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REVIEW ARTICLE

The current therapeutic strategies in ovarian cancer treatment

Estrategias terapéuticas actuales en el tratamiento del cáncer de ovario

Estratégias terapêuticas atuais no tratamento do câncer de ovário

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ABSTRACT

Introduction: ovarian cancer is one of the most common and lethal tumor in women. This happens as a result of late-stage cancer detention and an increased chemoresistance to standard therapy. The current development in therapies to kill the cancer cells and its spread tendencies has emerged as a key alternative to treat tumors. **Objective:** to describe the current therapeutic strategies lead to confront different capabilities of tumor cells found in the ovarian cancer treatment. **Method:** a search of literature was carried out in the following databases ScienceDirect, Redalyc, Latindex, ResearchGate, PubMed, Elsevier, ClinicalTrials.gov, SpringerLink, LARVOL's CLIN, Cuban Public Registry of Clinical Trials, from January to April 2023. A total of 50 text concerning ovarian cancer subject and alternative for treatment were selected. **Development:** the driving factors that promoted the use of ovarian cancer therapies were pointed out. The current therapeutic targets used in the treatment of this neoplasia were described, as well as the use of multiple approved drugs or in process of approval, including the synergistic drug combinations. **Final considerations:** there are a lot of options currently being implemented in ovarian cancer treatment. Despite clinical efficacy of targeted therapy, it´s presented still restricted to specific molecular subtypes and none of the assays illustrated survival benefit in general; the results obtained in the process of drugs development specifically targeting genome instability and sustained angiogenesis have been remarkable.

Keywords: ovarian cancer;epithelial ovarian cancer; antitumor drugs; chemoresistance; molecular targeted therapy; therapeutic strategy

RESUMEN

Introducción: el cáncer de ovario es uno de los tumores más frecuentes y letales entre las mujeres. Esto se debe a su detección en estados tardíos y al desarrollo de quimiorresistencia a la terapia estándar. El desarrollo de terapias dirigidas contra las propiedades distintivas de las células cancerosas y sus características habilitadoras ha surgido como una alternativa promisoria para el tratamiento de estos tumores. **Objetivo:** describir las actuales estrategias terapéuticas dirigidas contra las distintas capacidades de las células tumorales en el tratamiento del cáncer de ovario. **Método:**se realizó una búsqueda en las bases de datos ScienceDirect, Redalyc, Latindex, ResearchGate, PubMed, Elsevier, ClinicalTrials.gov, SpringerLink, LARVOL´s CLIN, Registro Público Cubano de Ensayos Clínicos, entre enero y abril de 2023. Se seleccionaron 50 artículos referentes al cáncer de ovario y las alternativas para su tratamiento. **Desarrollo:** se mencionaron los diversos factores que influyen en la elección de terapias contra el cáncer de ovario. Se describieron las actuales dianas terapéuticas utilizadas en el tratamiento de esta neoplasia, así como el empleo de múltiples fármacos aprobados y en fases de estudio, y las combinaciones sinérgicas de los mismos. **Consideraciones finales:** actualmente existen disímiles opciones de tratamiento del cáncer de ovario. A pesar de que la eficacia clínica de los agentes dirigidos todavía está restringida a subtipos moleculares específicos y ningún ensayo ilustra un beneficio en la supervivencia general, son notorios los resultados alcanzados en el desarrollo de fármacos específicamente dirigidos contra la inestabilidad del genoma y angiogénesis sostenida.

Palabras clave: cáncer de ovario; cáncer epitelial de ovario; fármaco antitumoral; quimiorresistencia; terapia molecular dirigida

RESUMO

Introdução: o câncer de ovário é um dos tumores mais frequentes e letais entre as mulheres. Isso se deve à sua detecção em estágios tardios e ao desenvolvimento de quimiorresistência à terapia padrão. O desenvolvimento de terapias direcionadas contra as propriedades distintas das células cancerígenas e suas características facilitadoras surgiu como uma alternativa promissora para o tratamento desses tumores. **Objetivo:** descrever as atuais estratégias terapêuticas dirigidas contra as diferentes capacidades das células tumorais no tratamento do câncer de ovário. **Método:** foi realizada uma busca nas bases de dados ScienceDirect, Redalyc, Latindex, ResearchGate, PubMed, Elsevier, ClinicalTrials.gov, SpringerLink, LARVOL's CLIN, Registro Público Cubano de Ensaios Clínicos, entre janeiro e abril de 2023. 50 artigos referentes ao câncer de ovário e as alternativas para o seu tratamento. **Desenvolvimento:** foram mencionados os vários fatores que influenciam a escolha das terapias contra o câncer de ovário. Foram descritos os atuais alvos terapêuticos utilizados no tratamento desta neoplasia, bem como o uso de múltiplas drogas aprovadas e em fase de estudo, e suas combinações sinérgicas. **Considerações finais:** atualmente existem opções de tratamento dissimilares para o câncer de ovário. Apesar de a eficácia clínica dos agentes direcionados ainda estar restrita a subtipos moleculares específicos e nenhum ensaio mostrar benefício na sobrevida global, são notáveis os resultados alcançados no desenvolvimento de fármacos direcionados especificamente contra a instabilidade do genoma e a angiogênese sustentada.

