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Ovarian Cancer Therapy in Transition, Innovation, Update, and Challenges: A Review Article

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A B S T R A C T

Ovarian cancer continues to be one of the deadliest cancers in women, with a poor prognosis despite many therapeutic advances; it has an ominous outcome. In the last decade, a giant leap in ovarian cancer therapy was made, which has reshaped ovarian cancer management and given hope for improved survival odds in some of the affected population. An online search was conducted through an electronic repository to find up-to-date reports and studies regarding newer and innovative therapies in ovarian cancer. We collected data regarding the method of action, efficacy, patient demographics, side effects, and suggested future work to address research gaps. Six therapeutic strategies were identified and discussed and comprehensively compared, including [Immune Checkpoint Inhibitors (ICIs, Poly (ADP-ribose) polymerase (PARP) Inhibitors, Anti-angiogenesis Drugs, Antibody-Drug Conjugates (ADCs), Oncolytic Viruses (OVs), and Cancer vaccines]. The analysis identified key areas that require attention, including biomarker development, rationale for combination therapy strategies, mechanisms of resistance development during treatment, immune modulation methods, and preventive approaches for ovarian cancer. Future studies are warranted to address the current gap in knowledge and validate optimistic cancer research results, especially for high-risk patients, to reduce ovarian cancer burden and improve survival odds.

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INTRODUCTION

One of the most challenging gynecological malignancies is Ovarian Cancer (OC). It has a high mortality rate, mainly due to its subtle clinical features that lead to delayed diagnosis, which is further complicated by the lack of effective screening methods (1). It is estimated that over 20,800 women in the USA are projected to be diagnosed with OC, with an age-adjusted rate of 10.3 per 105 women. Globally, OC accounts for more than 300.000 new cases and 200.000 deaths/year, which signifies its persistent public health burden (2).

About 70% of all OC cases present at stage III or IV at the time of diagnosis, which inversely affects prognosis and 5-year survival rates, dropping from 91% for local disease to 35% for advanced cases. The OC strategy involves cytoreduction surgery combined with platinum-based chemotherapy, achieving a 70-80% response rate. Still, the relapse rate is high within 2 years, and most of them develop platinum resistance (3).

Fortunately, we are witnessing a modest decline in OC in the last decade owing to the use of oral contraceptive pills and reduced use of hormonal replacement therapies (4).

The conventional therapeutic strategies are hindered by resistance, high recurrence, and drug-related toxicities that impact patients' quality of life. Moreover, there is inequality in accessing health care due to racial, social, and financial factors, which raised an urgent need for equitable, personalized therapeutic strategies(5). The therapeutic landscape of OC has expanded significantly in the last decade with the introduction of targeted agents and immunotherapies; these approaches have the advantage of enhanced efficacy and reduced systemic toxicity(6). Despite the optimistic results of these newer agents, there are unaddressed challenges, such as variable response rates in the non-BRCA population, acquired resistance, and unwanted side effects that have been reported among some (7).

This review aims to discuss the recent advances in OC therapy, evaluating each approach's mechanism of action, drug efficacy, and limitations

By highlighting critical knowledge gaps, we aim to optimize patient satisfaction, overcome resistance, and possibly enhance patient survival and quality of life. As we integrate up-to-date clinical data and translational research, a personalized, durable, and

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less toxic therapeutic strategy is likely to be introduced for OC cases.

Searching strategies

An online search was conducted throughout electronic repositories, including Google Scholar, Scopus, PubMed, and WOS, using the keywords. Eligible studies were extracted and checked by independent reviewers, exclusions were made for studies that fell outside the aim of interest, duplicated data were omitted, and extracted data were synthesized into six therapeutic strategies, highlighted in Fig.1. For each therapeutic category we discussed the suggested mechanism of action, indication of use, patients that most likely to get benefit and side effect.

