebananib) in the two main types of cancer (1) platinum resistant and (2) platinum-sensitive recurrent ovarian cancer, it was shown that PFS progressed well in both groups., while the OS is obviously better in the platinum-sensitive group, but may not be important in the platinum antagonist group [49]. These data suggest that it is possible to improve survival through the personal use of anti-angiogenic agents.

fix the way proteins make a mistake in DNA repair in a painful cell modified by BRCA, the activation of two alleles of BRCA1 or BRCA2 promotes the malfunction of homologous recombination deficiency (HRD). Treatment of such cells with PARP i promotes severe DNA damage and cell death [72].

6.2-PARP inhibitors

Poly (ADP-ribose) Polymerase (PARP) is a group of 17 enzymes associated with a wide range of cellular functions, of which PARP1 and PARP2 are known to live with DNA repair. Cancer treatment with PARP inhibitors (PARP i) abuses the concept of artificial insemination, a phenomenon in which genetic mutations are harmless when they occur spontaneously, but can bring about cell proliferation when they appear in combination. Key clinical preliminaries acknowledging the clinical significance of this phenomenon include the investigation of PARP i in BRCA1 and BRCA2 (BRCA) transformation agents with advanced tumors. In wild BRCA cells, PARP and BRCA proteins play a role in DNA repair in a variety of ways. Within recognizing the inhibition of PARP, BRCA and other chemical regenerative proteins make the mistake of repairing DNA. In the BRCA-mutated cancer cell by BRCA, the activation of two alleles of BRCA1 or BRCA2 promotes the malfunction of homologous recombination insufficiency (HRD). Treatment of such cells with PARP i promotes greater DNA damage and cell death [72]. Similarly, another defect of tumor-expression reconstruction may be affected, for example, by major BRCA modifications, changes in ATMs, ATR, RAD51, and others [73, 74]. The first PARP inhibitor approved for clinical use was olaparib [75].

Various initiatives were intended to evaluate PARP inhibitors in ovarian disease: (1) first-line treatment (SOLO1 /

NCT01844986, NCT02470585, PRIMA / NCT02655016, PAOLA1 / NCT02477644, NEO / NCT02489006), (2) in the treatment of sensitive platinum-backslide (ENGVO / 24 NCT02354131, NCI-O008 / 080/0/0/0/0/0/03), (3) post-chemotherapy support for platinum-sensitive disease (ENGOT-OV16 NOVA / NCT01847274, SOLO 2 / NCT01874353, ARIEL3 / NCT01968213) or (4) in the treatment of platinum-resistant disease, and (5) a combination of experimental inhibitors and other natural remedies [54, 76-78].

i. Olaparib

Olaparib (AZD2281) received in 2014 an accredited FDA approval for the treatment of advanced ovarian cancer in patients with known or suspected BRCA mutations, treated with at least three previous chemotherapy regimens [75]. That same year, the European Medicine Agency (EMA) approved olaparib as a monotherapy in the treatment of patients with platinum sensitive, relapsed BRCA-mutated (germline or somatic) highgrade serous epithelial ovarian cancer who are in complete response (CR) or incomplete response (PR) following chemical treatment with platinum.

Olaparib approval is based on data from Study 19 (AZ19 / NCT00753545), the first clinical trial to evaluate its efficacy and safety compared with placebo treatment, in platinum-sensitive recurrent patients with high serous ovarian disease [79]. Studies have shown that Olaparib maintenance treatment has taken longer to progress, compared with placebo treatment, in patients with BRCA

ovarian cancer-modifying cancer (median PFS 11.2 compared to 4.3 months; HR = 0.18; 95% CI 0.10-0.31; $p < 0.0001$). adverse events identified with olaparib were usually assessed 1 to 2 and included nausea, fatigue, vomiting, taste changes and anorexia, although adverse events of grade ≥ 3 were more common in olaparib meeting (40%) than in the treatment collection of placebo (22%). The most pronounced were disorders (2 versus 0%), fatigue (7 versus 3%), iron deficiency (5 versus 1%), neutropenia (4 versus 1%).

In a number of different articles, olaparib was tried as a stand-alone treatment or in spite of conventional chemotherapy, such as pre- and post-surgery surgery, and in combination with various new drugs. The SOLO1 (NCT01844986) study, led as a group by the Gynecologic Oncology Group (GOG), was intended to evaluate the olaparib support component after chemotherapy adjustments for OC patients with mutations in the germline BRCA. SOLO2, working in partnership with the European Network of Gynecological Oncological Trial (ENGOT) Groups, was looking at the role of olaparib support after at least two lines of chemotherapy for OC patients with germline BRCA mutations. The first two were randomly assigned, two blinds, placebo treatment was administered. The final significant point was the PFS median trial that was 19.1 months in the group compared with 5.5 months in the placebo treatment circle (HR 0.30; 95% CI 0.22-0.41; $p < 0.0001$). The results of a blinded review of the SOLO2 study were released in March 2017 at the Annual General Conference on Society of Gynecologic Oncology on Cancer in Women, showing PFS (30.2 months with olaparib compared to 5.5 months with placebo treatment; HR = 0.25 (95) % 0.18 –0.35), $p < 0.0001$) [80]. Based on this information the FDA has approved a review of the need for another olaparib program as a supportive treatment for rehabilitated patients with platinum-sensitive ovarian cancer.