Palavras-chave: câncer de ovário; câncer epitelial ovariano; droga antitumoral; quimiorresistência; terapia molecular direcionada

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INTRODUCTION

Ovarian cancer (OC) is the most frequent and deadly gynecologic neoplasm among women. It does not constitute a single pathology, but can be subdivided into histological subtypes that have different identifiable risk factors, cells of origin, molecular compositions, clinical characteristics and treatment alternatives. One of the main characteristics of OC is the absence of symptoms during early stages; therefore, diagnoses of these tumors at advanced stages are associated with poor prognoses.[1]

In general, the main factors that increase the risk of OC of the different histological subtypes include: age (higher incidence in postmenopausal women older than 65 years), ovulation, and endometriosis, some types of benign ovarian cysts, obesity and high cholesterol intake. However, the most important risk factor for this neoplasm is a family history of breast cancer or OC; where 65 to 85% of hereditary ovarian tumors are due to BRCA (Breast Cancer Gene) germline mutations and 10 to 15% of all cases of inherited OC are associated with patients carrying mutations in the mismatch repair genes responsible for Lynch syndrome.[2]

The history of OC has been scientifically known for more than 150 years. During this time there have been no changes in its mortality rate, but there have been changes in its incidence. In the last two decades there have been only small improvements in the overall five-year survival rate. While the five-year survival rate has steadily increased from 30% to 50% with the use of cisplatin, overall there is only a 5% increase, from 20% to 25% in women with advanced tumors.[3]

For the year 2020, the number of new cases of OC was 313,959 worldwide, with about 207,252 deaths; among these new cases, 7,761 were registered in Cuba. During the year 2021, 333 cases of death from this cause were registered in this same country, with a mortality of 5.9 per 100,000 inhabitants.[4,5]

Despite multiple standard treatment strategies of surgery and chemotherapy, chemoresistance prevents significant improvements in the overall survival rate. Therefore, the study of the distinctive capabilities of cancer cells (sustained proliferative signaling, evasion of growth suppressors, resistance cell death, replicative immortality, sustained angiogenesis, activation of invasion and metastasis, reprogramming of energy metabolism, evasion of immune destruction, unlocking phenotypic plasticity and cellular senescence) and their enabling features (genome instability, tumor-promoting inflammation, non-mutational epigenetic reprogramming and polymorphic microbiomes) to gain an in-depth understanding of the genetic and protein alterations involved in carcinogenesis in order to develop OC-specific therapeutic strategies.[6,7,8]

Based on the high mortality rates associated with OC and the resistance to conventional treatments, it was decided to conduct an updated review with the aim of describing new therapeutic strategies directed against the different capabilities of tumor cells, as well as synergistic combinations of these strategies in the treatment of OC.

METHOD

A bibliographic review was carried out by means of electronic searches in the databases ScienceDirect, Redalyc, Latindex, ResearchGate, PubMed, Elsevier, ClinicalTrials.gov, SpringerLink, LARVOL's CLIN, Cuban Public Registry of Clinical Trials, in the period from January to April 2023.

The following HSD (Health Sciences Descriptors) were used: "Ovarian Neoplasms"; "Ovarian Epithelial Carcinoma"; "Antineoplastic Agents" and their equivalents in English: "Ovarian Neoplasms", "Epithelial Ovarian Carcinoma", "Antineoplastic Agents". The terms "chemoresistance"; "targeted molecular therapy"; as well as their English translations: "chemoresistance", "targeted molecular therapy" were also used.

A total of 67 articles were reviewed and 50 were selected for their bibliographic contribution to thisresearch.

DEVELOPMENT

Treatment strategies

OC is heterogeneous in nature. Three fundamental histologic types are included within this pathology: epithelial, germinal, and stromal. Most cases are included within epithelial tumors and, in turn, these are composed of several histological subtypes that are characterized by different microscopic appearances and biological and genetic backgrounds.[9,10]

Among the subtypes of epithelial ovarian cancer (EOC) are: serous, which can be high-grade (EOC-SHG) or low-grade (EOC-SLG); endometrioid (EOC-E); clear cell (EOC-CC) and mucinous (EOC-M). These tumors are classified into type I and type II carcinomas. Type II tumors are commonly associated with a higher mortality rate than type I tumors, which is due to the fact that they are diagnosed at more advanced stages and present greater genetic instability, related to a high percentage of BRCA1 and BRCA2 gene mutations and loss of TP53 function.[11,12]

The heterogeneity observed among the different ovarian neoplasms, whose histologic subtypes also differ among racial and ethnic groups, extends to various clinical outcomes of the disease; that is, patients with different histologic subtypes respond in different ways to the same treatments and have different prognoses. In addition, therapeutic strategies for different types of OC depend on their pathological stages, where early detection provides better treatment options. In this regard, biomarkers play a key role. That said, there is a need to better characterize these differences, find reliable biomarkers and develop appropriate targeted therapies.

Among the most widely used biomarkers in recent decades are cancer antigen-125 (CA125) and human epididymal protein 4 (HE4), the combination of which appears to have a more rigorous prognosis of malignancy than either one individually. Also, recently, the potential benefit of using exosomes fromurine, serum, plasma or ascites as biomarkers was demonstrated. OC-derived exosomes may contain multiple molecules related to tumor development and progression, including: epithelial cell adhesion molecule (EpCAM), which is associated with epithelial cell proliferation during tumorogenesis; and CD24, overexpression of which indicates increased invasion rate, poor prognosis and reduced survival rate in patients with OC.

