ICIs in Ovarian Cancer

Subjects: Oncology
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Ovarian cancer (OC) represents the fifth leading cause of cancer-related deaths among women. In the advanced disease setting, OC recurrence after chemotherapy is over 70% in the first 2 years, with few therapeutic options. Immunotherapy with the immune checkpoint inhibitors (ICIs) showed high efficacy and changed the therapeutic scenario of many tumors in the last 10 years.

Keywords: ovarian cancer ; checkpoint inhibitors ; ICIs ; immunotherapy ; PARP ; avelumab ; pembrolizumab ; nivolumab ; bevacizumab ; platinum

1. Introduction

Ovarian cancer (OC) accounts for about 2% of tumors, representing the eighth most common cancer among the female population. The incidence is around 11 cases/100,000 inhabitants/year, and it is higher among white women [1][2]. The frequency of OC rises with age, being uncommon before 30, and more frequently presenting at 50–70. Globally, ovarian cancer represents the fifth leading cause of female cancer-related deaths, with a 5 y survival rate falling from 90% at stage I to 25% at stage IV [2]. The majority of OCs have an epithelial origin, among whom serous carcinoma has the most aggressive features and is usually diagnosed at advanced stages [3]. Platinum-based chemotherapy regimens represent the mainstay of treatment [4][5][6][7]. The response to these agents and the treatment-free interval (TFI) after platinum define the subsequent treatment, moving from the platinum-refractory (PR) (relapse < 6 months from the platinum end) to the platinum-sensitive (PS) patients (TFI > 12 mos). Despite initial benefits, disease recurrence occurs in over 2/3 of patients within the first two years. Therefore, new drugs were explored, and other agents such as the PARP-inhibitor (PARPi) agents and the anti-vascular endothelial growth factor (VEGF) bevacizumab were approved in the advanced setting [8][9].

Immunotherapy has represented a breakthrough therapy for many solid tumors [10]. Thus far, the best-studied mechanisms for inducing an immune response against tumors rely on inhibiting the immune checkpoint. The immune checkpoint inhibitors (ICIs) consist of monoclonal antibodies targeting Programmed Cell Death Protein 1 (PD-1)/Programmed Death-Ligand 1 (PD-L1) or Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4), expressed by tumor or immune cells. After binding with these ligands, ICIs remove the inhibition signals for the immune system, unlocking the anti-tumor response [11]. However, in OC, ICIs reported modest results, and some phase III trials were prematurely terminated for futility. Combinations with other compounds, such as PARPis or anti-angiogenic drugs, represent promising opportunities to enhance the clinical effectiveness of immunotherapy [12][13][14][15][16][17][18][19][20][21][22][23][24][25][26][27][28][29][30][31][32][33][34][35][36].

2. ICIs in Ovarian Cancer

Given the impact on morbidity and mortality among the female population, the search for new therapeutic options represents an unmet need for OC. Immunotherapy has revolutionized the treatment landscape of many solid tumors in the last ten years, and it now represents the first therapeutic approach with impressive survival benefits in diseases such as lung cancer, melanoma, renal cell carcinoma [10]. However, limited benefits have emerged in OC, even leading to premature termination due to the futility of some studies. Different components of the OC tumor microenvironment (TME) contribute to this failure, such as myeloid-derived suppressor cells (MDSCs), tumor-associated macrophages (TAMs), T-cells, cytokines, and soluble factors [37][38][39][40]. MDSCs exert immunosuppressive functions, such as the inhibition of T-effector and natural killer (NK)-cells, and are induced under pro-inflammatory cytokines, IFNγ, tumor necrosis factor-alpha (TNFα), interleukin (IL)-6 [41]. In OC, IL-6 plays a negative prognostic role and is associated with high MDSCs, and tumor progression [42][43]. The inflammatory cytokines cooperate to induce cyclooxygenase-2 (COX-2) and lead to prostaglandin E2 (PGE2) synthesis, which limits T-cell recruiting at tumor sites, together with VEGF [44][45]. TAMs are recruited at ovarian tumor sites, and IL-6, IL-10, transforming growth factor (TGF)-β promote their differentiation in M2 macrophages,

