PARP Inhibitors and ICIs in Ovarian Cancer

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Ovarian cancer (OC) has a high impact on morbidity and mortality in the female population. Survival is modest after platinum progression. Therefore, the search for new therapeutic strategies is of utmost importance. *BRCA* mutations and HR-deficiency occur in around 50% of OC, leading to increased response and survival after Poly (ADP-ribose) polymerase inhibitors (PARPis) administration. PARPis represent a breakthrough for OC therapy, with three different agents approved. On the contrary, immune checkpoint inhibitors (ICIs), another breakthrough therapy for many solid tumors, led to modest results in OC, without clinical approvals and even withdrawal of clinical trials. Therefore, combinations aiming to overcome resistance mechanisms have become of great interest.

1. Introduction

Ovarian cancer (OC) represents the eighth most common tumor among the female population, with an incidence of around 11 cases/100,000 women/year [1]. OC is the most lethal of gynecological tumors, with less than 25% of patients alive after five years from diagnosis at an advanced stage [1][2]. Almost all OC subtypes have an epithelial origin. Among them, high-grade serous OC (HGSOC) represents around 70% of cases, with aggressive features and often being metastatic at diagnosis [3]. Platinum-based chemotherapy represents a cornerstone of advanced OC treatment, still associated with a high relapse rate, particularly in the first two years. However, most patients will recur and develop resistant disease [4][5][6][7]. Thus, searching for new therapeutic strategies is mandatory for advanced OC.

2. BReast CAncer Gene Mutations and Poly (ADP-ribose) Polymerase Inhibitors in Ovarian Cancer

2.1. The 'Synthetic Lethality' in Ovarian Cancer

Double-strand DNA breaks (DSB) constitute the most severe type of DNA damage, as they disrupt both DNA reading frames, leading to mutations or chromosome rearrangements, increasing the oncogenic risk, and determining cell death [8]. Homologous recombination (HR) represents a key mechanism for DSB repair [8][9]. Other pathways, such as non-homologous end joining (NHEJ), are efficient in DNA repairing but also more error-prone, potentially causing DNA rearrangements [9]. HR is highly accurate for DSB repair, as an undamaged DNA template for neo-synthesis derives from a donor single-strand DNA (ssDNA) fragment [10]. *BRCA 1* and *2* are two essential proteins for the HR mechanism, as *BRCA1* is part of a surveillance complex for DSBs, and *BRCA2* cooperates with RAD51-Recombinase (RAD51) in repairing DSBs [11][12][13]. Several studies showed a survival advantage for *BRCA*-mutant patients with OC and a better response to DNA-damaging chemotherapeutic agents like platinum compounds [14][15]. Besides germline mutations of *BRCA1* and *2*, several genes confer a similar sensitivity to Poly (ADP-ribose) polymerase (PARP) inhibitors (PARPis) in case of somatic mutations, named under the term 'BRCAness'. These include mutations in *BRCA1* and *BRCA2*, *RAD51* (locator of the DNA repair complex to the broken DNA strand), Ataxia-Telangiectasia Mutated (*ATM*), ATR Serine/Threonine Kinase (*ATR*—two DNA-damage sensory proteins), *BRCA1* Associated RING Domain 1 (*BARD1*), *BRCA1* Interacting Protein 1 (*BRIP1*), cyclin-dependent kinase 12 (*CDK12*), Partner and localizer of the *BRCA2* (*PALB2*), and Fanconi anemia complementation group (*FANC*—that constitutes a complex cooperating with *BRCA* in DNA repair) [16][17].

Single-strand DNA breaks (SSB) represent another type of DNA damage. SSBs are fixed by three mechanisms: base excision repair (BER), nucleotide excision repair (NER), and mismatch repair (MMR). The PARP family is a group of 17 proteins, of which PARP1-3 are deputed to repair DNA breaks through BER that supplies *BRCA* inefficiency. PARP 1 and 2 determine the poly-ADP ribosylation (called 'PARylation') of chromatin and auto-PARylation. PARP1 opens up chromatin and recruits factors to repair DNA [18][19]. PARP1 can recruit *BRCA1* for HR or NHEJ-associated factors. PARP2 is