In addition, high levels of non-coding RNA molecules that are promising non-invasive biomarkers of OC are found in exosomes. Among them, microRNAs (miRNAs) show high specificity in post-transcriptional gene regulation and stability over time after plasma isolation. Thus, increased miRNA-552 and miRNA-216a, are associated with poor patient survival, while some members of the miRNA-200 family (miR-200a, miR-200b and miR-200c) are significantly increased in women with CEO-S.[13]

Today the standard treatment for OC is maximal surgical debulking followed by platinum-based chemotherapy. After surgery, patients are treated with intravenous platinum/taxane regimens. In advanced stages, complete cytoreduction is often not possible due primarily to seizure of the small bowel mesentery and lesions in the hepatic hilum. Patients with inoperable lesions or due to poor performance status are first treated with induction (neoadjuvant) chemotherapy. After three cycles of chemotherapy if there is a response to treatment, interval reduction surgery followed by chemotherapy can be performed.[14,15,16]

However, there are also new drugs currently in development and tested in the treatment of OC. These are directed against the vast catalog of physiological changes that translate into enabling characteristics and new capabilities acquired during tumor development. In this context, a specific set of capacitative properties and enabling characteristics of tumor cells plays a more notable role in the progression of CO compared to the rest.(6)

Genome instability

Genome instability is an enabling feature that plays a crucial role in both carcinogenesis and tumor progression, as it generates the genetic diversity typical of tumor cells. In CEO-SAG cases, BRCA1 and BRCA2 gene mutations are frequent and a relevant proportion of sporadic CEO-SAG patients share features of the BRCAness phenotype. In these patients with homologous recombination deficiency due to loss-of-function BRCA gene mutations there is an increased reliance on the poly (ADP-ribose) polymerase (PARP) single-chain repair pathway.

This is why the OC treatment landscape was transformed in 2014 with the first approval of PARP inhibitors, which take advantage of BRCA mutations and deficiencies in the DNA (deoxyribonucleic acid) damage response. PARP inhibition leads to inhibition of repair of single-stranded DNA breaks by base excision, whereby these single-stranded breaks can be converted into double-stranded breaks, which are toxic to cells and, in turn, can be repaired by homologous recombination. However, in tumorcells deficient in homologous recombination, double-stranded breaks cannot be repaired, leading to massive DNA damage and cell death by apoptosis.[15,17,18]

PARP inhibitors were initially developed as maintenance therapy in patients with sustained partial or complete response after platinum-based chemotherapy for recurrent disease. The marked improvement in progression-free survival (PFS) in three randomized phase III trials led to the regulatory approval of niraparib, olaparib, and rucaparib as maintenance therapy for platinum-sensitive recurrent OC.[18]

In the maintenance setting, the SOLO-1 trial compared maintenance olaparib (up to 2 years or longer in patients with partial response at 2 years) with placebo in newly diagnosed patients with advanced OC with a BRCA1 and/or BRCA2 mutation. All but 3 patients had germline BRCA1/2 mutations. Most patients (82 %) showed no evidence of disease after chemotherapy and a normal cancer antigen-125 (CA-125) level as well as a good performance status was observed. However, a limitation to the general applicability of the SOLO-1 results is the restriction of eligibility to patients with BRCA-mutated tumors.[18]

Niraparib is an oral PARP-1 and PARP-2 inhibitor that was tested in preclinical studies to induce synthetic lethality in PTEN and BRCA1 or BRCA2 loss-of-function tumors. Clinical studies showed that niraparib significantly improved PFS in patients with platinum-sensitive recurrent OC, regardless of BRCA mutation or homologous recombination deficiency status, although its efficacy was maximal in patients with BRCA mutations. For its part, rucaparib is a PARP inhibitor based on small molecules that is administered orally. The latter was tested as a maintenance treatment for platinum-sensitive patients, and a significant increase in PFS was observed.[15, 18, 19]

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Global hypermethylation of promoter-associated CpG islands is another factor related to genome instability. This is due to the silencing of genes important for cellular homeostasis, such as tumor suppressor genes. DNA methylation induces a repressive and tightly bound chromatin structure, which can reduce the expression of genes involved in DNA repair, apoptosis, differentiation, drug resistance, angiogenesis and metastasis. Accordingly, extensive loss of CpGhypermethylation in ovarian cancer correlates with inhibition of cancer cell growth.

The DNA methylation reaction is catalyzed by the DNA methyltransferase (DNMT) family of enzymes, so DNA methyltransferase inhibitors (DNMTi) can lead to the re-expression of silenced tumor suppressor genes. These DNMTi have been successful in the treatment of chemoresistant OC, restoring sensitivity to platinum in patients refractory to standard chemotherapy.[20]

Decitabine is a DNMTi that sensitizes CO patients to platinum-based therapy. DNA hypomethylation caused by decitabine correlates with good clinical outcome and prognosis. Under this concept, Esim, et al.(20) developed a pH-sensitive lipid-coated nanoparticle system that was co-loaded with carboplatin and decitabine to modulate platinum resistance. These studies demonstrated that the cytotoxic effect of carboplatin was achieved at significantly lower doses in platinum-sensitive and platinum-resistant OC cells. Furthermore, confirmation of apoptosis by caspases and PARP in both cells strongly supported the efficacy of the nanoparticle system. Notably, nanoparticles loaded with both drugs led to MLH1 re-expression in resistant CO cells, which may be attributed to increased drug sensitivity in the cells.

