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Leveraging Immunotherapy for the treatment of Gynecologic Cancers in the Era of Precision Medicine

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Abstract

During the past decade significant progress in the understanding of stimulatory and inhibitory signaling pathways in immune cells has reinvigorated the field of immuno-oncology. In this review we outline the current immunotherapy based approaches for the treatment of gynecological cancers, and focus on the emerging clinical data on immune checkpoint inhibitors, adoptive cell therapies, and vaccines. It is anticipated that in the coming years biomarker-guided clinical trials, will provide for a better understanding of the mechanisms of response and resistance to immunotherapy, and guide combination treatment strategies that will extend the benefit from immunotherapy to patients with gynecologic cancers.

Keywords

Immunotherapy; Ovarian Cancer; Cervical Cancer; Endometrial Cancer; Gynecologic cancers; Checkpoint Inhibitors; Immuno-oncology

Introduction

The immune system plays a key role in eliminating and controlling early tumor growth [1, 2]. Recognition and elimination of tumors by the immune system involves a series of steps coordinated by the various parts of the innate and adaptive immune system. The immune recognition of cancer begins at the tumor site, where fragments of malignant cells get taken up by professional antigen-presenting cells (APC) such as dendritic cells (DC). Activation of DCs in turn requires several maturation signals, which are in part provided by the “danger” signals released from the dying tumor cells, known as damage-associated molecular patterns (DAMPs) [3]. Following activation, APCs migrate to tumor-draining lymph nodes, where they present tumor-associated antigens (TAAs) in the form of antigenic peptides bound to

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Conflicts of Interest

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the major histocompatibility complex (MHC) class I and II molecules. This enables antigen recognition by antigen-specific CD4 and CD8 T cells. In addition to recognition of specific antigenic peptides bound to MHC, activation of T cells requires another immunostimulatory signal, which is provided by engagement of a co-stimulatory receptor such as CD28 on the surface of T cells [4]. Activated T cells then migrate to tumors through the systemic vasculature by following a chemokine gradient [5, 6] and extravasate through a series of interaction with adhesion molecules in the tumor endothelium [7]. Finally, recognition of tumor targets proceeds through interaction between the T cell receptor (TCR) and specific antigenic tumor peptide bound to MHC, ultimately leading to T-cell mediated tumor destruction.

Starting with the process of antigen presentation, tumors have evolved a variety of resistance mechanisms that allow for successful escape from immune recognition and elimination [8]. Hence, immunotherapeutic approaches aim to improve recognition of tumors by the immune system and to inhibit the mechanisms of immune escape. Many of these approaches have been explored in gynecologic malignancies, with recent data demonstrating promising activity in various tumor types. Here we will discuss several examples of such modalities, primarily focusing on the more recently reported studies, though the list is certainly not exhaustive and multiple other approaches could be considered to be applicable. With emerging data, it is likely that a combination of several different modalities will be needed for optimal activation of anti-tumor immunity and therapeutic efficacy.

I. Immunotherapy of ovarian cancer

Epithelial ovarian cancer (EOC) is the fourth most common cancer in women and accounts for the highest number of gynecologic cancer deaths. Although EOC has not been traditionally considered a type of cancer that would be amenable to immunotherapy, multiple lines of evidence have demonstrated that the immune system likely plays a key role in eliminating and controlling ovarian cancer growth. In particular, the presence of tumor-infiltrating lymphocytes (TILs) has emerged as an important prognostic biomarker in EOC, with increased number of TILs predicting longer survival [9, 10]. Tumor-reactive antibodies and T cells have been demonstrated to be present in the peripheral blood of EOC patients [11, 12], and oligoclonal tumor-directed T cells have been directly isolated from the tumors and ascitic fluid [13–20].

Based on these findings, several immunotherapeutic strategies have been explored in EOC. These approaches can be broadly subdivided into three categories: 1) Direct targeting of tumors with tumor-specific antibodies; 2) modalities that aim to enhance antigen presentation, such as vaccines, toll-like receptor (TLR) agonists, and oncolytic viruses, and 3) strategies focusing on activation of tumor-specific T cells, either through direct adoptive transfer or by targeting of activating and inhibitory pathways in T cells and tumor microenvironment.