associated with tumor invasiveness, spread, and angiogenesis [46][47][48]. M2 macrophages increase with the OC stage when contemporary M1 macrophages decrease, playing a negative prognostic role [49][50][51]. Moreover, they promote immunosuppression by producing cytokines (IL-1R, IL-10, C-C Motif Chemokine Ligand [CCL]17, CCL20, CCL22) that inhibit T-effectors proliferation and enhance Tregs function [52][53][54]. Treg cells are associated with advanced stages of OC and have a negative prognostic and immunosuppressive role [54]. They produce IL-10 and TGFβ, contributing to the inhibition of effector T-cells [55]. High levels of immunosuppressive elements within OC TME can also weaken dendritic cells and antigen-presenting cells (APCs) activity [56]. More accurate knowledge of the TME of the primary tumors and the metastatic sites will facilitate the design of more effective treatment combinations (**Figure 1**).

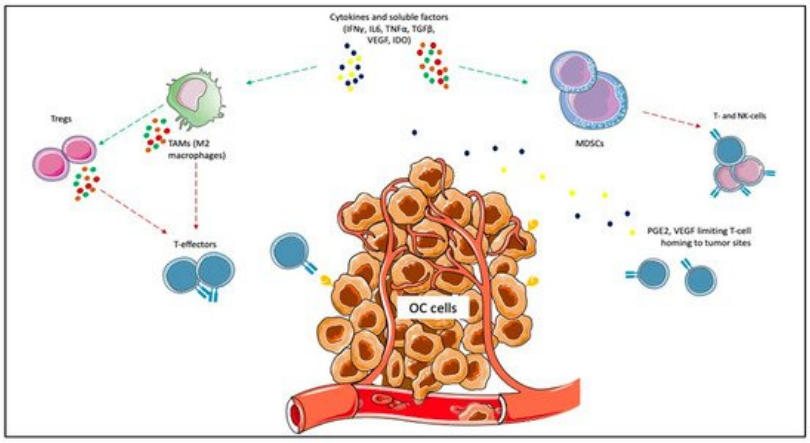

Figure 1. Immunosuppressive elements of ovarian cancer (OC) microenvironment. Cytokines and other soluble factors, such as interferon-gamma (IFNγ), tumor necrosis factor-alpha (TNFα), interleukin (IL)-6, IL-10, and transforming growth factor-beta (TGFβ) induce the proliferation of myeloid-derived suppressor cells (MDSCs) and the polarization of tumor-associated macrophages (TAMs) towards the M2 subtype. MDSCs exert immunosuppressive functions, such as the inhibition of T-effector and natural killer (NK)-cells. The inflammatory cytokines cooperate to induce cyclooxygenase-2 (COX-2) and lead to prostaglandin E2 (PGE2) synthesis, which limits T-cell recruiting at tumor sites. M2 macrophages promote immunosuppression by producing cytokines (e.g., IL-1R, IL-10, C-C Motif Chemokine Ligand [CCL]17, CCL20, CCL22) that inhibit T-effectors proliferation and enhance Tregs function.