Decitabine has also been shown to alter the methylation status of the tumor antigen NY-ESO-1, which could allow for increased expression of this known target for immunotherapy. Decitabine additionally affects pathways known to promote tumor progression, such as the sonic hedgehog (Hh) and transforming growth factor-β (TGF-β) signaling pathway. The hypomethylation caused by decitabine increases the expression of Hh antagonists and alters TGF-β expression, resulting in an improved response to platinum therapy.[20]

Increased proliferative signaling

Arguably, the fundamental feature of cancer cells involves their ability to maintain chronic proliferation. In this regard, the role of cell surface receptors is highlighted, which proceed to signal through branched intracellular signaling pathways that regulate cell cycle progression as well as cell growth. HER2 is known to be overexpressed in CEO. For this reason, different inhibitors of these receptors were tested in therapy against OC, such as erlotinib, cetuximab and lapatinib. However, none showed promising results in clinical trials due to tumor resistance mediated by the PI3K pathway through p38 MAPK activation and subsequent DNA repair. Hence, inhibition of these receptors together with inhibition of p38 MAPK or DNA repair could improve the efficacy of HER-mediated treatment in OC.(7,15,21)

On the other hand, the folate receptor alpha (FRα), which under physiological conditions is present only in some polarized epithelia and its expression is strictly confined to the apical/luminal cell surface, is overexpressed in tumors of epithelial origin, where it loses its polarized localization and is present on the entire cell surface. In the case of serous ovarian cancers, it is estimated that more than 80% show FRα expression, which constitutes a promising therapeutic target through the use of specific antibodies.

In another order, farletuzumab, a humanized monoclonal antibody (AcM) with high affinity for FRα, exerts its antitumor activity through several mechanisms: promotion of tumor cell lysis by antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity, induction of sustained autophagy, and inhibition of the interaction between FRα and Lyn kinase. These mechanisms effect a reduction in intracellular growth signaling. However, results from trials to measure the effectiveness of farletuzumab treatment with carboplatin and taxane in platinum-sensitive OC patients were not significant.[16,22,23]

Also, a new generation of MDAs known as drug-conjugated antibodies (DCAs) has recently been developed. These are composed of three elements: AcM, cytotoxic drug and a cleavable link that allows the conjugation of both. The AcM allows specific recognition of the antigens overexpressed in the tumors. After binding, the ACF-antigen complex is introduced into the cell by endocytosis and initiates lysosomal degradation. As a consequence of enzymatic cleavage, the cytotoxic agent is released into the tumors, triggering tumor death by various mechanisms. Mirvetuximabsoravtansine (MIRV) and Upifitamabrilsodotin (UpRi) are examples of ACFs specific for FRα and sodium-dependent phosphate transporter protein (NaPi2b) overexpressed in CEO-SAG, respectively conjugated to tubulin-binding molecules that inhibit microtubule polymerization, resulting in G2/M phase arrest and apoptosis of tumor cells.

MIRV demonstrated in the Phase II SORAYA trial clinically significant consistent antitumor activity and favorable tolerability and safety in patients with platinum-resistant CEO, while UpRi in the Phase Ib/II NCT03319628 trial demonstrated encouraging single-agent antitumor activity and a favorable tolerability profile in heavily pretreated patients with platinum-resistant CO. Multiple trials of potential application in the treatment of OC are currently underway in conjunction with this principle.[24,25]

The PI3K/AKT/mTOR signaling pathway regulates multiple processes and characteristics of tumor cells, such as: cell cycle, cell survival, dysregulation of energy metabolism, angiogenesis and genome instability. Immunohistochemistry studies demonstrated that this pathway is activated in approximately half of CEO-SAGs and genetic alterations are more common in CEO-CC and endometrioid adenocarcinoma. Therefore, the PI3K/AKT/mTOR signaling pathway constitutes a therapeutic target for OC.

Allosteric mTOR inhibitors, such as temsirolimus, and rapamycin derivatives such as everolimus, can predominantly inhibit mTORC1 function, which induces apoptosis and cell cycle arrest in the G1 phase. Several studies were conducted to evaluate the efficacy of these as monotherapy for CEO; however, no promising results have been obtained. While so far no inhibitor of the PI3K/AKT/mTOR pathway yet reached the clinic for the treatment of OC, several compounds that have the potential to restore platinum sensitivity and improve clinical outcomes for patients are under evaluation and in various phases of clinical trials.[26,27,28,29]

The Ras/Raf/MEK/ERK/ERK mitogen-activated protein kinase (MAPK) pathway mediates cellular responses to different growth signals and is often dysregulated in cancer, either because of genetic mutations or because the pathway is constitutively activated. Because MEK1 and MEK2 are closely related to the Ras/Raf/MEK/ERK signal transduction cascade, inhibition of MEK1/2 is considered animportant therapeutic target for oncological indications. In this regard, selumetinib is inserted as a potent non-ATP-competitive and highly specific inhibitor for MEK1/2, which showed 63% disease control and 15% response rate in a phase II trial in patients with recurrent CEO-SBG.[30]

This type of inhibitor also includes pimasertib, which selectively binds to MEK1/2, preventing the activation of effectors proteins and MEK1/2-dependent transcription factors, leading to the inhibition of cell signaling mediated by growth factors and tumor cell proliferation. Pimasertib has been evaluated in combination therapies with other antitumor drugs, primarily PI3K inhibitors.

Arend, et al.(31) conducted a study to compare the combination of pimasertib and a PI3K inhibitor (SAR245409) with pimasertib alone in CEO-SBG or in recurrent unresectable CEO-SBG. The results demonstrated that, for the selected population, the response to pimasertib alone suggests that MEK inhibition could be used as an alternative treatment method to cytotoxic chemotherapy in this population. Furthermore, pimasertib alone was as effective as the combination.

Growth suppressor evasion

Cancer cells must also evade powerful programs that negatively regulate cell proliferation; many of these programs depend on the actions of tumor suppressor genes. One of the prototypical tumor suppressors encodes the TP53 protein. Pathogenic TP53 mutations have been identified in 97% of CEO-SAG cases. Nonsense mutant p53 (mutp53) proteins accumulate to very high levels in the nuclei of tumor cells and not only lose their tumor suppressor function, but often acquire new oncogenic functions to actively drive increased proliferation, metastatic capacity and chemoresistance.