A. Targeting of ovarian tumors with tumor-specific antibodies—Antibodies targeting surface antigens have been demonstrated to be effective against different cancer types [21, 22]. While some of these agents target tumor driver pathways (e.g. trastuzumab

and cetuxumab), some in addition mediate antibody-dependent cellular cytotoxicity (ADCC), allowing for recognition of the antibody-labeled cancer cells with immune effectors, such as natural killer cells. In ovarian cancer, however, such strategies have been more elusive, likely secondary to lack of an optimal surface antigen. Indeed a 2014 Cochrane review of trials in ovarian cancer using antigen-specific targeting failed to establish a conclusive evidence for efficacy of such strategies in EOC [23].

CA-125: The extensive expression of CA125 and its cell-surface precursor MUC16 in the majority of ovarian carcinomas prompted several trials targeting CA125 [24–26]. Oregovomab, an antibody targeting CA-125 has been evaluated in several studies, with early studies demonstrating the development of anti-CA-125 T cell responses [27–29]. However, a randomized placebo-controlled phase III trial in patients with advanced EOC in first clinical remission failed to demonstrate benefit to oregovomab therapy, with no significant difference between the placebo and oregovomab groups [30].

EpCAM: Epithelial cell adhesion molecule (EpCAM) is a surface integrin receptor commonly overexpressed on cancer cells and appears to be associated with worsened prognosis in ovarian cancer [31]. Catumaxomab is a bispecific antibody recognizing EpCAM and T cell antigen CD3. In addition, catumaxomab possesses an ADCC-mediating Fc region, making it a trifunctional antibody. Catumaxomab mediates anti-tumor effect through two different immune mechanisms: via recruitment and activation of T cells to the EpCAM expressing tumor cells and via binding to Fc receptor-expressing effectors such as NK cells. In a phase II/III trial randomizing patients with advanced cancer with malignant ascites to standard paracentesis or paracentesis with intraperitoneal catumaxomab, catumaxomab delayed ascited re-accumulation, but had no impact on overall survival [32]. A variation on this strategy has been recently developed using bispecific T cell engagers (BiTE) recognizing EpCAM and CD3. This strategy has been demonstrated to be effective in xenograft models of human colorectal and ovarian cancer [33]. More recently, in preclinical models of ovarian carcinoma, a novel EpCAM-CD3 BiTE solitomab has demonstrated significant activity against human ovarian tumor cells *in vitro* and *ex vivo* [34, 35].

FRa: Folate receptor alpha is expressed in high frequency in epithelial ovarian cancer [36]. Farletuzumab, a monoclonal ADCC-mediating antibody against folate receptor alpha, was evaluated in several studies, with earlier studies demonstrating promising efficacy [37, 38]. Despite these findings, later larger studies in combination with chemotherapy in platinum-sensitive and resistant patients, however, failed to meet the primary endpoints (NCT00849667, NCT00738699). More recently, data from phase I study using IMGN853, a folate receptor alpha targeting antibody-drug conjugate in patients with FRa positive epithelial ovarian cancer and other Fra positive solid tumors demonstrated clinical benefit rate of 25–33% depending on schedule, with responses seen in different treatment schedule groups [39]. While this strategy is certainly promising, it is unclear whether there is any contribution of the immune system to the observed effect and further studies would be needed to answer this question.

B. Enhancement of recognition of tumor antigens by the immune system

Vaccines: Several different vaccination approaches have been explored in ovarian cancer [40–44]. Those include simple vaccine preparations consisting of specific peptides and proteins, as well as more complex strategies, such as engineered cellular vaccines, DC vaccines, virus-vectored vaccines, and oncolytic viruses [45–54]. A comprehensive review of different vaccination strategies that have been explored in ovarian cancer is published elsewhere [55]. The majority of the vaccines have focused on using cancer-testis antigens (e.g. NY-ESO-1), and proteins known to be overexpressed in EOC (e.g. p53, survivin, MUC1). In general, while the majority of the studies demonstrated evidence of cellular and antibody response to the antigens, clinical benefit afforded by vaccination has unfortunately been marginal at best. Since most of the strategies have relied on self-antigens, it is likely that vaccination alone is not sufficient to overcome the T cell tolerance and combinatorial therapies may be necessary. Indeed, studies in preclinical models indicate that combination of vaccines with immune checkpoint blockade result in enhancement over either approach alone [56–63], thus generating rationale for exploration of similar strategies in human trials.