OC encompasses a heterogeneous group of malignancies that in over 95% of cases have an epithelial origin and are more frequently represented by high grade serous ovarian carcinoma (HGSOC) (70% of cases), followed by endometrioid ovarian cancer (EOC) (10%), clear cell OC (ccOC) (10%), low-grade serous OC (LGSOC, less than 5%), and mucinous OC (MOC, around 3%) [3]. Among them, the ccOC seems to be the most immunogenic: it more frequently carries the DNA microsatellite instability (MSI), has higher CD8+ tumor-infiltrating lymphocites (TILs), CD8+/CD4+ ratio, and higher PD-L1 levels [57][58]. Effectively, it is five times more responsive to ICIs than other OC subtypes [19]. Even among HGSOC, at least four different genomic classes were identified in The Cancer Genomic Atlas registry, differing for immunoreactivity. A unique subtype expresses genes related to immune sensitivity such as Toll-like receptor (TLR), TNF and is characterized by higher TILs infiltration [59][60]. Moreover, proteomics studies showed that the four subclasses of HSGOC are characterized by different expressions of proteins involved in DNA replication, ECM and cellular interaction, and cytokine signaling that contributes to immune responsiveness [61]. In our opinion, the different ICIs response observed among OC patients is rooted in the inter-tumor heterogeneity. Therefore, a deeper insight into the genomics characteristics of OC and their relationship with the immunological profile could allow us to better clarify the predictive factors for ICIs response. Ideally, specific immunogenomic scores could be developed for more accurate patients selection.

OC has been indicated as potentially more immune responsive when carrying BRCA mutations or homologous recombination deficiency (HRD). In fact, the impaired DNA repair leads to neo-antigens production, resulting in a higher tumor mutational burden (TMB) (even if <10 mutations per megabase are usually detected) and recruiting TILs at tumor sites. However, HRD or BRCA mutations were not linked to a higher sensitivity to ICIs in the IMagyn050 nor in the Javelin Ovarian 100 trials [23][27]. BRCA-mutant/HRD OC is associated with higher CD3+ and CD8+ TILs, PD1/PD-L1 levels, and genes related to cytotoxicity, such as T-Cell Receptor (TCR), γ-IFN, and TNF-Receptor pathway [62][63][64][65]. As proof of this, in the NCT02484404 trial, durvalumab plus olaparib determined a longer PFS in case of increased γ-IFN production [33]. Another mechanism of immune responsiveness is represented by the mismatch repair (MMR) deficiency, harboring the DNA MSI. MSI tumors produce neo-antigens, with a 10–100-fold higher TMB than MS stable (MSS)-tumors, resulting in high immunogenicity. Some genes triggering MSI were also identified in a percentage ranging from 17% to 59% of OC (more commonly in non-serous subtypes): the oncosuppressor TP53; Dihydropyrimidinase-related protein (DPYSL)-2, involved in microtubules function; Alpha Kinase (ALPK)-2, with a role in apoptosis and DNA repair [66]. In Lynch syndrome,

a germline mutation of the MMR genes MutL homolog (MLH)-1, MutS homolog (MSH)-2 and -6, PMS1 homolog (PMS)-2 leads to an increased risk to develop some cancer subtypes, including OC [67]. Therefore, these tumors may be good candidates for ICIs treatment. Other genes could be involved in ICI response, justifying the different results observed among OC patients. The SWItch/Sucrose Non-Fermentable (SWI/SNF) complex consists of around 15 subunits, acting as a chromatin remodeler. In other tumor subtypes, the loss of function of the SWI/SNF complex predicts ICI response, increasing MMR deficiency, TMB, and neo-antigens production [68]. SWI/SNF complex mutations were frequently detected in OC [69]. We can assume that genetic diversity contributes to different ICI responses among OC patients. A more extensive genetic characterization could allow more accurate identification of responders and non-responders.

The possible relationship between platinum- and immunotherapy-sensitivity/resistance is also a field that merits further investigation [70]. A series of genetic and epigenetic elements were identified to drive platinum response: alterations of p53, specific microRNAs, elements driving the epithelial-to-mesenchymal transition (EMT), HRD, and BRCA mutations [71]. Since BRCA mutation and HRD were proposed to correlate with platinum sensitivity in contemporary deficient nucleotide excision repair, the co-administration of PARPis and ICIs in PS-ROC could result in higher ORR and survival rates [29][30][31]. PARPis enhance ICIs activity because they induce the release of neoantigens, increasing the TMB, promote PD-L1 expression, and directly activate the IFN genes; however, this was determined in OC [17][29][30][31][72][73]. Many ongoing trials are addressing this combination strategy in the advanced setting.