Compiled data from the first six olaparib studies (the first two phases and four phase II trials) enrolled in women with relapsing diseases were used to investigate olaparib function according to the number of previous treatments in patients with germline BRCA - altered ovarian cancer. In a combined population of 273 patients who had been referred at least three lines of previous chemotherapy, the rate of objective response rate (ORR) was 36% with a median duration of 7.4 months [81].

Olaparib is also being investigated in combination with chemotherapy. In randomized, open-label, stage II research (NCT01081951), patients with platinum-sensitive, retained OC received olaparib and paclitaxel and carboplatin, followed by olaparib support, or paclitaxel and carboplatin without medical treatment. PFS was gradually improved in the olaparib group compared with chemotherapy alone (12.2 months compared with 9.6 months; HR = 0.51, 95% CI 0.34-0.77; $p = 0.0012$), especially in patients with BRCA mutations (HR = 0.21, 95% CI 0.08 –0.55; $p = 0.0015$) [82]. SOLO3 (NCT02282020) begins at random, phase III first in patients with altered germline BRCA, a recurrent OC that has failed at least two lines of chemotherapy, in which olaparib will be compared to one special chemotherapy.

Alternative therapies with various different agents are also being evaluated. Olaparib was concentrated in combination with an anti-angiogenic multikinase inhibitor, cediranib. Middle PFS was 17.7 months for women treated with cediranib and olaparib ($n = 44$) compared with 9.0 months for those treated with olaparib alone ($n = 46$; HR = 0.42; $p = 0.005$) [81, 83]. Application details were not upgraded; however, there was a pattern towards a long OS in the combination group. Treatment-related side effects were more common in patients treated with cediranib than olaparib than monotherapy.

Recently, the results of the first phase of olaparib research in combination with PI3K inhibitor BKM120 (NCT01623349) [84] and AKT inhibitor AZD5363 (NCT02208375) [85] have been calculated with evidence of efficacy in OC.

ii. Niraparib

Niraparib (MK4827) is an oral, selective inhibitor of PARP-1 and 2 that was detected in preclinical tests for tumor-induced killings in the absence of PTEN and BRCA1 or BRCA2 [77]. Clinical studies have shown that niraparib basically improved PFS in patients with recurrent platinum-sensitive ovarian cancer, with little attention to BRCA mutations or HRD status, although its efficacy is most noticeable in patients with BRCA mutations.

In late April 2017, niraparib received FDA approval for supportive treatment of patients with recurrent OC in CR or PR to platinum-based chemotherapy [86]. approval is based on information from the first phase III ENGOT-OV16 / NOVA (NCT01847274) first, a double-blind trial, placebo treatment selected 553 patients. About 66% of study members had no germline BRCA mutations. The PFS in the germline BRCA mutated circle was 21.0 months, while in the placebo treatment group — 5.5 months ($p < 0.0001$). In conjunction with the unchanged BRCA but with positive HRD scores, the PFS was 12.9 months while placebo treatment-collection was 3.8 months ($p < 0.0001$). Indeed, even in the noninvasive and HRD negative circles, PFS was

longer in patients treated with niraparib (6.0 versus 3.9 months, $p = 0.02$). Niraparib reduced the incidence of progression or death by 74% in patients with mutant germline BRCA ($HR = 0.26$) and by 55% in non-mutable patients ($HR = 0.45$). The most well-known trials of 3/4 antagonistic responses to niraparib to NOVA preliminary include thrombocytopenia (29%), weakness (25%), neutropenia (20%), and high blood pressure (9%). Most hematologic adverse events were successfully managed using dose modification [87].

The progressive development of niraparib includes first phase III phase in patients receiving first-line treatment for ovarian malignancy (PRIMA / NCT02655016) and enrollment of Phase II first-line patients who have received different lines of ovarian treatment (QUADRA / NCT02354586). Many types of combinations are more progressive, including the beginnings of niraparib over potro luzumab (TOPACIO / NCT02657889) and niraparib over bevacizumab (ENGOT-OV24 / AVANOVA / NCT02354131).

iii. Rucaparib

Rucaparib (CO338, AGO14699, PF01367338) is administered orally, a small molecule based on PARP-1, -2 and 3 inhibitors. In December 2016, the FDA approved the acceleration [approval of rucaparib as monotherapy in the treatment of patients with advanced ovarian cancer associated with BRCA mutations (germline and more apparently) treated with two or more lines of chemotherapy [88, 89].

