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Advances In Immunotherapy For Gynecological Cancers: Review Of Current And Emerging Immunotherapies For Ovarian, Cervical, And Endometrial Cancers

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Abstract

Globally, these gynecological cancers (ovarian, cervical, and endometrial) have a significant burden on both morbidity and mortality from cancer. However, for advanced and recurrent cases, traditional treatments such as surgery, chemotherapy, and radiotherapy haven't greatly improved survival. Except for very rare diseases, immunotherapy is a promising approach, which combines the power of the immune system against cancer and is discussed in this review as a promising approach and its application in gynecological malignancies.

Immune checkpoint inhibitors that used to have promising results in concentrated patients with recurrent or advanced gynecological cancers include pembrolizumab and nivolumab. Further, adoptive cell therapies, such as chimeric antigen receptor (CAR)-T cells, and therapeutic cancer vaccines directed to specific tumor-associated antigens, represent possible novel treatments. Challenges to resistance and patient response variability have

prevented immunotherapies from successfully using melanoma as a model for gynecological cancers, but the success of immunotherapy in other cancers has paved the way for its application to gynecological cancers.
This review is important in its possibility to change gynecological cancer treatment. Further research into combination therapies and biomarkers could greatly improve patient outcomes with immunotherapy. More clinical trials and research will nevertheless be necessary to optimize these treatments for patients outside of the reduced subgroup studied in Phase 3 studies.

Keywords: *Gynecological cancers; Immunotherapy; Immune checkpoint inhibitors; CAR-T cells; Cancer vaccines*

1. Introduction

Gynecological cancers (ovarian, cervical, and endometrial) account for a major proportion of cancer-related morbidity and mortality worldwide. Ovarian cancer has the highest mortality rate of gynecological cancers and is often diagnosed at advanced stages most cases of cervical cancer are still leading causes of death predominantly due to infection with human papillomavirus (HPV) [1]. Endometrial cancer is the most common gynecological malignancy in developed countries and incidence is rising due to factors, including obesity and metabolic disorders. Conventional treatments such as surgery, chemotherapy, and radiation are the mainstays of treatment, but their use has not led to improvement in the overall survival rate for patients of these cancers, especially in advanced and recurrent cases. This exemplifies the need for novel treatment approaches, which currently include immunotherapy [2].

It's a particularly exciting time for solid tumors like melanoma and lung cancer because their treatment landscape is dramatically changing with immunotherapy – essentially harnessing your immune system to fight cancer. This therapeutic approach has become popular in gynecological oncology as well [2][3]. Like all concepts studied for the treatment of cancer, the notion that the immune system can be harnessed to treat cancer cells is not new; however, advances in understanding the immune system and tumor biology have made this a more viable therapy. The treatment of cancers has been revolutionized with the introduction of immune checkpoint inhibitors, therapeutic cancer vaccines, and adoptive cell therapy, providing new hope to patients with few treatment options [3].

The gynecological cancers warrant immunotherapy based on their unique malignant features. For example, HPV infection leading to cervical cancer is a prime case for bivoetennargic interventions given that the majority of cases of cervical cancer result from persistent HPV infection [4]. Therapeutic vaccines targeting HPV antigens have demonstrated the promise of eradicating virus-infected cells as well as blocking the progression towards cancer. Additionally, ovarian and endometrial cancers are marked by tumor-associated antigens, including WT1 and mesothelin, for which immune-based therapy can be targeted [4, 5].

Several cancers have responded well to immune checkpoint inhibitors, which block proteins that normally suppress the immune response. In clinical trials of patients with recurrent or advanced gynecological cancers, these inhibitors of these inhibitors, such as pembrolizumab and nivolumab, have shown promising results. For example, the repeat or metastatic cervical cancer that expresses PD-L1, a protein that helps tumors evade detection, is approved for pembrolizumab. Combination therapies using anti-tumor combinations such as checkpoint inhibitors with chemotherapy or radiotherapy are also being studied looking to augment the anti-tumor immune response [5][6]. A promising area is the adoption of cell therapy, a delivery method for immunoactivity cells that have been altered to better identify and destroy cancer cells. Application of this approach, with chimeric antigen receptor (CAR)-T cells in particular, has been shown at least to be feasible for hematologic malignancies and is currently being evaluated in solid tumors, including in gynecologic cancer. Also, the work continues to identify biomarkers that

would predict patient response to immunotherapy and thus more personalized and more effective immunotherapy [7, 8].
Finally, the addition of immunotherapy to the armamentarium of gynecological cancers represents a major shift from traditional empiric therapies to immunologically precise therapies. While challenges of administration and resistance to immunotherapy remain considerable, and specificity to the most effective combinations of immunotherapy with other treatments and/or combinations in patients with ovarian, cervical, and endometrial cancers is not assured, the potential for improved survival outcomes for these patients is beyond doubt. Further research and clinical trials are needed to fully realize the therapeutic potential of such novel treatments and to deliver better results for patients with these abominable diseases.