Due to their aberrant conformation, mutp53 proteins depend on the permanent folding support of Hsp90, a multicomponent cancer-induced chaperone machinery of the heat shock family. This stable interaction between mutp53 and Hsp90 protects mutp53 from degradation by its E3 ubiquitin ligases MDM2 and CHIP and is largely responsible for mutp53 accumulation, specifically in tumor cells. Pharmacological inhibition of the central Hsp90 ATPase machinery destroys the complex between Hsp90 and mutp53, thereby releasing mutp53 and inducing its degradation. Therefore, Hsp90 inhibitors have a strong potential in antitumor therapy.[7,32,33]

Ganetespib is the most clinically advanced Hsp90 inhibitor applied in more than 1600 individuals (patients and healthy volunteers) across studies, which also lacks the ocular and hepatic toxicities that are commonly associated with this type of inhibitors. Ganetespib showed a synergistic effect in combination with paclitaxel in patients with platinum-resistant OC in a phase I study, which forms the basis for more advanced studies of this treatment.[33]

Another biologic compound directed against p53-derived antigen used in the treatment of patients with progressive metastatic malignancies is ALT-801, which was well tolerated and elicited a clinical antitumor response with IFN-gamma production and antibody titers.[34]

Evasion of immune destruction

Accumulating evidence suggests that OC cells have the ability to escape the immune system, which favors a highly immunosuppressive system in the peritoneal cavity through interactions between tumor cells and host immune cells in the tumor microenvironment. Based on this, the manipulation of immune checkpoints became the modern revolution in cancer immunotherapy. Under physiological conditions different immune checkpoint proteins stimulate or block the activity of T lymphocytes to regulate the balance between immune response and tolerance.

Checkpoint receptors such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) act to reduce autoimmune responses against self tissues. In cancer patients, their activity is often increased, resulting in impaired natural anticancer immunity. The rationale behind the use of immune checkpoint inhibitors is to unblock antitumor responses. It is estimated that more than half of CEO-SAGs represent an adaptive immune resistance pattern and are likely to respond to immune checkpoint inhibitors, whereas in other histologic types this phenotype is less frequent (about 25% in CEO-CC and CEO-M).[15]

Among the most widely used therapeutic strategies for immune checkpoint inhibition in CEO are the AcMs. The most studied anti-CTLA-4 AcMs in advanced/recurrent OC have been ipilimumab and tremelimumab, with unsatisfactory results. In the phase II NCT01611558 trial with ipilimumab, 38 of 40 patients did not complete treatment due to severe toxicity or death. However, recent studies suggest that the combination with PARP inhibitors appears to be tolerated and induces antitumor responses. In the case of tremelimumab, its combination with olaparib was tested in patients diagnosed with OC with BRCA gene mutations in the phase I trial NCT02571725, showing a good safety profile and a decrease in tumor size after three cycles.[35]

Pembrolizumab is a high-affinity humanized PD-1-targeted AcM that demonstrated robust antitumor activity and a favorable safety profile in multiple tumor types. Studies have been developed to evaluate the efficacy and safety profile of this AcM in the treatment of OC. Among them, pembrolizumabmonotherapy was evaluated in KEYNOTE-100, a phase II study for patients with advanced recurrent OC. That study demonstrated that responses to pembrolizumab were quite durable in a subset of patients and there was a trend toward a better response rate in CEO-CC.

The objective response rate was low (8%), this minimal efficacy could be attributed in part to the lack of tumor T-cell infiltration in certain patients and high local immunosuppression consisting of tumor cells, regulatory T cells and tolerance-inducing myeloid cells. Despite this, the results indicate that a population with a combined positive score ≥10 may benefit to some extent from pembrolizumab as monotherapy after treatment with standard chemotherapies.[36]

Nivolumab, another anti-PD-1 mAb, has also been tested as a single agent in patients with platinum-resistant OC. In the phase II UMIN000005714 trial nivolumab showed encouraging clinical efficacy; however, 10% of patients experienced serious treatment-related adverse effects and 11% discontinued treatment mainly due to thyroid disorders. Against this background, the phase II NRG-GY003 study compared the efficacy of nivolumab administration alone or in combination with ipilimumab. The results of the latter concluded that the combination followed by maintenance with nivolumab is associated with a superior response rate and improved PFS compared with nivolumab alone, and toxicity levels were manageable. However, these benefits were reported in the minority of patients and a short duration of PFS was observed.[35,37]

Likewise, TGF-β constitutes a therapeutic target in the treatment of OC. This is because its overexpression confers a potent immunosuppressive role within the tumor microenvironment that affects dendritic and natural killer cell activity, cytokine production, and T-cell function. The potential for immunotherapy to abrogate the effect of TGF-β in the advanced OC setting is a current area of research, where trabedersen is inserted as a synthetic TGF-β2 antisense oligonucleotide therapy. That said, preclinical models have been developed to study the tolerability and efficacy of trabedersen in combination with paclitaxel. Recent studies demonstrated that the combination is well tolerated, significantly reduces tumor burden, and increases overall survival compared to paclitaxel alone.[38]

Resistance to cell death

Tumor cells have evolved a variety of strategies to limit or evade apoptosis. The most common is loss of TP53 tumor suppressor function, a critical damage sensor of the apoptosis-inducing circuitry. Alternatively, tumors may achieve similar ends by increasing the expression of anti-apoptotic regulators (Bcl-2, Bcl-XL) or survival signals (Igf1/2). Therefore, current research efforts are focused on the identification of molecules capable of restoring apoptosis in cancer cells without affecting nearby healthy cells.[39]