TLR agonists: Toll like receptors (TLR) are a class of proteins recognizing signature molecules that are broadly shared by various pathogens, and play a role in the innate immune response and tumor antigen processing and presentation by APC. Ligands for various TLRs are actively being explored as anti-cancer agents and there is a rationale for using such ligands in ovarian cancer [64]. VTX-2337 (motolimod) is a small molecule agonist of TLR8, which stimulates a strong innate immune response. VTX-2337 has been evaluated with systemic administration in combination with liposomal doxorubicin in animal models and in phase I study in patients with advanced ovarian cancer. The combination appeared to be safe, with evidence of immune activation and clinical benefit [65]. A phase 2 study evaluating motolimod in combination with liposomal doxorubicin is ongoing (NCT01666444). Another phase 1/2 study using combination of motolimod with liposomal doxorubicin and anti-PD-L1 antibody MEDI4736 is upcoming (NCT02431559).

Type I IFN: Type I IFN is an innate immune response cytokine, which plays a role in antiviral immune response. In addition, recent studies have demonstrated a critical role for the type I IFN pathway in anti-tumor immune response [66, 67], where type I IFN was demonstrated to be indispensible for tumor antigen cross-presentation by dendritic cells. Studies with systemic or intraperitoneal IFNα in patients with EOC failed to demonstrate significant efficacy, while often being associated with frequent dose-limiting toxicity [68–70].

Oncolytic viruses: Although not initially thought of as immunotherapeutic agents, with evolving understanding of the interplay between oncolytic viruses and the immune system, came the recognition that virus-induced anti-tumor immune response, rather than direct tumor lysis, may be a dominant player driving the efficacy of these therapies. Several trials with intraperitoneally-administered oncolytic viruses have been conducted in ovarian cancer [71–82]. In the majority of the studies, the treatment was well tolerated and while responses were rare, a good percentage of patients demonstrated stable disease, which was often durable. These studies suggest that intraperitoneal oncolytic viruses present a viable

therapeutic strategy in ovarian cancer, though for optimal efficacy their evaluation in combination with other modalities (e.g. chemotherapy, other immunotherapies) is likely warranted.

C. Activation of tumor-specific T cells

Cytokines: IL-2 is a T-cell growth factor, which is FDA approved for treatment of renal cell cancer and malignant melanoma [83, 84]. IL-12 is a cytokine mainly produced by activated monocytes, tissue macrophages, and B cells. It can induce IFN-γ and together with IL-2 becomes a potent activator of cytotoxic T lymphocytes and NK cells [85, 86]. While both cytokines are associated with significant toxicity with systemic administration, the toxicity appears to be lower with locoregional (e.g. intraperitoneal) administration. A phase 1–2 study of IP IL-2 in patients with persistent or recurrent ovarian cancer had shown an overall response rate of 25.7%, with an overall 5-year survival probability of 13.9% [87]. As a different strategy, IL-12 expressing plasmid DNA was evaluated in patients with malignant melanoma with patients showing promising responses with intratumoral injection and electroporation [88, 89]. In ovarian cancer, an IP-administered IL-12-expressing plasmid was evaluated in combination with chemotherapy, and appeared to be well-tolerated, though responses did not exceed what would be expected with chemotherapy alone [90]. A subsequent study evaluated intraperitoneal EGEN-001, an IL-12 plasmid formulated with lipopolymer in patients with persistent or recurrent ovarian cancer. In this study of 22 patients, 35% had stable disease [91].