2. Background on Gynecological Cancers and Overview of Immunotherapy

The most common gynecologic malignancies include ovarian, cervical, and endometrial cancers, with ovarian the most common [9]. These cancers are a threat to women's health everywhere and at different rates of occurrence as well as risk factors [10,11]. Ovarian cancer is a rare but very deadly disease that is often diagnosed late because you don't notice any symptoms. This has multiple origins [10] and no single definite etiology and its subtypes are heterogeneous. The most common gynecologic cancer (endometrial cancer) has a greater survival rate, and it is usually attributed to too much estrogen [10]. Although its incidence is lower than the ovarian and endometrial cancers in many areas, cervical cancer continues to be of grave health importance [9].
These cancers have varying risk factors. The risk of ovarian cancer has been increased in patients with endometriosis, especially in patients with clear cell and endometrioid subtypes, but there is no association between endometrial cancer and reduced risk of cervical cancer [12]. Age, hormonal factors, and genetic predisposition are other risk factors [10].
Surgery, chemotherapy, radiotherapy, and chemoradiotherapy are current treatment approaches for gynecological cancers [11]. CRISPR Cas9 gene editing and AIC therapy have emerged therapies that show promise for potential improvements in treatment outcomes [13, 11]. Although, these cancers have unique challenges to treatment including complex surgical procedures, prolonged radiation techniques, and myelosuppressive chemotherapy [14]. The COVID-19 pandemic complicates further management of gynecological cancers, which have necessitated careful triaging of patients for treatment depending on the urgency of their condition [14]. In addition, treatment-related side effects including sexual dysfunction and decreased bone mineral density complicate greatly the patient's overall quality of life [15,16].
Cancer immunotherapy is a field rapidly evolving from harnessing the body's immune system to fight cancer. Immunotherapies are mainly categorized into cancer vaccines, effector cell therapy, and immunosuppression inhibition [17].
Immunosuppression inhibition occurs via checkpoint inhibitors, which block proteins that regulate the immune system to allow T cells to recognize and attack cancer cells [24]. Adoptive T cell therapy includes genetically engineering a patient's T cells to target a tumor-associated antigen (TAA), including CAR T cell therapy [23]. The goal of cancer vaccines is to activate the immune system to 'see' and attack cancer cells by presenting tumor antigens [18, 21].
Finally, work has been done on understanding and treating gynecological cancers, but important questions have yet to be answered. More effective diagnostic tools, precision treatments, and prevention strategy is the subject of ongoing research [9, 10]. The extremely complex nature of these cancers indicates a need for multidisciplinary involvement from many different fields to improve patient outcomes [10].

3. Current Immunotherapies for Gynecological Cancers

a. Ovarian Cancer:

The immunotherapies currently approved for use in the treatment of ovarian cancer are not specific to this malignancy. Immune checkpoint inhibitors as a monotherapy have demonstrated modest efficacy in ovarian cancer response rates up to 10% [21]. Trials with single-agent checkpoint inhibitors in platinum-resistant ovarian cancer have been disappointing [22]. As a result, researchers have tried different strategies, such as immunotherapy adjuvants of chemotherapy, anti-angiogenics, PARP inhibitors, and other targeted agents [21, 23]. For example, prostate cancer vaccines combined with immune checkpoint inhibitors are theoretically possible to improve clinical endpoints by recruiting and boosting tumor-specific T cells while improving their functional effector of cells [25]. It was interesting to see that immunotherapy sensitivity is higher in clear-cell ovary cancer as compared to other histological subtypes [25]. PARP inhibitors also have shown impressive efficacy for the treatment of ovarian cancer, with maximal benefit seen in BRCA mutated and homologous recombination deficient patients [26]. Combinations of immunotherapy with PARP inhibitors, tyrosine kinase inhibitors, and anti-angiogenic therapies are ongoing trials [26]. These combination approaches show promise, but their real impact and cost-effectiveness will need further research in the context of platinum-resistant ovarian cancer [26]. Continuing to define the precision use of immune checkpoint inhibitors in ovarian cancer requires our ability to identify predictive biomarkers and understand immune resistance mechanisms in this disease [26].

b. Cervical Cancer:

Proven therapies and ongoing clinical trials now explore combination strategies as immunotherapy for cervical cancer. FDA has recently approved pembrolizumab (an anti-PD-1 monoclonal antibody) for relapsed or metastatic PD-L1 positive cervical cancer as initial treatment after frontline chemotherapy [26]. And, as a monotherapy, its response rate is relatively low [27]. In 2011, bevacizumab, an anti-VEGF therapy, was approved for intractable melanoma, and showed encouraging results in cervical cancer trials [28].