Navitoclax is an inhibitor of Bcl-2, Bcl-XL and Bcl-w crucial for the Bcl-mediated pathway. This inhibitor mimics the interaction of the BH3 domain of Bad proteins with the Bcl-2 family of proteins that triggers apoptosis. The combination of navitoclax with chemotherapy has been evaluated and showed a promising synergistic effect. Subsequent studies examined the effects of this combination on drug-resistant OC cells in vitro and in xenograft models, demonstrating that navitoclax, despite inhibiting growth with low potency, sensitized the cells to carboplatin cytotoxicity by inducing more rapid apoptosis. This evidence suggests that navitoclax may enhance the efficacy of chemotherapy drugs in OC cells. However, the phase II MONAVI-GINECO study of navitoclax as monotherapy in women heavily previously treated for recurrent CEO demonstrated that the drug has poor activity that did not correlate with Bim, Mcl-1 and P-ERK expression.[39,40]

Another mechanism that allows cancer cells to evade apoptosis is the overexpression of inhibitor of apoptosis proteins (IAP). This is why second mitochondrial caspase activator (SMAC) mimetics, the most widely used IAP antagonists, are currently being tested in clinical trials as monotherapy and in combination with different chemotherapeutic drugs.

Birinapant is a highly potent SMAC mimetic known to target cIAP1/2 and XIAP. The outcome of the NCT01681368 clinical trial, which tested birinapant as monotherapy in advanced ovarian, fallopian tube and peritoneal cancers, has demonstrated its tolerability in a dose-dependent manner, although it was not found to be effective as a single agent. Singh, et al.(41) used the combination of birinapant with carboplatin to augment carboplatin-induced cell death in platinum-resistant OC cells in in vitro and in vivo models.The results demonstrated that cotherapy was effective in targeting a subset of platinum-resistant OC cell lines and ovarian tumors from platinum-resistant patients.

DEBIO 1143 (Xevinapant) is also an orally active SMAC mimetic targeting cIAP1, cIAP2 and XIAP. Thibault, et al.(42) demonstrated that xevinapant is able to restore carboplatin sensitivity in OC cells. In platinum-resistant cell lines A2780R and SKOV-3, the carboplatin/xevinapant combination resulted in an increase in the number of early apoptotic cells compared to monotherapy treatment. In this study, it was further demonstrated that xevinapant induces necroptosis in ovarian cells in which apoptosis is blocked by the caspase inhibitor Z-Vad. Therefore, the discovery of this synergistic combination, which is effective even when apoptosis is blocked, has important implications for the development of new treatment strategies.

Induction of angiogenesis

Angiogenesis is a tightly controlled dynamic process that occurs primarily in embryo development, during wound healing, and in response to ovulation. However, it can be aberrantly activated during many pathological conditions, among which cancer is one.[43]

A key player in the development of the pathological tumor vascular network is vascular endothelial growth factor (VEGF) and its signaling pathway. In OC, hypoxia induces transcription of vascular endothelial growth factor receptor (VEGF-R) in endothelial cells, with subsequent binding of VEGF. Thus, overexpression of this receptor has prognostic value as it is related to tumor grade, disease status and patient survival. Elevated VEGF levels inhibit T-cell trafficking to the tumor microenvironment and increase Fas ligand expression on aberrant tumor endothelial cells, leading to T-cell apoptosis.

They also promote the expansion of inhibitory immune cell subsets, including regulatory T cells and myeloid-derived suppressor cells, resulting in an inherently immunosuppressive tumor microenvironment; and, furthermore, by increasing vascular permeability within the peritoneum, VEGF is responsible for the formation of ascitic fluid in patients with OC. Consequently, inhibition of pathological angiogenesis is one of the new therapeutic options widely tested in the treatment of CO.[43]

Bevacizumab is a recombinant anti-VEGF-A humanized AcM. This AcM has been shown to lead to normalization of tumor vasculature and reduction of interstitial tumor pressure, thus improving the efficacy of standard therapy. That said, the GOG-0218 and ICON7 trials demonstrated that the use of bevacizumab as maintenance after standard chemotherapy prolongs median PFS in patients with advanced CEO. In the randomized multicenter phase II ANTHALYA trial aimed at evaluating the safety and efficacy of bevacizumab in a neoadjuvant setting in patients with initially unresectable advancedOC, it was shown that the rate of complete resection was significantly higher in a group that received additional bevacizumab. In addition, bevacizumab has been tested in combination therapies with immune checkpoint inhibitors.

In this regard, Zsiros, et al.(43) conducted a non-randomized phase II clinical trial to evaluate the safety and synergistic effect of anti-PD1 and antiangiogenic therapy with metronomic cyclophosphamide by combining pembrolizumab, bevacizumab and oral cyclophosphamide in patients with recurrent OC. The treatment was well tolerated and demonstrated clinical benefit in 95 %, and durable treatment responses (>12 months) in 25 % of patients.[14]

Another anti-angiogenic inhibitor, in this case of the tyrosine kinase activity of VEGF-R, is cediranib. The ICON6 trial evaluated the activity and safety of this compound combined with platinum-based chemotherapy followed by maintenance cediranib, showing a median PFS of 11 months, while in a group treated with cediranib combined with chemotherapy and then maintenance with placebo the median PFS was 9.9 months. However, this inhibitor is associated with various toxic effects, such as neutropenia and hypertension.[15]