Immune checkpoint blockade: Activation of tumor-specific T cells requires binding of the T cell receptor to the tumor-specific antigen peptide presented by major histocompatibility complex (MHC) class I and II molecules on the surface of APC. In addition to recognition of cognate MHC-peptide complex, there is a requirement for another immunostimulatory signal, which is provided by activation of a co-stimulatory receptor such as CD28 on the surface of T cells [4]. In addition to CD28, T cells express a wide repertoire of other co-inhibitory and co-stimulatory receptors, which integrate a complex immune signaling network regulating T cell activation, differentiation, survival, and effector function [4]. Targeting of such receptors demonstrated significant activity in pre-clinical models and in early clinical trials [92]. The CTLA-4 and PD-1 inhibitory immune checkpoint blocking antibodies are the most advanced in clinical development and were recently approved by the FDA for treatment of metastatic melanoma [93, 94]. Based on these findings, therapy with immune checkpoint blockade (ICB) is being evaluated in preliminary trials in patients with EOC. A recent phase II study of Nivolumab in platinum resistant ovarian cancer patients showed response and disease control rates of 15 and 45%, respectively, including two patients with a durable complete response [95].

-CTLA-4: The CTLA-4- blocking antibody ipilimumab was the first immune checkpoint blocking antibody that has entered clinical testing and has an FDA-approved indication for treatment of metastatic melanoma on the basis of survival benefit demonstrated in a phase III study[93]. In eleven patients with ovarian cancer, who previously received autologous tumor cell vaccine expressing GM-CSF (GVAX), treatment with ipilimumab led to an objective response in one patient, which was durable for over 4 years [96].

-PD-1/PD-L1: A rationale for targeting PD-1/PD-L1 pathway in gynecologic malignancies was initially demonstrated in a phase I study of anti-PD-L1 antibody in patients with advanced cancer, which included 17 patients with ovarian cancer [97]. Of the ovarian cancer cohort, 22% of the patients had evidence of objective response or stable disease, lasting at least 24 weeks [97]. Preliminary clinical data have now in addition been reported for the EOC patients treated with PD-1 blocking drugs nivolumab and pembrolizumab, as well as PD-L1 blocking antibody avelumab. In a phase I study of nivolumab in 20 EOC patients, best overall response was 15%, including 2 patients with durable CR, with a total disease control rate of 45% [95]. In a phase Ib open-label expansion trial of avelumab in 75 patients with recurrent or refractory ovarian cancer, efficacy data from the first 23 patients demonstrated PR in 4 patients (17%), stable disease in 11 patients (48%), and 2 patients with PR after initial progression. In a phase I study of pembrolizumab in 26 ovarian cancer patients selected for PD-L1 positivity, the drug demonstrated activity with one patient with CR, 2 patients with PR, and 6 patients with stable disease. In all studies, the drugs were very well tolerated [95, 98, 99]. Based on these studies PD-1/PD-L1 blockade thus demonstrates promising activity in advanced ovarian cancer patients and larger studies are currently underway.

The development of CTLA-4 and PD-1/PD-L1-targeting antibodies has provided for an opportunity for evaluation of combinations of these agents, which resulted in additive or even synergistic activity in animal models of melanoma and ovarian cancer [100, 101] and in phase I dose escalation studies in metastatic melanoma and renal cell carcinoma [102, 103]. In melanoma, combined CTLA-4 and PD-1 blockade with ipilimumab and nivolumab, respectively, was recently demonstrated to enhance response rate and PFS in comparison to either agent alone, although with increased toxicity [104]. To determine whether addition of CTLA-4 blockade would increase therapeutic efficacy in EOC, there is an ongoing NRG Oncology Group randomized phase II study comparing the combination of nivolumab and ipilimumab to nivolumab alone in patients with relapsed EOC (NCT02498600).

D. Adoptive T cell therapies—Adoptive cell therapies (ACT) aim to overcome the immunosuppressive effect of tumor microenvironment through infusion of large numbers of autologous tumor-reactive T cells that have been expanded from tumor infiltrating lymphocytes (TILs) in vitro. Significant activity of such therapies have been reported in patients with metastatic melanoma [105]. Two trials have evaluated the efficacy of adoptive cell therapy in ovarian cancer with evidence of clinical benefit seen in the majority of the treated patients [106, 107]. These studies are obviously biased by selection of the patients from whom sufficient amount of TILs could be isolated, as patients with high numbers of TILs would be expected to have a more favorable prognosis. Additional studies using TIL ACT in ovarian cancer are ongoing (NCT02482090, NCT01883297).