ARIEL2 (NCT01891344) was a phase II biomarker study that tested whether the loss of heterozygosity (LOH) level, could expect a response to rucaparib. ARIEL2 selected patients with platinum-sensitive, recurrent, high serous or endometrioid ovarian cancer after any single line of platinum-based chemotherapy and its final treatment was based on platinum.

The primary objective was to evaluate the clinical development of rucaparib in three subgroups, indicated by BRCA mutations and HRD status (given LOH level, estimated by preoperative assessment): (1) BRCA modified, (2) BRCA-wild type / LOH-high and (3) BRCA-wild kind / LOH-low. Median PFS after treatment with rucaparib in association with BRCA mutations was 12.8 months (9.0-14.7), in LOH the highest incidence was 12 months -5.7 (5.3-7.6.), And the lower incidence of LOH was 5.2 months (3.6-5.5). The PFS was at a very low level in the BRCA oddity with the LOH of the upper class is divided and the lower is the LOH. These results suggested that LOH tumor testing could be used to identify patients with advanced BRCA cancer of the wild type with cancer that could benefit from rucaparib.

Highly suggested tests 3 adverse reactions to rucaparib to ARIEL2 primer include anemia or low hemoglobin (22%), increased alanine aminotransferase or aspartate aminotransferase (12%), inhibition of small intestine (5%), malignant tumor development (5%) [90, 91].

Rucaparib also tried as a maintenance treatment for platinum sensitive patients, divided into three circles in ARIEL3, double-blind n, placebo treatment, phase III selected 564 women (NCT01968213). The PFS after treatment of rucaparib in the BRCA and BRCA mutations was 16.6 months ($HR = 0.23$, $p < 0.0001$), in the HRD collection (counting patients with BRCA mutation or wild type BRCA / LOH- high) was 13.6 months ($HR = 0.32$, $p < 0.0001$), and "for therapeutic purposes" collection (counting patients with BRCA mutation, BRCA-wild / LOH-high, BRCA wild / LOH-low and BRCA-wildtype / intermediate LOH) were 10.8 months ($HR = 0.37$, $p < 0.0001$), while in the placebo treatment group PFS was 5.4 months. The well-known 3 or more adverse reactions to rucaparib in previous ARIEL3 included pallor (18.8 versus 0.5% in a placebo treatment round) and elevated alanine / aspartate aminotransferase (10.5 versus 0 %) [91]. In a parallel study of ARIEL4 (NCT02855944), a key role was played to assess the adequacy and well-being of rucaparib compared with conventional chemotherapy in the treatment for relapsed ovarian cancer in patients with BRCA mutation.

iv. Other PARP inhibitors

There is a different PARP i now available for the treatment of various tissues, including ovarian. Veliparib (ABT888) is an oral inhibitor of both PARP-1 and 2 which is widely regarded (currently there are 26 registered preliminaries for ovarian damage), in combination with chemotherapy, and as a single agent [77].

Talazoparib (BMN673) was promising in a pre-clinical trial, but has now been routinely tried in the first phase. The first phase II (NCT 02326844) attempted talazoparib as a monotherapy for patients with BRCA-induced ovarian disease that had previously had PARP i treatment.

Summary of PARP inhibitors

PARPi (olaparib, niraparib) has recently become a standard of care for patients with recurrent BRCA cancer that has replaced ovarian cancer. Also, it has been shown that olaparib basically improved PFS in patients with a repetitive strain of platinum-like growth, with little regard for BRCA changes. Niraparib has shown the development of PFS in the same situation, with little regard for BRCA changes and HRD status. It suggests that unless the adequacy of these two agents is highly recommended for BRCA-converted people, a variety of patients could also benefit. Various settings are now being widely tested, e.g., PARP i for primary treatment and in maintenance after primary treatment, PARP i as monotherapy or combined with chemotherapy and other biological agents. However, the use of PARPi in combination with chemotherapy is counteracted by toxicity, in this way also promoting strategies joining PARPi with anti-angiogenic agents, or with P13K / AKT method inhibitors and a new generation of immunotherapy [92].

Just as BRCA1 or BRCA2 mutations and cisplatin sensitivity were adopted predicting response to PARP i. After that, it is now widely accepted that the BRCA test should be given to all women with ovarian risk.

The exact characteristics of long-term respondents will still be considered and high-level HRD testing is required [93]. The Astra Zeneca AZ HRR trial analyzes 15 genologically related mutations (BRCA1 / 2, ATM, RAD51B / C / D, RAD54L, FANCI, FANCL, FANCN, BARD1, CHEK1 / 2, CDK12, PPP2R2A). Other than that, the numbers for these changes are slightly diminished and some exist without a doubt, very little sensitivity to PARPi. Examination of my many choices is based on a test of three free points of genome unsteadiness: telomeric allelic abnormalities, major changes, and LOH. The test is based on the entire genome profile of single nucleotide polymorphisms (SNPs) [51, 94].

However, the current data show that PARPi is all well tolerated, with moderate to severe toxicity testing, as these drugs are recommended for long-term use.