supposed to limit 53BP1 in favor of *BRCA1* accumulation, promoting HR over NHEJ [20]. Auto-PARylation is useful for releasing PARP from DNA binding and allowing DNA repairing proteins to access DNA and complete the repair process [18]. Therefore, since *BRCA* mutant cells are inefficient in HR, if PARP is blocked, SSBs are more likely to accumulate and generate potential DSBs, inducing a genomic instability ending in cell death: the so-called 'synthetic lethality' represents the rationale for PARPis use in *BRCA* mutant tumors, OC included [19]. Initial studies on synthetic lethality postulated that PARPis cause SSBs determining the collapse of the replication fork, inducing the more effective DSBs, the more defective the HR pathway is [21]. More recently, it has been demonstrated that PARP could be trapped in DNA by PARPis, which block both PARylation of downstream substrates and auto-PARylation, enhancing PARP1 avidity for DNA after allosteric changes in its structure [22]. As a result, the progression of the replication fork is stopped, resulting in a cytotoxic effect, as unrepaired SSBs convert into DSBs [21][23]. A further hypothesis is that PARPis enhance NHEJ, leading to further genomic instability and cell death [24]. Taken together, PARP trapping and NHEJ enhancement make the effect of PARPis stronger than PARP depletion [25]. All the clinical approved PARPis potently inhibit PARP1 and PARP2.

2.2. Clinical Applications of Poly (ADP-ribose) Polymerase Inhibitors in Ovarian Cancer

Currently, three different PARPis have been FDA/EMA approved in OC: olaparib, rucaparib, and niraparib. In OC, PARPis demonstrated efficacy in metastatic OC patients as maintenance after frontline chemotherapy or in the platinum-sensitive recurrent disease [26][27][28][29][30][31][32][33]. Starting from 2014, PARPis were introduced in the clinical practice for the treatment of PS-ROC, as the three randomized phase III trials NOVA, SOLO-2, and ARIEL3 demonstrated a significant progression-free survival (PFS) benefit (Hazard Ratio [HR] for PFS ranging from 0.12 to 0.54) with niraparib, olaparib, and rucaparib maintenance versus placebo (PBO), respectively. Median PFS (mPFS) ranged from 8.4 to 21 months with PARPis versus 3.8–5.5 months with PBO [26][27][28][29][34]. In the three phase III trials SOLO-1, PRIMA, and VELIA, the maintenance with PARPis demonstrated a reduction of the risk of progression between 32% and 80% compared to PBO in patients achieving a stability/response after frontline platinum-based chemotherapy [30][31][32][34]. In *BRCA* mutant patients, the benefit was particularly significant, as PFS was almost doubled with PARPis versus PBO (mPFS ranged from 22 to 37 months with PARPis versus 10–22 months with PBO). Moreover, in the PAOLA-1 trial, the combination of olaparib and bevacizumab determined a PFS advantage in HR-deficient (HRD) patients as maintenance after first-line platinum (37 vs. 17 months), enlightening the value of synthetic lethality when approaching these patients [33]. Of note, the above-mentioned studies were designed to assess PFS as the primary endpoint, and overall survival (OS) results are still ongoing [26][27][28][29][30][31][32][33].

However, more than 40% of OC patients failed to respond to PARPis, and different mechanisms have been addressed: the secondary reversion mutations in genes such as *BRCA1*, *BRCA2*, *RAD51*, *PALB2* that can restore the open reading frame; loss of p53 promoting NHEJ; mutations in PARP1 DNA-binding domain that increase auto-PARylation; modifications of regulators of the replication fork degradation such as Pax Transactivation-Domain Interacting Protein (PTIP) and Enhancer of zeste homolog 2 (EZH2) [35][36][37].

Many studies focused on overcoming resistance to single-agents PARPis for broadening the responding population. The immune response arising against dying tumor cells triggered by synthetic lethality, associated with neo-antigens release, led to the hypothesis that PARPis and ICIs could reciprocally potentiate, reducing resistance mechanisms. Further confirmations derived after a series of immunomodulant effects of PARPis were evidenced: the interaction with the tumor microenvironment (TME) of OC, the increased number of TILs, the upregulation of PD-L1, the enhanced antigen presentation and tumor mutational burden (TMB), and the interaction with the stimulator of interferon genes (STING) pathway [38][39][40][41][42][43].