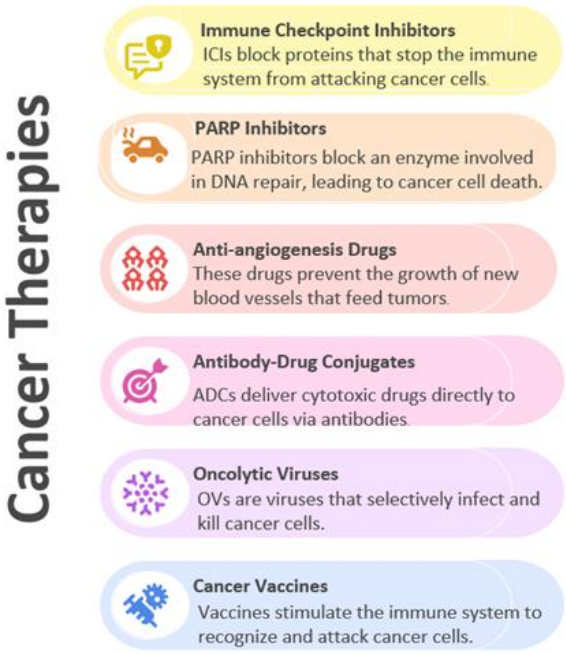

Fig 1. New and innovative therapies in ovarian cancer

Immune Checkpoint Inhibitors (ICIs)

These groups represent a class of immunotherapy agents that act by triggering the body's own immunity system against the cancer cells to fight them. In OC, the ICI aims for programmed cell protein 1 and its ligand (PD-1 and PD-L1), respectively(8).

It is customary for OC cells to exploit these points to escape the body's immune system. Once these interactions (i.e., tumor cells vs PD-1 and PD-L1) are blocked by the ICI, the body's immunity will be unleashed, and the T cells will recognize these OC cells. T-cells' cytotoxic activity will effectively destroy malignant cells by apoptosis and will be subsequently eliminated(9).

The use of PD-1 in treating malignancies is not new; in fact, it has shown remarkable efficacy in melanoma and renal cell carcinoma. Unfortunately, this is not the case in OC. Their efficacy is modest in platinum-resistant cases, with a response rate of 15% when using nivolumab, a PD-1 therapy(10). Upon assessing therapeutic outcome in clinical studies a CPS scoring system is used; which refers to Combined Positive Score; a measure of programmed death ligand 1 expression on both malignant cells and body own immune cells.it was shown that cases with CPS of 10 showing an objective response rate (ORR) of 17% compared to those with CPS <1 who showed ORR of 5%(11).This implies that the higher the PD-L1 expression, the better the therapeutic response to pembrolizumab use. It is worth mentioning that pembrolizumab efficacy was unaffected by prior chemotherapy use, which underscores its utility among different treatment settings. Although cases with high PD-L1 expression and CPS ≥10 are more likely to respond to ICI, this biomarker alone is not perfect; some high PD-L1 patients may not experience significant benefit(12).Conversely, negative PD-L1 cases do show benefit. This underscores the need for more refined biomarkers that correlate best with ICI therapy.

One of the most important limitations of ICI monotherapy in OC is the relatively low response rates compared to other cancers owing to the complex immune mechanisms expressed by OC.(13). The OC microenvironment is characterized by an abundance of immunosuppressive cells and factors that suppress T cell activity, thereby hindering drug efficacy. Another important limitation of the ICI is the widespread activation of immune cells against healthy body tissue that leads to unwanted side effects (immune-related adverse events): as rashes, colitis, thyroiditis(14). Although these can be managed by corticosteroids, there are more drastic and sometimes fatal reactions that require prompt intervention, so cases on ICI therapy need to be under close observation(15).

There are a few gap areas that are worthy of future studies in ICI monotherapy. We need more reliable predictors, other than PD-L1 expression, such as gene expression signature, tumor mutation burden. We need to overcome the tumor immune-suppressive microenvironment either by investigating novel immunotherapies or a combination of more than one therapeutic approach, such as PARP inhibitors. Finally, we need to optimize the dose given for an enhanced patient profile and reduced toxicity(16).