Clinical trials recommend that PARPi may significantly affect the extension of PFS in BRCA-modified patients and then anti-angiogenic treatment. Similarly, PARP i is better tolerated, and has the potential for oral administration. In addition, the cost-effectiveness of this treatment is currently being evaluated; e.g. It was also suggested by these creators that with limited healthcare resources, the first basics of treatment should include future costs, long-term medical toxicity, and health quality.

An effective study of Olaparib and rucaparib was an ancient one presented at the Annual Meeting of the American Society of Clinical Oncology. The platinum-based compound was found to be more effective at \$ 1672 / PFS, compared to non-platinum agents (\$ 6688 / month), regimens containing bevacizumab (\$ 12,482 / month), Olaparib (\$ 13, 3731 / month), and rucaparib (\$ 14,034 / month). Considering the \$ 114,478 cost of Olaparib and the \$ 137,068 rucaparib pre-progression, PARPi-related costs were 7.1-8.3 times higher than the platinum compound [95, 96]. The authors of the report noted that "while the information on PARP inhibitors is promising, the shocking view of new treatments is their indivisible costs associated with significant development costs".

6.3-EGFR tyrosine kinases inhibitors

The ErbB family contains four tyrosine kinases that are basically targeted and related: Epidermal Growth Factor Receptor (EGFR / HER1 / ErbB1), Human Epidermal Growth Factor Receptor 2 (HER2 / neu / ErbB2), HER3 / ErbB3 / ErbB4. The main ligand of ErbB1 (EGFR) is the Epidermal Growth Factor (EGF). ErbB2 has no known ligands, while ErbB3 does not have a strong kinase site. ErbB receptors may incorporate homodimers or participate in the formation of heterodimers, two types of connections that bring about active signaling in the form of Ras-Raf-MAPK and PI3K / AKT, which promote cell proliferation and inhibition of apoptosis. Therefore, ErbB proteins may be indicative of a therapeutic target for many diseases.

In ovarian injury, high-level EGFR expression has been shown to be linked to disease-free survival (DFS) and OS. Unfortunately, none of the EGFR inhibitors (erlotinib, cetuximab or lapatinib) have shown promising results in early clinical trials investigating their satisfaction in ovarian cancer treatment. The depressing effects are also caused by pertuzumab-directed HER2.

6.4-Folate receptor α inhibitors

Folate receptor alpha (FR α) is a protein glycosylphosphatidylinositol, bound to the cell membrane. In physiological cases, it is found only in some embedded epithelia and its appearance is carefully limited to the apical / luminal cell area. In any case, it is usually excessive pressure on the epithelial tissue, where it loses its shape and is found throughout the cell. In this way, FR α is a potential biomarker of malignant tumor growth cells and a promising therapeutic purpose [97].

Similarly, anti-FR α antibodies (NCT02111941; NCT02764333) and FRcy-focused treatment of T cells are exploited [98, 100].

i. Farletuzumab

Farletuzumab (MORAb-003) is an autoimmune-mediated immune response with a high affinity for FR α [99]. Pre-clinical trials suggest that farletuzumab utilize its anti-tumor action through a variety of methods, either by increasing tumor cell lysis or dependent cytotoxicity. Various systems rely on supportive autophagy induction, which results in reduced proliferation, or inhibition of interactions between FR α and lyn kinase, resulting in reduced cell growth [101]. The first stages of the Phase I / II clinic demonstrated the efficacy and safety of farletuzumab; The most common adverse events were responses to hypersensitivity, fatigue and diarrhea. The first phase of the study (NCT00318370) showed that farletuzumab containing carboplatin and taxane may improve the response rate and response time in platinum -sensitive ovarian patients with relapse after 6 and a half years of remission [102]. unfortunately, sufficient data in the first phase III are contradictory [103]. One phase III randomized, placebo-controlled initial treatment (NCT00738699) was scheduled to test farletuzumab in combination with weekly paclitaxel in patients with EOC-resistant or anti-EOC. The investigation came to an end because periodic tests showed that it would probably not meet the key point of the two-year PFS.

A randomized, placebo-controlled III phase III trial (NCT00849667) was designed to monitor the efficacy and safety of six carboplatin and taxi patterns with and without weekly farletuzumab in patients with EOC relapse for the first time. There were no significant differences in PFS between treatment arms observed. Be that as it may, experimental post hoc studies have revealed a pattern in the development of PFS in some subsets of patients [101]. It is suggested that the lack of progress in PFS in the above investigation is due to the way patients are enrolled without violating the FR α speaking rate. On the other hand, the extent of FR α as a scientific biomarker is unclear. Next, other trials are important to identify biomarkers that will help identify a small group of patients who will benefit from this treatment.