Engineered T cells present an alternative strategy that avoids the need to isolate a sufficient number of TILs. Using this strategy, autologous lymphocytes isolated from peripheral blood are transduced either with a T cell receptor recognizing a specific tumor antigen within the context of MHC, or with a chimeric antigen receptor (CAR) recognizing a tumor-associated surface antigen [108]. Preclinical studies demonstrated that targeting of MUC16 with engineered T cells expressing a MUC16-specific CAR could induce complete eradication of

orthotopic ovarian xenografts [109, 110], and a phase I study targeting MUC16 with CAR T cells is upcoming [111] (NCT02498912). It is conceivable that any antigens expressed on the surface of ovarian cancer could be targeted with these strategies, and studies are currently underway using T cells targeting differentiation proteins such as folate receptor alpha [112], and mesothelin (NCT01583686), and cancer testis antigens such as NY-ESO-1 (NCT01567891, NCT02457650).

While ACT, including engineered T cells, have demonstrated significant promise against several tumor types, they can be associated with significant toxicities, which include cytokine release syndrome (CRS) and toxicities from 'on target, off tumor' recognition [108]. CRS, resulting from activation of the infused tumor-specific T cells, can lead to a range of clinical toxicities, including fever, hypotension, hypoxia, and neurologic toxicities, and requires prompt recognition and treatment with steroids or anti-interleukin-6 receptor antibody tocilizumab [113, 114]. On target toxicities include recognition of normal tissues expressing the tumor antigen, and can lead to severe toxicities which have been fatal in some instances [115]. Engineering of additional safety features such as suicide genes into T cells may provide a safety switch and will likely be required in future studies exploring tumor antigen targets that are also expressed on normal tissues.

E. Other immunotherapeutic modalities on the horizon for ovarian cancer

Antibodies targeting co-stimulatory receptors: In addition to the antibodies targeting CTLA-4 and PD-1/PD-L1, antibodies to other T cell co-stimulatory and co-inhibitory receptors are currently in development. Amongst those are the agonistic antibodies targeting activating T-cell surface receptors (e.g. anti-GITR, anti-OX40) as well as other blocking antibodies to the inhibitory receptors on T-cells and NK cells (e.g. anti-LAG3, anti-KIR) (NCT01968109, NCT02061761, NCT01750580, NCT01714739, NCT01239134) [92]. Some of the studies are using combination of these drugs with PD-1/PD-L1 blocking antibodies, with the aim of reversal of T cell dysfunction or enhancement of T cell activation.

Targeting mechanisms of immunotherapy resistance: Several inhibitory mechanisms that play a role in immune evasion have been demonstrated to be associated with poor prognosis in ovarian cancer, including increased tumor-infiltrating regulatory T cells (Tregs) [10, 116, 117] and tumor-associated macrophages with an M2-immunophenotype (CD163+/CD68+) [118, 119], and expression of the immune inhibitory ligands such as PD-L1, B7-H3, and B7-H4, and of the inhibitory enzyme indoleamine 2,3-dioxygenase (IDO) by the tumor or stromal cells [120–123]. Drugs targeting these mechanisms are currently being explored against solid tumors, including ovarian cancer.

Depletion or inhibition of the immunosuppressive cells in the tumor microenvironment has the potential to enhance the efficacy of immunotherapies. In animal models, combination of CTLA-4 blockade and depletion of regulatory T cells with anti-CD25 antibody resulted in improved therapeutic efficacy of CTLA-4 blockade [124]. Strategies targeting CD25 in humans with daclizumab [125] or denileukin diftitox (Ontak) [126] have also been evaluated, though benefit so far has been demonstrated to be marginal, likely because CD25

is not a marker specific for regulatory T cells and is also expressed on activated T effector lymphocytes. An anti-CCR4 antibody has been demonstrated to selectively deplete regulatory T cells from humans [127, 128], and a phase I study of the anti CCR4 antibody mogamulizumab in patients with solid tumors is currently ongoing (NCT01929486). In separate studies, mogamulizumab is being explored in combination with PD-L1 blocking antibody MEDI4736 and CTLA-4 blocking antibody tremelimumab (NCT02301130) and anti-PD-1 antibody nivolumab (NCT02476123).