Mixed clinical outcomes have been obtained. Pembrolizumab approval represents a milestone, but its use as a single agent is limited [27]. Therapeutic dendritic cell vaccine sipuleucel-T achieved a 4.1-month survival advantage in prostate cancer, and similar approach may be feasible in cervical cancer [24]. Enhancement of efficacy is being researched as a combination therapy. Combination strategies of PD-1/PD-L1 inhibitors with other immunotherapies or biotherapies are currently under study for their ability to improve antitumor efficacy [27]. Combinations of immune checkpoint inhibitors, PARP inhibitors, angiogenesis inhibitors, antibody drug conjugates, therapeutic vaccines and adoptive T cell therapies are being evaluated in ongoing trials [24, 25, 27, 28].

Finally, cervical cancer approved immunotherapies are limited, however, many combination approaches are in development. Overall, vaccines combined with immune checkpoint inhibitors are particularly interesting combinations [25, 28]. Strategies combining immunotherapy with standard chemoradiation are being studied to improve outcome for locally advanced disease [24, 28]. In the future as research progresses so does immunotherapy in cervical cancer treatment, it is hoped that this type of treatment will result in better outcomes for patients with advanced or disease recurrence.

c. Endometrial Cancer:

Endometrial cancer is now shown to be particularly responsive to immunotherapy, in particular, for microsatellite instability high (MSIH) tumors. Approval of an anti-PD-1 antibody (pembrolizumab) for advanced and recurrent endometrial cancer has been shown to have promising single agent activity in MSI-H tumors [24, 25]. But the success of the immune checkpoint inhibitors (ICIs) in MSS endometrial cancer as a single agent has been

disappointing [23].

Interestingly, combination therapies resulted in improved outcome for MSS endometrial cancer. It was indicated that in pembrolizumab resistant patients, the combination of lenvatinib (a VEGF inhibitor) and pembrolizumab showed efficacy [26]. Furthermore, a retrospective study reported that patients with ICI combinations with non-immunotherapy agents had both better progression free survival and overall survival compared to patients treated with ICI monotherapy or ICI only combinations [28].

Finally, immunotherapy, as a treatment for endometrial cancer, displayed promise for MSI-H tumors, but combination strategies are explored to improve efficacy in MSS tumors. One way to overcome resistance to ICI monotherapy exists with the lenvatinib-pembrolizumab combination. Future research will target the identification of biomarkers predictive of response to immunotherapy and novel combination approaches of immunotherapy to improve outcome of endometrial cancer patients [27, 28].

Table 1: Adoptive Cellular Therapy Clinical Trials in Gynecologic Malignancy

Trial Number	Category	Target	Pretreatment Conditioning	Immunomodulators
Ovarian Cancer				
03412526	TIL	broad	Fludarabine, Total body radiation (2 Gy)	IL-2
03158935	TIL	broad	Cyclophosphamide, Fludarabine	IL-2, Pembrolizumab
00101257	PBL - CD4	NY-ESO-1 reactive	NY-ESO-1	Cyclophosphamide
03318900	PBL - CD8 tetramer	PRAME	Cyclophosphamide	IL-2, Anti-CD137 (utomilumab)
03585764	CAR	Folate receptor	Cyclophosphamide, Fludarabine	–
03017131	TCR - CD8	NY-ESO-1	Cyclophosphamide	IL-2, Decitabine
02096614	TCR - CD8	MAGE-A4	Cyclophosphamide, Fludarabine	–
03691376	TCR - CD8, TCR - CD4	NY-ESO-1	Melphalan	IL-2, Decitabine, Hematopoietic stem cells (HSC)
Cervical Cancer				
03108495	TIL	broad	Cyclophosphamide, Fludarabine	IL-2
02111850	TCR - CD4	MAGE-A3	Cyclophosphamide, Fludarabine	IL-2
02379520	PBL – HPV-16/18 E6, E7 reactive	HPV-16, 18	Cyclophosphamide, Fludarabine	Nivolumab
Solid Tumors – including Ovary				
01174121	TIL	broad	Cyclophosphamide, Fludarabine	IL-2, Pembrolizumab