ii. Vintafolide

Vintafolide (MK-8109, EC145) is a water-soluble folate made of microtubule destabilizing agent, vinca alkaloid derivative, desacetylvin-blastinemonohydrazide (DAVLBH). DAVLBH disrupts the formation of the mitotic cycle, which stimulates cell cycle binding and cell death. The form of Folate-drug binds to FR α and enters the cell with endocytosis [99]. Preliminary clinical evidence suggests that vintafoto may have an anti-tumor effect in women with advanced ovarian cancer [104]. Phase II of the Open-label II PRECEDENT preliminary (NCT00722592) examined the effects of vintafelius supplementation on PLD in patients with recurrent ovarian disease. The median PFS was 5.0 months in the trial group compared with 2.7 months for PLD alone. Studies have shown that patients with FR α -positive (in the light of etarfolatide imaging) have benefited from combined treatment of vintafoto and PLD, although patients with FR α -negative tumors did not [103]. unfortunately, the first phase of PRECEDENT preliminary (NCT01170650) ended because the test arm did not meet the predetermined effect of PFS development [105].

iii. Mirvetuximab soravtansine (IMGN853)

IMGN853 has a class with anti-drug conjugates; contains an anti-FR α antibody combined with a potent cytotoxic agent may pay tansinoid payload. The first three phases are currently being tried (NCT02996825, NCT01609556, NCT02606305) and phase III (NCT02631876), which is an open label, a randomized controlled trial aimed at analyzing the well-being and adequacy of IMGN853 women-alone FRFpositive advanced EFPC resistant platinum.

6.5-Immunotherapy for ovarian cancer

Cancer immunotherapy involves a variety of methods aimed at the human immune system to shed tumor cells. EOC is an immunogenic tumor that can be understood by a host-controlled system; T cells are accepted by the tumor and antibodies can be isolated from the blood, tumor and ascites of EOC patients with advanced disease [106]. It has also been further demonstrated that high tumor infiltration by CD8 + T cells (lymphocytes invading tumors - TILs) is determined to be associated with patient survival [107, 108].

Several approaches were intended to improve the immune response of the immune system or to initiate a clear response against tumor antigens, including ineffective or effective immunotherapy (commonly tested, e.g., [109-111]). unfortunately, even if part of the study reported positive results from the treatment of ovarian disease with explicit immunotherapy, these results were not

significant in a meta-analysis [112]. Increased prominence appears to be new approaches involving immune checkpoint inhibitors, alone or in combination with other therapies and medications [110].

6.6-Checkpoint inhibitors and safe modulators

In physiological conditions, different immune test proteins stimulate or inhibit T lymphocyte action, regulating the correlation between response and resistance. Checkpoint receptors, for example, Cytotoxic T Lymphocyte Associated Protein 4 (CTLA-4) and Program Cell Death Protein 1 (PD-1) act to reduce the immune response to immune cells. In patients with the disease their activity is often increased, what brings about the body's immunity to cancer.

The reason behind the use of non-preventable test inhibitors is to prevent hostility in the tumor response. Then again, creating motivating molecules, they may be killed to improve the immune system's early immune response [109, 113, 114].

There are two observed factors, too far from the point, that help anticipate tumor response to immune checkpoint inhibitors, particularly tumor exposure by non-invasive cells and the dependence of tumor cells on resistant pathways. Substitute markers for this feature, e.g., the presence of TILs in the tumor and the PD-1 ligand (PD-L1) expression, respectively. According to these labels, it has been shown that more than half of the high grade serous ovarian malignant growth signals an immune response and is likely to respond to invasive test inhibitors, while in some histological forms those compounds do not progress slowly (approximately 25% of clear tumor cells and tumors). mucinous) or lost (second SOC ratio) [Gaillard et al. 2016].

Currently, several unavoidable experimental barriers are in the first phase of testing for the treatment of damaging ovarian growth (stages I and II) [110, 113].

Pembrolizumab is an anti-PD-1 antibody, approved by the FDA for the treatment of melanoma and NSCLC. Currently, it is being tried as monotherapy (NCT02608684, NCT02440425, NCT02537444, Keynote-100 / NCT02674061) or combined with PLD (NCT02865811) or bevacizumab and cyclophosphamide (NCT02865811), in patients with persistent ovarian malignancy. Pembrolizumab has also been tested in combination with carboplatin and paclitaxel as first-line chemotherapy (NCT02520154, NCT02766582);

Nivolumab is an antagonist of the PD-1 antibody, FDA approved for the treatment of melanoma. It is currently being piloted in patients with advanced impairment, including OFPC, who have joined the simple WT1 peptide vaccine over montanide (a rare Freund adjuvant), and GMCSF (a major stimulant for dendritic cell development) (phase I, NCT02737787). Nivolumab was also studied in combination with oregovomab (anti-CA125 immune response) in a phase I / II study (NCT03100006); with bevacizumab (phase II, NCT02873962); or ipilimumab (NCT02498600, NCT02834013, NCT02923934) and in combination with epacadostat (an inhibitor of indoleamine 2,3-dioxygenase; IDO1) (phase I / II, ECHO-204 / NCT02327078).

Ipilimumab is a repetitive anti-monoclonal antibody, based on FDA-approved CTLA-4 in the treatment of melanoma. Attempts to treat ovarian cancer with common platinum-sensitive ovarian malignancy (NCT01611558) and in combination with nivolumab.