As ICIs monotherapies showed only minimal results in terms of response rate and survival in OC, the combination with agents with different mechanisms of action appears a promising strategy to increase efficacy. Although chemotherapy represents a cornerstone in the treatment of advanced OC, it was historically perceived to play an immunosuppressive role. On the contrary, more recently, it has emerged that platinum derivatives promote APCs and their function, activating the immune response [74][75][76][77]. Doxorubicin plays an immunomodulatory effect, reducing the immunosuppressive state and improving tumor sensitivity to NK and CD8+ T-cells [78]. Low-dose cyclophosphamide also holds immunomodulatory properties, such as Tregs reduction and CD8+ cells induction [79][80]. However, the studies conducted so far did not lead to survival improvements. Besides the immunological potential, timing and schedule should be more deeply investigated and optimized for improving efficacy. The combination of ICIs and anti-VEGF agents seems attractive because the anti-angiogenic drugs directly influence OC TME [20][31][32][81][82][83]. Other combinations with multikinase inhibitors targeting VEGF/VEGFRpathway, such as cabozantinib or lenvatinib, are now under evaluation. The association with other agents with immunotherapeutics role, such as the anti-Lymphocyte-activation gene 3 (LAG-3) Relatlimab, as well as monoclonal antibodies such as the anti-Cluster of differentiation (CD)27 Varlilumab, the anti-CD47 Magrolimab, is under investigation. Actually, overcoming the immunosuppressive pathways in the TME could represent a complementary way to potentiate ICIs effect on the immune system. Therapeutic vaccines were administered in OC, inducing cellular and humoral responses but rarely survival improvement as monotherapies [84]. Hence, several tumor-associated antigens were found in OC, such as p53, folate receptor (FR), New York Esophageal Squamous Cell Carcinoma-1 (NY-ESO-1), and Ca125 [85][86][87][88]. Therefore, combinations of ICIs and vaccines need to be explored. New approaches such as autologous TILs, cancer cell therapy, and adoptive cell therapy (ACT) also represent future possibilities for improving ICIs efficacy.

Currently, a uniformly accepted predictive role of PD-L1 for ICIs response was not yet identified in solid tumors, including OC. PD-L1 expression varies between primary tumors and metastases, implying heterogeneity [89]. However, even if PD-L1 positivity was retrieved in around 1/3 OCs, the clinical impact was not elucidated, with conflicting results regarding the association with higher tumor stage/grade or shorter survival [90][91][92][93][94]. Indeed, some of the published trials reported better results for PD-L1 positive than PD-L1 negative patients [12][13][27]. In other studies, PD-L1 positivity was not predictive of ICIs response [19][20]. Recent research has focused on the post-transcriptional modifications of PD1, and even more PD-L1, which N-glycosylation of specific sites functionally modulates. PD-L1 and PD1 N-glycosylation ensure stability, prevents clearance, and influences mutual interactions [95][96]. The N-glycosylation of the PD1/PD-L1 receptors and its aberrations should be better investigated as possible immune resistance mechanisms in OC since specific glycoproteomic signatures were found in HGSOC: the immunoreactive subtype was richer in mannose than the mesenchymal, which was mainly fucosylated [97]. Moreover, it was evidenced that the antibodies used in the immunohistochemical analysis for PD-L1 accessed the highly glycosylated PD-L1 with difficulty, resulting in a certain percentage of PD-L1 false-negative results partially explaining ICIs efficacy also in PD-L1 negative patients [98]. More profound knowledge of the post-transcriptional status of PD1/PD-L1 and the search for biomarkers with a predictive role for ICIs' efficacy is warranted to ensure the best patient selection.

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