02876510	PBL - CD8 tetramer	8 targets, 12 HLA	Cyclophosphamide	IL-2, Atezolizumab
03054298	CAR	Mesothelin	Cyclophosphamide, Fludarabine	IL-2
02713984	CAR	HER2	Cyclophosphamide, Fludarabine	IL-2
02830724	CAR	CD70	Cyclophosphamide, Fludarabine	IL-2
02650986	TCR - CD8	NY-ESO-1	Cyclophosphamide	IL-2
03132922	TCR - CD8	MAGE-A3	Cyclophosphamide, Fludarabine	IL-2
03139370	TCR - CD4	MAGE-A3/A6	Cyclophosphamide, Fludarabine	IL-2
03412877	TCR - neoantigens	Neoantigens	Cyclophosphamide, Fludarabine	IL-2
Solid Tumors – including Uterine				
01174121	TIL	broad	Cyclophosphamide, Fludarabine	IL-2, Pembrolizumab
Solid Tumors – including Cervix				
02111850	TCR - CD4	MAGE-A3	Cyclophosphamide, Fludarabine	IL-2

Noted: TIL: tumor infiltrating lymphocytes, PBL: peripheral blood lymphocytes, CAR: chimeric antigen receptor, TCR: T cell receptor, IL-2: interleukin-2. Reference: https://clinicaltrials.gov, Accessed Oct 1 2024.

4. Emerging Immunotherapies and Clinical Trials

Several novel immunotherapy approaches are undergoing development that are revolutionizing cancer treatment. New checkpoint inhibitors, adoptive cell therapies, cancer vaccines, and bispecific antibodies all have a unique mechanism to harness the immune system against cancer [29, 30].

In particular, new checkpoint inhibitors targeting PD1, CTLA4, and TIM3 are being explored in acute myeloid leukemia (AML) [31]. In particular, chimeric antigen receptor T-cell (CAR-T) approaches have successfully employed adoptive cell therapies in many different malignancies [30, 31]. Antigen selection and delivery systems are being developed to generate de novo T cell responses against tumor antigens in cancer vaccines with ongoing efforts [32]. With encouraging clinical activity in non-Hodgkin's lymphoma and multiple myeloma, bispecific antibodies, in particular, bispecific T cell engagers (BiTEs), have been shown [32, 33]. Interestingly, although these new approaches appear promising, they are also beset by problems. For example, many of patients treated with immune checkpoint inhibitors do not benefit from clinical effects, and tumor response rates are heterogeneous among tumor types [32]. Secondly, cancer vaccines have not advanced clinically to the point of breakthrough clinical outcomes despite development because of resistance to immune suppression of the tumor immune microenvironment and identification of optimal vaccine candidates [33].

In oncology, especially, clinical trials are especially important in evaluating the efficacy and safety of new therapies in Phase II and III. There are 52 ongoing phase III clinical trials of antibody-drug conjugates (ADCs) in solid tumors, implying great potential for these targeted therapies [34]. Several solid tumors and cancer settings have shown encouraging results, and 8 out of 30 investigated ADCs have gained regulatory approval [34].

Yet, importantly, there is a high failure rate in phase III clinical trials in oncology, in particular. Less than one of

11 (9%) phase III studies in glioblastoma showed an improvement in overall survival and changed standards of care [34]. This suggests the need for more reliable Phase II trials and more rigorous Phase III predictions. It turns out that early phase results systematically overestimate subsequent phase III results, with an odds ratio of 1.66 for overall response rates for PD-1 or PD-L1 inhibitor trials [35].

Several strategies have been proposed to increase the success rate of the phase III trials. Included in these regards are the use of adaptive trial designs, Bayesian statistics, biomarkers, volumetric imaging, and mathematical modeling [32]. The phase II setting also requires optimizing and standardizing clinical trial design such that biomarkers are increasingly incorporated consistently for the optimal identification of promising therapeutic areas for phase III evaluation [33]. Together with robust donor screening, the use of biomarkers to select potent mesenchymal stromal cell (MSC) subpopulations and rigorous quality testing, the clinical efficacy of MSC products in immune and inflammatory conditions can be improved [36].

In conclusion, these novel immunotherapeutic approaches represent significant advancements in cancer treatment. Ongoing research focuses on refining these strategies, exploring combination therapies, and identifying biomarkers to predict treatment response [35]. As the field continues to evolve, these innovative approaches hold the potential to improve outcomes for patients with various malignancies, including those previously considered difficult to treat [36].