Recent studies also evaluated the combination of antiangiogenic therapy with PARP inhibitors, demonstrating in a study comparing the effect of cediranib and olaparib with olaparib alone that synergistic therapy increases PFS in women with recurrent platinum-sensitive OC. However, in the BAROCCO trial it was proven that the combination of cediranib and olaparib is not superior to chemotherapy in terms of PFS in heavily pretreated platinum-resistant OC patients; but despite this, this oral doublet is active and may offer an option for the difficult-to-treat population without resorting to chemotherapy.[44]

In addition to the current therapeutic strategies used to inhibit the binding of VEGF to its receptor, other pathways involved in angiogenesis are also being studied. An example of this is the binding of angiopoietin 1 and 2 (Ang1/2) to the Tie-2 receptor, which leads to stimulation of endothelial cell proliferation, motility and survival; whereby, one study developed a fusion protein that selectively binds to Ang1/2, preventing signaling through Tie-2: trebananib.

Trebananib, in clinical trials NCT00479817 and TRINOVA-1, demonstrated in women with recurrent primary peritoneal cancer partially sensitive or platinum-resistant, a prolonged PFS combined with weekly paclitaxel.[15]

Main targeted therapies for the treatment of ovarian cancer

CD/CH	Drug	Effect	Clinical Trials	Manufacturer
Genome instability	Olaparib*	PARP-1 and PARP-2 Inhibitor	Completed (maintenance monotherapy	Astra Zeneca and Merck & Co.
	Niraparib*	PARP-1 and PARP-2 Inhibitor	Completed (maintenance	Janssen, Merck & Co. and Glaxo Smith Kline
	Rucaparib*	PARP-1 and PARP-2 Inhibitor	Phase III (maintenance	Clovis Oncology
	Pamiparib*[45]	PARP-1 and PARP-2 Inhibitor	Phase III (maintenance	BeiGene
	Fluzoparib*[46]	PARP-1 inhibitor	Phase III (maintenance	Jiangsu Hengrui Pharmaceuticals Co.
	Decitabine	Hypomethylation by DNA methyltransferase inhibition	Phase II/III (first line combination	Janssen-Cilag and Otsuka Pharmaceutical
Increased proliferative signaling	Mirvetuximab soravtansine*	AcM anti-FRα conjugated to microtubule polymerization inhibitor DM4	Phase III (CEO	ImmunoGen
	Upifitamabrilsodotin	AcM anti NaPi2b conjugated to microtubule polymerization inhibitor AF-HPA	Phase III (maintenance	Mersana Therapeutics Inc.
	Farletuzumab	AcM anti FRα	*Phase III (combination	Eisai Inc.
	temsirolimus	mTOR inhibitor	Phase II (OC Rec, OCRefP) / Phase II (first line combination	Pfizer
	Everolimus	mTORC1 protein complex inhibitor	Phase II / Phase III (combination	Abbott Laboratories y Novartis
	Selumetinib	MEK1/2 inhibitor	Phase II (alone and/or combination	AstraZeneca
	Pimasertib	MEK1/2 inhibitor	Phase II (alone and/or combination	Day One Biopharmaceuticals, Merck Serono y Sanofi
Growth suppressant evasion	Ganetespib	Hsp90 inhibitor	Phase II (combination - OC SP)	Aldeyra Therapeutics y Synta Pharmaceuticals
	ALT-801	Induction of anti p53 immune response via IL-2	Phase I (AOC)	Altor BioScience Corporation
Evasion of immune destruction	Ipilimumab	Anti-CTL-4 (IgG1) MCAs	Phase II/III (combination - AOC) / Phase II (monotherapy - OC Rec SP)	Bristol-Myers Squibb
	Tremelimumab	AcM (IgG2) anti CTL	Phase II (combination - AOC, OC Rec, OC Rec RP, OCRefP)	AstraZeneca y Pfizer

	Pembrolizumab	AcM (IgG4) anti PD	Phase III (combination - OC Rec RP)	Merck & Co.
	Nivolumab	AcM (IgG4) anti PD	Phase III (maintenance combination - OC SP)	Ono Pharmaceuticals y Bristol-Myers Squibb
	Trabedersen	TGF-β2 synthesis inhibitor.	No clinical trials	Autotelic Inc. y Oncotelic Therapeutics
Resistance to cell death	Navitoclax	Induction of apoptosis by inhibition of Bcl-2, Bcl-XL and Bcl-w	Phase II (OC Rec RP, OC Rec RefP)	AbbVie
	Birinapant	Induction of apoptosis by IAP inhibition	*Phase II (AOC) / Phase I/II (combination - CEO-SAG Rec)	Medivir AB
	Xevinapant	Induction of apoptosis by IAP inhibition	Phase II (combination - AOC)	Debiopharm and Merck & Co
Induction of angiogenesis	Bevacizumab*	Anti-VEGF-A MCA	Phase IV (first line - AOC) / Phase IV (combination)	Genentech and Roche Holding AG
	Cediranib	Inhibitor of the tyrosine kinase activity of VEGF-R	Phase III (single and/or maintenance combination - OC Rec SP, OC Rec RP, OC Rec RefP)	AstraZeneca
	Trebananib	Inhibition of angiogenesis by binding of fusion protein to Ang1/2	*Phase III (first-line combination - AOC) / Phase III (combination - CT Rec PS, CT Rec PR)	Amgen Inc.

DC/CH: Distinctive capabilities and enabling characteristics of tumor cells. AOC: advanced ovarian cancer. Rec: recurrent. PS: platinum-sensitive. PR: platinum-resistant. PRef: platinum refractory. Drugs*: in commercialization for the treatment of CT. Clinical trials*: terminated prematurely by investigator's decision.