Avelumab is an anti-monoclonal anti-PD-L1 antibody that does not inhibit PD-1 and PD-L2 interactions. In March 2017, it was FDA certified for the treatment of Merkel cell skin carcinoma. Two clinical trials are currently underway for phase III ovarian growth: one first-line treatment combined with carboplatin and paclitaxel (Javelin ovarian 100 / NCT02718417) and one for the treatment of recurrent platinum-resistance / refractory disease, in combination with PLD versus PLD PLD only (Javelin ovarian 200 / NCT02580058)

Atezolizumab is a man-made antibody, an FDA-targeted monoclonal antidote approved by the FDA for the treatment of bladder / urothelial carcinomas. Several attempts are being made for further detrimental ovarian growth, e.g., a third-phase randomized, double-dose ATALANTE (NCT02891824) aimed at testing atezolizumab versus placebo treatment combined with plotherapy-based chemotherapy and bevacizumab. The first phase II randomized trial (EORTC-1508 / NCT02659384) is expected to evaluate atezolizumab with bevacizumab or acetylsalicylic acid in patients with common platinum-resistant ovarian malignancy. Randomized Stage II / III trials (NCT02839707) tested the safety and efficacy of PLD with atezolizumab and bevacizumab in addition.

Durvalumab (MEDI4736) is an anti-monoclonal antibody that fights PD-L1. It is currently being tested in phase I / II trials (NCT02484404) in combination with Olaparib and cediranib in advance or recurrent ovarian cancer; in phase I / II research (NCT02431559) in combination with PLD and motolimod (Toll-like receptor 8 agonist), in recurrent platinum-resistant ovarian

disease; a phase I studying (NCT01975831) in combination with tremelimumab (a human monoclonal antibody against CTLA-4) ; and in combination with azacitidine (section I read METADUR / NCT02811497) in platinum-resistant ovarian malignancy. Durvalumab is also being tested in combination with TPIV200 / huFR-1 (a multi-epitope with folate receptor antibody), in patients with ovarian malignancy disorders (phase II). Another phase of I / II testing (NCT02726997) is expected to test pharmacodynamics and the effectiveness of durvalumab combined with chemotherapy for the treatment of primary ovarian malignancy.

To date, clinical data indicate a limited adequacy of these agents in ovarian malignant growth with targeted response rates of 10-15% and specific strong responses. In this way, it is always set, why a few patients do not respond to invisible experimental inhibitors and get predictable biomarkers. Another task is to determine the best combination therapy [113].

6.6-Therapeutic vaccines

The cancer vaccine is designed to induce cell-mediated immunity, so non-invasive cells are introduced to detect and dispose of cancer cells. For this reason, selected tumor-related antigens are transmitted using a variety of methods; there are cell-based vaccines, peptide / proteins, epigenetic, and genetic vaccines that try to fight off various tissues, given alone or in combination with various additives, for example, cytokines or other stimulants [106, 115, 116].

In cancer ovary, there are a number of tumor-related cells found at the surface or within cells that can be unintentionally fulfilled as focusing on the body's perception and response; these, e.g., CA125, p53 protein, FR α , HER2, and antigen testis antigen, such as MAGE-A4 and NY-ESO-1 [117]. Currently, there are early pilot and phase I or II pilots in the use of a vaccine to treat ovarian cancer [106].

In patients with OFPC there are ongoing studies on the p53MVA vaccine, based on modified vaccinia virus associated with p53 protein (NCT02275039); to autologous tumor oxidized tumor cell lysate antibody given montanide and PolyICLC (Toll-like receptor 3 energizer) (NCT02452775); in gemogenovatulcel-T vaccines involving autologous tumor cells induced by FANG vector encoding GMCSF, and bi-shRNA-focused furin convertase, thereby reducing immunosuppressive TGF- β 1 and β 2 (VITAL / NCT023467; and IDO1 inhibitor INCB024360, in combination with CDX-1401 (a composite protein, containing the NY-ESO-1 antigen and a single-agent neutralizer against endocytic dendritic cell receptor, DEC-205) and Poly-ICLC (NCT02166905) .

In ovarian disease, antibodies to intra-nodal autologous alpha-DC1 tumor test phase I / II NCT02432378 tests. Dendritic cell (DC) antibody and ontak (denileukin diftotox), a cytotoxic fusion protein containing diphtheria poisoning compounds and human interleukin-2 were tested in a completed NCT00703105 trial, but no results have been published so far. CVac, which focuses on MUC1 on DC antibody, was tested in the CAN-003 / NCT01068509 study. Estimation of CVac inferred, mucin 1-expression T cell reaction is estimated. PFS was not a treatment group, but one small group (patients in the second place) showed improvement in PFS and OS [118]. Some investigations into CVac (NCT01617629) have been completed, but no results have been published, so far.