Poly (ADP-ribose) polymerase (PARP) Inhibitors

PARP enzymes are essential for repairing single-stranded DNA breaks by recruiting DNA repair proteins to facilitate DNA repair, thereby maintaining genomic stability. When PARP) Inhibitors are used to block PARP enzymes on DNA, leading to the accumulation of single-strand breaks that are converted into more lethal double-strand breaks during DNA replication(17). Cells with homologous recombination deficiency (HRD), a critical DNA repair pathway, examples of these cells are those with BRCA I /II mutation. Once the unrepaired double-strand breaks accumulate in these cells, the cells will undergo death through a mechanism called synthetic lethality. For tumors with BRCA mutations or HRD, this class of drugs

(PARP inhibitors) selectively kills cancer cells while sparing normal cells that have intact HRD(18).(PARP) Inhibitors have a good clinical outcome among patients, especially those with BRCA mutation or HRD. Many of these drugs did receive FDA approval. Olaparib was the first to be used in practice and showed promising results for recurrent platinum-sensitive OC, while other drugs like Niraparib showed efficacy in a broader population, such as those with HRD(19). Rucaparib showed promising results in overcoming BRCA wild-type cases. All these agents have good, prolonged progression-free periods, and some have extended overall survival periods. As expected, the best fit patients for (PARP Inhibitors are BRCA and HRD cases, which a genomic test can confirm(20). Generally speaking, PARP Inhibitors are well-tolerated but have some side effects, including gastrointestinal symptoms and hematological toxicity. However, the most significant long-term side effect is the loss of efficacy, which can result from the restoration of HDR function or secondary mutations in BRCA genes. This makes them of limited value in prolonged therapies, esp. among non-BRCA mutation carriers(21). Suggested studies should focus on identifying how to overcome resistance to PARP Inhibitors and determining the best sequencing, dosing, and timing for use. Finally, we are exploring the optimum combination with other agents, such as anti-angiogenic agents(22).

Anti-angiogenesis Drugs

The formation of newer blood vessels is an integral part of any tumor growth, supporting its invasion and metastasis. This process is called angiogenesis. It is important as the tumor needs a high blood supply to deliver oxygen, nutrients, and waste removal. AAD acts by blocking this process, thereby causing the tumor cell to starve(23).

AAD's primary goal is to target the OC endothelial growth factor (VEGF)pathway. One of these drugs is Bevacizumab, a humanized monoclonal antibody agent that binds to VEGF-A and prevents its binding to the VEGF receptor located on endothelial cells. The net result will be inhibition of endothelial cell proliferation and migration, consequently reducing vascular permeability and decreasing angiogenesis in the tumor cells(24).

Bevacizumab's performance in practice has been good; it's currently the most widely used AAD, especially in combination with chemotherapy. It was able to extend progression-free survival in newly diagnosed OC, even in high-risk groups, and in some advanced cases of OC, it extended the overall survival as well, which underscores the role of AAD in controlling disease progression(25). Bevacizumab is used for high-risk OC, i.e., those with suboptimal debulking and advanced disease. It is also used in combination with chemotherapy for newly diagnosed advanced-stage cancer, whether in platinum-sensitive or resistant recurrent cases. It is worth noting that AAD action on VEGF is a special added benefit for patients who suffer from ascites owing to AAD's role in fluid accumulation(26).

Although effective, Bevacizumab has numerous side effects, including hypertension, bleeding incidents (such as gastrointestinal hemorrhage and arterial thromboembolic events), and gastrointestinal perforation. Therefore, patients should be carefully selected and closely monitored. Another limitation of AAD is the development of resistance, as the tumor adopts alternative mechanisms for angiogenesis or becomes adapted to a hypoxic state; consequently, patients, despite being on therapy, experience tumor progression(27).

Antibody-Drug Conjugates (ADCs)

These are a complicated class of targeted drugs that combine monoclonal antibody specificity and chemotherapy's potent cytotoxicity.

Each of these drugs is composed of 3 subunits: a monoclonal antibody that specifically targets the tumor surface antigen, a highly potent cytotoxic payload(chemotherapy agent), and a chemical linker that binds the 1st two units together(28). Once the ADC is bound to a cancer cell antigen, the ADC complex will gain access inside the cell, where the linker is cleaved to release its cytotoxic payload and exert its lethal effect. This typically includes inhibiting cell division and inducing DNA damage, which consequently leads to programmed cell death(29). This drug delivery mode minimizes cytotoxic effects on the body and reduces off-target toxicity to normal body cells.

ADCs are promising drugs in OC therapy, especially among patients with recurrent or platinum-resistant OC. Many of these drugs are under investigation and have shown optimistic results in RCTs(30). Mirvetuximab is an example. The latter targets folate receptor alpha, which is frequently upregulated in OC cases, especially among high-grade serous OC, where the drug showed improved response rates and enhanced progression-free interval.