Treatment of ovarian cancer in Cuba

Cuba follows the standard treatment line for OC based on the integration of surgery and chemotherapy. Thus, primary cytoreductive surgery is the cornerstone in the treatment of OC and its major prognostic factor, while chemotherapy is used in two scenarios in the management of this disease: first, as adjuvant treatment following surgery and, second, as neoadjuvant or primary treatment in those patients for whom surgery is not advisable given significant comorbidity or because of extensively disseminated disease.

Currently, some drugs for the treatment of OC are being studied in this country. Oncoxin®-Viusid® is a nutritional supplement produced by Laboratories Catalysis S.L., which is being studied at the Institute of Oncology and Radiobiology (INOR). This is composed of several antioxidants, among which epigallocatechingallate, a polyphenol present in green tea extract with anticarcinogenic properties, stands out. Its effects include: inhibition of tumor necrosis factor (TNF) and potentiating of nuclear enhancer factor kappa light chain enhancer of activated B cells, which regulates anti-apoptotic genesand inhibits cyclooxygenase 2 expression; blocking growth factor signal transduction and inhibiting the enzyme urokinase, which stimulates tumor proliferation, tumor invasion, angiogenesis and metastasis; and restoring cell apoptosis by inducing Bcl-2-associated X protein expression.

In the phase II clinical trial conducted at INOR, it was shown that administration of the drug as an adjuvant to carboplatin/paclitaxel-based chemotherapy in patients with advanced metastatic or epithelial OC appears to improve tolerance to chemotherapy. In addition, it showed a good safety profile and improved quality of life, which allows further studies on the benefits of neoadjuvant therapy with Oncoxin®-Viusid® in Phase III clinical trials.[47]

CIGB-247 is a vaccine for cancer therapy developed at the Center for Genetic Engineering and Biotechnology (CIGB), which uses a recombinant molecule representative of VEGF isoform 121 as antigen and VSSP adjuvant of bacterial origin. In Phase I clinical trials (CENTAURO and CENTAURO-2) and Compassionate Use Program, the antibody response was shown to block the interaction between VEGF and the VEGFR2 and VEGFR1 receptors, and the treatment was shown to be safe and immunogenic in patients with advanced cancer. Because the vaccine demonstrated potential therapeutic application for OC, following these trials, the phase II/III CENTAURO-4 clinical trial was initiated in patients with advanced CEO.[48]

In addition, the racotumomab-alumina vaccine (Vaxira®) produced by the Center for Molecular Immunology (CIM), composed of a gamma-type murine anti-idiotype monoclonal antibody that specifically induces an antibody response against the NeuGcGM3 ganglioside that is overexpressed in several solid tumors, had its approval to test in the clinical trial RPCEC00000199 the efficacy and safety of the vaccine in the maintenance treatment of recurrent platinum-sensitive CEO.[49]

Future perspectives

OC does not yet have treatments that ensure a significant increase in the overall survival rate. However, there are currently multiple therapeutic options. Among them, the choice of the best treatment option will depend on dissimilar factors including histological type and stage of cancer presented by each individual. In this sense, the targeted therapy approach represents a more specific and efficient alternative to conventional treatments such as chemotherapy and radiotherapy. In addition, they allow for greater precision in treatment, as they can be tailored to the characteristics and needs of each patient.

While all strategies directed towards capacitative properties and enabling characteristics are promising targets in the treatment of OC, so far there are only results in the clinic for drugs directed against genome instability, increased proliferative signaling and induction of angiogenesis, where PARP, MEKand VEGF inhibitors demonstrated significantly longer PFS. However, many of the potential therapeutic strategies among which even more remarkable results could be expected, are currently unsuccessful in the clinic due to the multiple limitations of efficient drug design.

It should be noted that one of the most attractive avenues for the treatment of OC is through gene therapies against the dissimilar mutations in TP53 and restoration of p53 functionality, which have mutations in up to approximately 95% of CEO-SAG cases. This is because p53 as a transcription factor shapes the expression of genes that promote multiple functions, such as: cell cycle arrests, apoptosis, DNA repair; and independently of the transcription mechanisms, it exerts antiproliferative effects. In addition, loss of p53 function causes nonautonomous cellular effects in the tumor immune microenvironment, allowing evasion of immune destruction. Therefore, due to the multiple effects against thetumor-enabling properties and tumor-enabling characteristics that restoration of p53 functionality brings about, it is expected that as a therapeutic strategy the study of new approaches will yield compelling results in the treatment of OC.

Despite almost three decades of studies to develop therapies based on p53, the acquisition of new knowledge, better understanding of the mechanisms of action and progress in drug design in recent years has increasingly increased the possibility of using this pathway as a treatment. An example of this is the recent hypothesis of using CRISPR/Cas9 for base editing of mutated TP53, which aroused great enthusiasm in the scientific community as a possible cancer treatment option. Thus, gene therapy via p53 is a potential target for future research.[50]

FINAL CONSIDERATIONS

Currently, there are dissimilar OC treatment options, which target both modifications of conventional approaches and the addition to standard treatment of new targeted drugs. Clinically, significantly longer PFS was observed with the sole use of PARP, MEK, VEGF inhibitors. However, the clinical efficacy of targeted agents is still restricted to specific molecular subtypes and no trials illustrate an overall survival benefit. Exploration of new drug targets or combination of feasible biologic agents hold great promise for improving outcomes in the treatment of OC. Further studies focused on investigating the crosstalk between cellular pathways within the tumor microenvironment and their response to drugs are required to improve understanding of the mechanisms adopted by cancer cells in the development of drug resistance.

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