3. Immune Checkpoint Inhibitors in Ovarian Cancer

3.1. Immune Checkpoint Inhibitors Pathways and Clinical Applications in Ovarian Cancer

In the current clinical practice, immunotherapy mainly relies on ICIs, a group of antibodies disrupting the negative signals for the anti-tumor immune system, dampening cytotoxic T-cells [44]. Antigen-presenting cells (APCs) activate T-cells after presenting antigens bound to major histocompatibility complex (MHC) to T-cell receptor (TCR), together with co-stimulatory signals developing after cluster of differentiation (CD)-80/B7-1 and CD86/B7-2 on APCs bind CD28 located on T-cells. Subsequently, activated T-cells express co-inhibitory molecules, such as Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and Programmed-Death (PD)-1 at immune checkpoints, whose equilibrium with the co-stimulatory signals is crucial for the correct activity and tolerance of T-cells [45]. CTLA-4 is constitutively expressed on Tregs and can be transported to the T-cell surface proportionally to antigen stimulation after antigen response. It binds B7 proteins with higher affinity than CD28, causing inactivation and anergy of T-cells [46]. Moreover, PD1 is widely expressed on immune

cells, T-cells, B-cells, Natural killer (NK)-cells, and Dendritic cells (DCs). PD1 natural ligands are represented by Programmed Death Ligand (PD-L)1 and PD-L2. After TCR binds antigen presented by MHC, PD1 binds its ligands, becoming functional. Subsequently, a downstream inhibitory cascade is started, which stops the activation signal. Blocking CTLA-4 and PD1/PD-L1 axes, ICIs leverage on this balance, shifting the immune system towards the activation.

Almost 20 clinical trials explored the efficacy and safety of ICIs in the advanced setting of OC. The majority of studies were phase I/II trials. Patients were often heavily pre-treated. Anti-PD1 (pembrolizumab, nivolumab), anti-PD-L1 (avelumab, atezolizumab, durvalumab), and anti-CTLA4 (ipilimumab, tremelimumab) agents were administered as monotherapy or in combination. Response rates and survival were unsatisfactory (overall response rate [ORR] < 10% with single-agents ICIs, reaching 47% with the addition of chemotherapy and bevacizumab; no survival differences), leading to the premature stopping of some phase III trials (reviewed in [47]). Only three phase III trials have been completed [48][49][50]. In JAVELIN 200 (NCT02580058), avelumab did not improve OS or PFS versus chemotherapy when used as a single agent and combined with chemotherapy [48]. In the IMagyn050, adding avelumab to chemotherapy and bevacizumab did not improve survival in the first-line (p = 0.28) [49]. In the NINJA trial (conducted in the Japanese population), no OS differences emerged between nivolumab and chemotherapy in patients with recurrent OC (HR = 1.03) [50].

3.2. Predictive Factors for Immune Checkpoint Inhibitors in Ovarian Cancer

A possible reason for these unsatisfactory results relies on different immunosuppressive factors within the OC TME. A series of cytokines, such as interferon-gamma (IFNγ), interleukin (IL)-6, IL-10, transforming growth factor-beta (TGFβ), and tumor necrosis factor-alpha (TNFα), induce immunosuppressive cells, such as myeloid-derived suppressor cells (MDSCs), and polarize tumor-associated macrophage (TAMs) towards the immunosuppressive M2 subtype. Effectively, M2 macrophages emerged as the predominant TAM subpopulation in OC, associated with an advanced stage and a negative prognostic role [51][52]. MDSCs inhibit T-effectors and NK-cells. Moreover, these cytokines induce cyclooxygenase-2 (COX-2) production, leading to Prostaglandin E2 (PGE2) synthesis and resulting in limited recruitment of T-cells at tumor sites. On their way, M2 macrophages produce cytokines that inhibit T-effectors and enhance Tregs (IL-1R, IL-10, C-C-Motif Chemokine Ligand [CCL] 17, CCL20, CCL22) [53][54]. Tregs produce IL10 and TGFβ that, together with other immunosuppressive cytokines such as IL6, inhibit T effectors and reduce DCs and APCs activity [55]. DCs can recognize damage-associated molecular patterns (DAMP) released from dead OC cells and activate CD4$^+$ and CD8$^+$ via MHC class I and II, respectively [56]. In OC patients, a tolerogenic DC group has been found, associated with lower levels of pro-inflammatory cytokines, but the release of enzymes that reduce T-effectors activity such as Indoleamine 2,3-Dioxygenase (IDO). Moreover, in mouse models of OC, it has been evidenced that, when the tumor stage increases, DCs gradually assume an immunosuppressive phenotype [57].

After years of ICIs use, it is well-known that no unique predictive biomarker exists. However, several factors can influence the response to ICIs: neo-antigens production and tumor mutational burden (TMB), number of TILs, TME, mismatch-repair deficiency (MMRd), leading to microsatellite instability (MSI) [58]. This led to the development of ICIs-based combination therapies, among which PARPis represent an option.

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