In support of the immunosuppressive role of the myeloid cells in tumor microenvironment, study by Zhu et al. recently used a mouse model of pancreatic ductal adenocarcinoma to demonstrate that depletion of MDSC with CSF1 receptor antibody synergizes with PD-1 and CTLA-4 blockade [129]. A CSF1R- targeting antibody emactuzumab (RG7155) has been evaluated in patients with advanced solid tumors. Treatment with antibody led to depletion of tumor associated macrophages, with partial metabolic responses and disease stabilization seen in 5/44 and 6/40 patients respectively [130]. A phase Ib study of emactuzumab in combination with anti-PD-L1 antibody MPDL3280A in solid tumors including ovarian cancer is ongoing (NCT02323191). PLX3397, a small molecule inhibitor of CSF1R and c-kit is currently being evaluated in combination with paclitaxel (NCT01525602), as well as anti-PD-1 antibody pembrolizumab (NCT02452424) in patients with advanced solid tumors.

II. Immunotherapy for Endometrial Cancer

Endometrial cancer is the most common gynecologic malignancy in developed countries. While hysterectomy alone results in excellent cancer-related outcomes for patients with grade 1 and 2, low stage endometrioid tumors, the prognosis for patients with advanced stage disease and high risk histological subtypes remains poor. The normal human endometrium can be viewed as having the unique immunological roles of serving as a barrier to ascending infections from the female genital tract, and at the same time, harboring an immunosuppressive state that is crucial to gestation and fetal development. Despite this long recognized dual function our knowledge of the immune function of the endometrium and its alterations in malignant an premalignant states is remarkably incomplete [131].

Until recently, immunotherapy approaches used in the treatment of endometrial cancers have been largely limited to small series of patients with dendritic cell vaccines and related approaches [132–134]. Not surprisingly, the recent success of immune checkpoint inhibitors in melanoma and other cancers has led to the investigation of these agents in endometrial cancers. Of particular interest is the fact approximately 20–30% of endometrial cancers are characterized by high microsatellite instability (MSI-H) due to genetic or epigenetic defects in components of the DNA mismatch repair pathway. These defects results in a high somatic mutation load and accordingly increased number of neoantigens in these MSI-H tumors [135, 136]. In colon cancer, MSI-H tumors have been shown to be more immunogenic with increased infiltration of immune cells and increased immune checkpoint expression[137, 138]. A recently published phase 2 study of pembrolizumab (an anti-PD-1 antibody) demonstrated object response rates of 40 and 71% in MSI-H colorectal and non-colorectal cohorts (which included 2 patients with endometrial cancer), respectively[139]. This same study found no responses in patients with microsatellite stable colorectal tumors (0 out of

18). Additionally, a third arm of the study was composed of non-colorectal MSI-H tumors, including two endometrial cancer cases. This group also showed improved objective response rate and progression free survival [139]. These results have generated great interest for clinical testing of immune checkpoint inhibitors in other MSI-H tumors including endometrial cancer.

Mutations in the replicative DNA polymerase epsilon (POLE) define another subset of highly immunogenic endometrial cancers characterized by ultra-high somatic mutations rates resulting from defects in the proof-reading function of this polymerase [136, 140, 141]. Approximately 5% of endometrial cancers are characterized by POLE mutations [142]. These tumor are predominantly endometrioid, grade III, and associated with peritumoral and tumor infiltrating lymphocytes [143]. POLE mutated tumors were reported to have the highest number of predicted neoantigens per tumor sample, followed by MSI-H tumors, and microsatellite stable tumors [136]. In addition, POLE and MSI-H tumors exhibited higher numbers of CD8+ TIL which were characterized by PD1 overexpression [136]. Taken together, these results provide a strong rationale for clinical investigations of checkpoint inhibitors and other immunotherapeutic approaches in endometrial cancers harboring the POLE ultramutated phenotype.

Other endometrial cancer immunotherapy targets currently under investigation include tissue factor (TF) [144], human trophoblast-cell-surface marker (Trop-2) [145], and survivin [146]. These targets are still in the preclinical or early clinical development with encouraging results.