The suitability of ADC drugs depends on the expression of surface antigens on tumor cells, which is ideally identified by immunohistochemistry or other molecular assays(31).

OCs showing high expression of folate receptor alpha are ideal candidates for mirvetuximab. Other ADC agents are currently under study to identify the most suitable cases for each drug. This personalized approach aims to deliver the drug to the tumor that most likely responds, thereby maximizing the effect while minimizing unnecessary exposure of healthy tissue to cytotoxic effects (32). Although these drugs are designed with minimized systemic effects, they do have side effects, including ocular toxicity, peripheral neuropathy, gastrointestinal disturbances, and hematological toxicity. The degree of side effects experienced by patients varies depending on the payload and the targeted antigen(33). Like many other agents, there is a risk of resistance development as the tumor reduces expression of the target antigen, or by impaired internalization of ACD, or by alternative activation

of other pathways that bypass these drugs(34).
There are currently many research gaps that are worthy of future investigation, including the development of newer, more specific tumor antigens that can replace classical ACD. Optimization of linker technology and the cytotoxic payload is another point to consider(35). Finally, a better insight into how resistance to ACD drugs develops will improve their clinical utility—exploring the optimal combination of ACD with PARP inhibitors or immunotherapies may improve patient outcomes through a synergistic effect.

Oncolytic Viruses (OVs)

These are sophisticated classes of therapies that selectively attack, infect, and lyse tumor cells and danger-associated molecular patterns from the killed cancer cells. This molecule acts as a powerful stimulus to the immune system, triggering a systemic anti-tumor immune response(36). The body's immune system, once it gets primed, can identify the tumor cells and eliminate them, even those that escape the viral infection. These OV can occur naturally or be artificially engineered and manufactured to enhance their affinity to tumor cells, replication, and immunogenic capacity. Interestingly, some of these OV are designed to express cytokine or immune checkpoint inhibitors to further strengthen anti-tumor response(37). These agents hold promise for OC treatment, especially in recurrent tumors that affect the peritoneal cavity, which allows direct loco-regional delivery. Early reports from clinical trials involving viruses like adenovirus and herpes simplex virus showed promising results by inducing regression in ovarian cancer cases. This dual action exerted by OV makes it a strong therapeutic approach(38). Additionally, combining them with chemo, radiotherapy, or even ICI offers a synergistic effect; such an approach will enhance the direct tumor killing action and the subsequent triggered immune response. The advantage that OV offers in loco regional delivery of the drug makes it an appealing option for peritoneal carcinoma, whereas other drugs may fail due to the tumor's immunosuppressive environment(39). OV has an important additive, its immune-activated property. The patient's selection is vital here; it may involve biomarkers related to viral receptor expression on the cancer cell, immune status, and patients' specific genetic status, all of which are related factors that may influence viral replication within the tumor cells(40). Oncolytic viruses' side effects are generally more favorable compared to other conventional therapies; they tend to cause flu-like illness, injection site reaction, but the most important is the pre-existing immunity to certain viral vectors that can cause rapid viral clearance, thus reducing the drug efficacy. It is important to keep in mind the heterogeneous nature of OC; some of them may show different susceptibility to the infection and to lysis (41).
Many areas need further investigation regarding OV, like optimal dosing, administration frequency, and strategies to optimize viral spread to the tumor. Future research should focus on developing a novel OC platform to increase tumor selectivity and replication, and simultaneously decrease immunogenicity to host defense. Studies addressing novel methods to overcome pre-existing immunity, using alternative viral vectors or immunosuppressive drugs, are vital(42).
Additionally, identifying reliable predictors for the OV response and optimizing the delivery system to maintain the drug's widespread presence within the tumor cells are crucial.