5. Challenges and Future Directions

Limitations have beset current cancer immunotherapies, including resistance mechanisms, problems associated with toxicity management, and the desire for more effective combinatorial and personalized therapies.

Major efforts are underway to develop more efficacious therapies but others have been met with challenges, including resistance to immunotherapies, with many patients either not responding to treatment or developing resistance over time [37, 38]. Often, the tumor microenvironment (TME) promotes therapy resistance through the generation of an immunosuppressive environment and may prevent the effectiveness of immunotherapeutic agents [39, 40]. Furthermore, the inaccessible nature of some tumors adds to the poor efficacy of treatment in some cases [41].

Another major concern in cancer immunotherapy is toxicity management. They also can cause severe impact to the quality of life, for example, immune-mediated toxicities that may be life-threatening as well [38, 39, 40]. These toxicity issues are due to contributory off-target side effects and poor pharmacokinetics of immunotherapeutic agents [37]. A significant concern of [37] is the risk of inducing autoimmune responses.

Personalized immunotherapy techniques and combinatorial approaches are being worked on to address these limitations. Some of this is believed to be possible when immunotherapy and nanotechnology are combined [40, 41]. Nanomedicine techniques, such as polymer micelles and biomimetic nanoparticles, have the potential to provide precise drug administration, increased bioavailability, and decreased toxicity [37, 38]. Immunotherapy in conjunction with more conventional treatments like radiation or chemotherapy may increase response rates and lessen adverse effects [42].

As a consequence, new personalized immunotherapy strategies are emerging to address the heterogeneity in the tumor responses [42, 43]. More tailored and effective cancer immunotherapies are becoming a reality through functional genomics analysis and immunogenomics [43]. These challenges, however, exist in the selection of appropriate combination therapies and the development of better biomarkers for personalized treatment [43].

6. Conclusion

This review highlights the pivotal role of immunotherapy in transforming the treatment landscape for gynecological

cancers. Key findings show that immune checkpoint inhibitors, such as pembrolizumab and nivolumab, have demonstrated efficacy in treating recurrent and advanced ovarian, cervical, and endometrial cancers, albeit with varying success across different cancer types. Pembrolizumab, for instance, has been FDA-approved for PD-L1-positive cervical cancer, representing a significant milestone. In ovarian cancer, immune checkpoint inhibitors have shown modest efficacy, especially in combination with other treatments, like PARP inhibitors. Endometrial cancer, particularly those with microsatellite instability (MSI-H), has been responsive to these treatments, though further research is required for microsatellite-stable (MSS) cancers.

Potential impact on gynecological cancer treatment: Immunotherapy's potential to improve survival rates and offer a better quality of life for patients, especially those with advanced or recurrent cancers, is substantial. The combination of immune-based therapies with chemotherapy, radiation, and other targeted therapies represents an exciting frontier in cancer treatment. The promise of personalized medicine is particularly compelling, as biomarkers like PD-L1 expression and BRCA mutations can guide therapy choices, optimizing treatment efficacy while minimizing side effects.

The success of adoptive cell therapies, such as CAR-T cells, in hematological malignancies suggests potential applications in solid tumors, including gynecological cancers. Although challenges remain in terms of tumor heterogeneity and immune resistance, ongoing clinical trials are investigating these therapies' efficacy in ovarian and endometrial cancers. Furthermore, therapeutic vaccines targeting HPV for cervical cancer and tumor antigens like WT1 and mesothelin for ovarian and endometrial cancers offer new treatment possibilities.

The future outlook for immunotherapy: The future of immunotherapy in gynecological cancers looks promising but hinges on overcoming current limitations, including resistance to immune checkpoint inhibitors and challenges in patient response variability. Combination therapies, particularly those involving immune checkpoint inhibitors with PARP inhibitors, chemotherapy, and angiogenesis inhibitors, are likely to dominate the future of treatment for these cancers. Additionally, the identification of predictive biomarkers will play a crucial role in advancing personalized immunotherapy, allowing for tailored treatments that maximize effectiveness for individual patients. Further research and larger clinical trials are necessary to validate the efficacy of these therapies across broader patient populations. The development of next-generation immunotherapies, including bispecific antibodies and advanced cancer vaccines, also holds great promise. As these innovative treatments evolve, they are expected to significantly improve outcomes for patients with gynecological cancers, particularly those who have few options left under traditional treatment paradigms. The ultimate goal is to enhance the longevity and quality of life for patients while continuing to refine and optimize immunotherapeutic strategies.

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