Various genes include the component I study (NCT01376505) on two HER2 peptide vaccines: MVFHER-2 (597-626) and MVF-HER-2 (266-296) which are tested on various mastatic tissues, including OC; investigation of the ID-LV305 antibody, which contains a lentiviral vector focused on DCs, and containing a coding sequence on the NY-ESO-1 antigen (NCT02122861); NCT02387125 preceding CMB305, a composite compound made from a growth hormone containing NY-ESO-1 antigen (LV305) and glucopyranosyl adjuvant in the lipid emulsion (G305). A mixed antibody vaccine (MBV / Coley poison) was tried as an indirect immunotherapy in patients with various tumors expressing the NYESO-1 antigen in the study (NCT00623831). Ten of the 12 patients showed a steady increase in serum IL-6 levels and body temperature. A small group of patients showed increased levels of TNF- α , IFN- γ , and IL1- β [119]. The MVA-5T4 vaccine (recombinant change vaccinia Ankara virus vector encoding the 5T4 fetal oncoprotein) is being tested in TRIOC / NCT01556841 preliminary. The first / second phase (MIMOSA / NCT00418574) on Govovomab (murine anti-idiotypic antibody against CA-125) in support treatment only, as there is no benefit in the last major prescription (recurrent free survival) was noted [120].

6.7-Adaptive T cell transfer

A third important pattern of ovarian immunotherapy is the flexible T cell transfer. This treatment uses autologous lymphocytes or allogeneic anti-tumors to make the induce cancer regression. In this procedure, the peripheral blood lymphocytes (PBLs) are separated by apheresis, and lymphocytes are selected and expanded in vitro, then re-introduced into the patient. Alternatively, PBLs can be genetically modified to improve their anti-tumor action (fire up. In: [109, 121]).

The first few and first stages of T cell receptor progression continue in patients with advanced disease, including ovarian, e.g., treatment with NY-ESO-1 active TCR (retroviral vector transduced) of spontaneous PBLs (I -NCT01567891), or NY-ESO Cells antigen-pulsed dendritic as antibody (NCT01697527). Other ongoing phase I / II initiatives are investigating anti-MAGE-A3 antigen-responding TCR (retroviral transduced) autologous PBLs (NCT02111850) and chimeric antigen receptor (CAR) T cell treatment targeting mesothelin (NCT01583686).

6.8-Palliative treatment for perilous ascites

Prolonged and recurrent ovarian disease is most often associated with malignant ascites in the peritoneal cavity. symptoms associated with severe ascites include anorexia, constipation and pain, dyspnea and respiratory problems, fatigue and insomnia [122]. The mechanisms causing ascites are linked to intraperitoneal proliferation of tumor cells; current data show that effusion increases, e.g., due to lymphatic obstruction and increased vascular permeability, mediated by VEGF and interleukin 6 and 8. Repeated paracentesis provides a temporary reduction in symptoms; however, it is linked to a few side effects, including protein loss and hypovolemia, circulatory problems and bowel obstruction. Various immunizations have now been followed by the administration of peritoneal metastases and ascites, including T cells, checkpoint inhibitors, antibodies and inoculation (dendritic cell-and virus based), with promising therapeutic effects [123]. Recent clinical trials suggest that drugs targeted at VEGF and EpCAM lead to a slower accumulation of ascites and increase the duration of subsequent paracentesis [122].

i-Catumaxomab

Catumaxomab is a rat /mouse hybrid antibody that binds to the epithelial cell adhesion molecule (EpCAM) present in tumor cells, CD3 antigen in T cells, and type I, IIa, and III Fc γ receptors in access cells (e.g., natural killer cells, dendritic cells, and macrophages). Catumaxomab exerts its antagonist effects on T-lysis-mediated lysis, antibody dependence, cell cytotoxicity, and phagocytosis in the early stages of Fc γ R cell development (fire ending in: [124, 125]). In 2009, catumaxomab was supported by EMA in intraperitoneal treatment for malignant ascites in patients with advanced EpCAM cancer, if standard treatment is not available. Phase II trials (NCT00326885) and IP catumaxomab in platinum-resistant ovarian disease and recurrence of symptomatic ascites have shown a longer duration of treatment for first therapeutic puncture and puncture-free interval, with a beneficial effect on quality of life and acceptable safety profile [126]. In the first phase II / III (EudraCT 2004000723-15 / NCT00836654), the highly overexpressed tolerance was significantly higher than the catumaxomab packet than in the control session (center 46 compared to 11 days; HR = 0.254; p <0.0001) as it was an institutional opportunity to subsequent paracentesis (77 days compared to 13 days; p <0.0001). Similarly, catumaxomab patients had fewer symptoms and side effects related to ascites than control patients [127].

It has been found that patients with insoluble EpCAM present in ascites survive for a while; the significance of the prediction was particularly strong in patients with threatening ovarian development. In any case, the free survival of the puncture and the time of subsequent insertion was not uncommon between EpCAM-positive and negative melting patients [128].