Cancer vaccine

They act by triggering the immune system to attack and destroy cancer cells. These therapeutic vaccines are designed to treat existing cancer or prevent its recurrence. In ovarian cancer, these vaccines present tumor-associated antigen (TAA) to the body's immune system, targeting antigen-presenting immune cells (APC), such as dendritic cells(43). These cells process the antigen and deliver it to T cells, leading to the activation and expansion of tumor-specific cytotoxic T-lymphocytes. The latter will spot and eliminate the malignant cells that express that TAA.(44) in other words, these vaccines aim to train the body's immune cells to distinguish the cells that are prone to transform into OC by targeting the specific antigen linked with early cancerous cell transformation. These drug categories are largely in the preclinical stage and are currently focusing on therapeutic as well as preventive approaches. Nevertheless, the preventive strategy developed by OvarianVax holds optimistic results for high-risk cases by preventing the development of diseases, such as those associated with BRCA mutations(45). On the other hand, therapeutic vaccines have demonstrated the ability to induce an anti-tumor immune response and improve patient outcomes in some cases, particularly when ovarian vaccines are combined with immune therapy or conventional therapies. These drug categories hold a promise of transforming OC into a preventable disease(46). Ovarian vaccines are a pleasant option for high genetically predisposed women such as BRCA mutation carriers, once the clinical studies are finished and he results are validated, these protective vaccines may be offered to all women with heightened risk of malignancy. As for the therapeutic vaccine, patient selection will be crucial in targeting individuals with favorable immune microenvironments that the vaccine can trigger(47). The side effects linked with the cancer vaccine are mild, including local injection swelling, fatigue, and low-grade fever. However, the significant drawback is the immunosuppressive nature of the ovarian tumor that reduces vaccine-induced immune response, thus hindering its clinical efficacy. Moreover, the heterogeneity of the tumor and its complex evasion mechanisms can limit the effectiveness of vaccines targeting a single

antigen(48). The preventive vaccine, on the other hand, requires a long time for validation, testing, and development before it can be available in the market.

Future research should focus on novel and highly immunogenic tumor-associated antigens expressed by many ovarian cancer subtypes(49). Additionally, approaches to overcome tumor-induced immunosuppression, optimize vaccine platforms, and develop effective delivery systems are crucial. For preventive vaccines, preclinical and clinical development is warranted to validate their efficacy and safety for public use(50).

DISCUSSION

Although there were many significant leaps in OC therapy, the long-term outcome remained limited, which necessitates further innovative research. Targeted therapy, immunotherapy, and improved surgical approaches have yielded significant improvements; however, substantial gaps remain to be addressed(51). One of the key challenges is the need for reliable predictive markers. While BRCA mutation carriers and HRD guide the use of PARP inhibitors, reliable biomarker panels that predict drug response across other drug modalities are still missing. Their presence is crucial for a truly personalized therapeutic approach(52). The development of resistance to drugs is another significant drawback; the presence of intrinsic and acquired resistance to chemotherapy, immunotherapies, and PARP inhibitors truly compromises their efficacy and use in everyday practice. Focusing on how these resistances develop and the strategies needed to counteract them is a priority, as it enhances surgical success and delays relapse and failure(53). The ovarian tumor immunosuppressive mechanism is a significant obstacle that blunts the effect of many immunotherapies. Combining immune checkpoint blockade with oncolytic viruses may help to overcome this barrier(54).

Stratification of patient genetic risk is important, especially for high-risk groups, which enables shifting paradigms from late-stage therapy into early intervention.

Addressing these research priorities (summarized in Fig. 2) calls for multidisciplinary teamwork to transform ovarian cancer from a deadly disease into a preventable one among high-risk populations and into diseases that are efficiently managed among diagnosed cases through personalized patient-centered therapies(55).

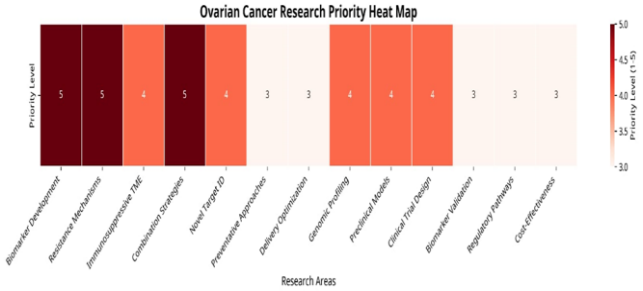

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Fig 2. Suggested future research in ovarian cancer to cover the gap in knowledge

CONCLUSIONS

Significant advancements in ovarian cancer therapy have reshaped the treatment paradigm, giving hope for a better quality of life and improved survival odds. However, there are still unmet challenges that need to be addressed, for instance, resistance, toxicity, and lack of reliable biomarkers, all of which necessitate further research to improve the precision of therapy choices, reduce disease burden, and improve patient outcomes.

Conflict of interest. Nil

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