A Phase III trial (CASIMAS / NCT00822809) found that IP catumaxomab administration activated NK cells and macrophages even though T cells in ascites also favored the interaction of CD8 (+) T cells in the peritoneal cavity [129]. In addition, catumaxomab, being a mouse / mouse antibody, can trigger a human anti-mouse reaction (HAMA). Symptoms can range from mild allergic reaction, such as a rash, to a life-threatening response, for example, renal failure. In any case, in ovarian cancer, it was found that elevated HAMA levels were linked to moderate long-term survival, which may indicate an insignificant ant- tumor immune reactivity in HAMA positive patients [130, 131].

Catumaxomab was also followed to apply for IV in patients with EpCAM-positive tumor; it does not matter, indicated in the section I was studying (NCT01320020) that it causes dose-dependent hepatitis. An important patient receiving 10 μ g IV catumaxomab experienced rare liver failure [132].

ii-Aflibercept

The development of Ascites is further related to the vascular permeability brought on by VEGF. Aflibercept is a soluble soluble receptor containing components of human VEGF1 and VEGF2 receptors associated with the stable IgG1 human region. It is the FDA and EMA approved for the treatment of acute macular degeneration and damage to metastatic colorectal disease.

Randomized controlled, placebo-controlled, phase II first treatment (NCT00327444) was intended to evaluate the safety and efficacy of IV aflibercept inhibition of ascites form in patients with advanced chemo resistant ovarian disease. The duration of

subsequent paracentesis was more significant in the trial session (55.1 days) than in the placebo treatment session (23.3 days). There was no significant difference in normal survival between the treatment groups and the placebo group [133]. The most common side effects were gastrointestinal problems, dyspnea, fatigue or asthenia and thirst. In the second phase of the study (NCT00396591), the median time at subsequent paracentesis was 76.0 days, which was 4.5 times longer than the first interval, before aflibercept (16.8 days). Adverse events include high blood pressure, migraine, anorexia, dysphonia, and gastrointestinal tract perforation (in one in 16 registered patients) [134]. Subsequently, it appears that aflibercept may be compelled to reduce the manifestations of threatening ascites, despite the fact that a significant limitation is associated with its significant disease (risk of bowel perforation) [133, 135].

VII. CONCLUSION

The most common treatment for ovarian cancer is surgery, for the purpose of complete tumor resection. The definition of "optimal debulking" has changed over the years, and now the survival benefit apparently depends on complete eradication, and at the same time leaving any remaining tumor, even <1 cm, connected to the worst forecast. To achieve full resection, advanced surgical techniques and sophisticated equipment are needed, which show the need for centralized treatment for ovarian cancer at specialized centers.

Currently, there are many more unconventional therapies that come up in the early stages of clinical practice, combined both in terms of modification of standard approaches and on the addition of a new biological drugs to the standard treatment.

Dosage-dense chemotherapy appears as an opportunity for patients with poor performance. Part of IP chemotherapy is currently unsatisfactory, like HIPEC. These two methods present a significant level of toxicity / complications and their adequacy should be conclusively verified in phase III.

Among the new drugs, bevacizumab and a few PARPi have recently been approved for the treatment of ovarian cancer. They are still being tried in a number of ways, including maintenance treatment which is actually a process that emerges with increasing efficiency and strength.

Up to this point, PARPi shows superior performance over anti-angiogenic treatment. Unfortunately, finding predictable markers in response to anti-angiogenic drugs can be a challenge, if possible. From now on, tangible topics in the search for such markers could include a better understanding of the micro-environmental component (hypoxia and perfusion, macrophage invasion, etc.) The PARPi response is linked to HRD, and a few HRD tests are a progressive activity. Surprisingly, few patients respond to this treatment even though there is no HRD signature; this complements the opportunity to discover vague HR management regions with new features. Besides, at the moment, introducing a standard BRCA test in all patients with ovarian risk should be objective.

Sadly, some new drugs appear to be ineffective, with no strong thinking behind them, e.g., EGFR inhibitors. Similarly, folate receptor signaling pathways are not mandatory, to date and require further testing. New immunotherapeutic approaches that rely on noninvasive test inhibitors currently alter the site in the treatment of melanoma, however in ovarian cancer potential success of this therapy relies on better understanding of tumor microenvironment and dominant immunosuppressive pathways, as well as finding reliable biomarkers.

Due to its high prevalence, most pre-surgical and clinical trials are related to high-grade serous ovarian disease. Further, more tailored therapies based on specific histological and biological factors should be designed to identify very different types, for example, a clear cell or low-grade serous carcinoma. Depending on the mutation factors of these subtypes, mTOR inhibitors and MEK inhibitors will work individually. A better understanding of the cells and genes of the various subtypes of ovarian disease is needed, if we consider the treatment designed.

So far, described biological drugs and new therapeutic approaches were not shown to cure ovarian cancer, but they bring the long-awaited promise of turning it into a manageable chronic disease. To bring this promise closer, price reduction of the new drugs is awaited.

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