III. Immunotherapy for cervical cancer and other HPV-related Gynecological Malignancies

Cervical cancer is unique among gynecologic malignant tumors because of its well-established and causative risk factor, chronic HPV infection. HPV, a double-stranded circular DNA virus, is the most common sexually transmitted infection, and it is estimated to infect 75–80% of women at one time or another during their lives [147]. The vast majority of HPV infections are cleared by the immune system, but a small fraction become chronic and result in cervical dysplasia and carcinoma. Over 170 HPV subtypes have been identified. However, HPV-16 and HPV-18 are the genotypes most commonly associated with cervical cancer, accounting for approximately 70% of invasive cervical cancers [148].

The infectious etiology of cervical cancer has led to the development of effective preventative vaccines. Discussion of preventative vaccines is beyond the scope of this review and interested readers are referred to excellent recent reviews [149, 150]. Despite the excellent potential for prevention, advanced stage/metastatic disease remain a principal cause of gynecologic cancer mortality in much of the world where there is limited access to vaccination and screening. Thus improved approaches for treatment of advanced cervical cancer including immunotherapy remain high clinical priorities.

Cervical cancer directed immunotherapies can be divided into several subtypes including therapeutic vaccines, immune checkpoint inhibitors, and adoptive cell therapies. These are briefly highlighted below.

A. Therapeutic vaccines—The success of preventative immunization has raised hopes for the successful development of a therapeutic vaccines. However, important differences between the two approach exist. To be effective prophylactic vaccines need only to block viral entry into cervical epithelial cells. In contrast, therapeutic vaccines must target integrated HPV virus that has become intracellular and is characterized by a non-lytic cycle. The main targets of therapeutic vaccine development have been HPV E6 and E7 proteins, since they are continuously expressed by infected cells and necessary maintenance of the malignant phenotype [151]. Targeting E6 and E7 has been accomplished using a number of different approaches including peptides, fusion proteins, and recombinant modified vaccinia and Listeria based vaccines [152, 153]. While a detailed discussion of these approaches is beyond the scope of this review, some of the main clinically relevant findings are briefly outlined below.

Vaccinia based vaccines: Modified vaccinia virus Ankara (MVA) is a double-stranded DNA virus derived from a Turkish smallpox vaccine strain. It is unable to replicate in most mammalian cells, has an excellent safety profile in humans, and can be genetically engineered to express foreign proteins [154]. MVA vaccines induce both humoral and cellular immune responses against the expressed foreign antigen. Vaccinia virus expressing the E6 and E7 proteins of HPV 16 and 18 has been developed and used for the treatment of HPV related intraepithelial neoplasia [155, 156]. In a study that included nearly 1200 women, subjects were injected with 10^7 virus particles directly into the dysplastic area (cervix, urethra, vulva, or anus). Complete elimination of the lesion was observed in 89.3% of patients and 83% had undetectable HPV DNA after treatment [155].

Listeria based vaccines: Similar to the vaccinia approach, Listeria monocytogenes (Lm) based vaccines use a genetically modified non-pathogenic form of this bacterium to present specific proteins/antigens to the immune system. ADXS11-001, is a vaccine designed to induce an immune response against HPV E7 [157]. The efficacy of ADXS11-001 against HPV-related human cervical, oropharyngeal and anal cancers is under evaluation in several ongoing clinical trials [158].

Peptide and protein vaccines: Peptide based-vaccines targeting HPV E6 and E7 [159] and non-HPV tumor associated antigens [160] are undergoing clinical testing. An alternative approach is the use of a Mycobacterium bovis heat shock protein (HSP65) linked to the entire HPV16 E7 sequence [161, 162]. Studies on high grade cervical intraepithelial neoplasia (CIN) have shown some complete responses, but due to the single arm design, the results are confounded by the potential for spontaneous regression [161, 162]. Another investigation using HPV16 E6 and E7 synthetic long peptide vaccine reported a complete clinical response in 47% of patients with VIN III [163].

Other vaccine approaches: Investigations using a number of other vaccine approaches targeting cervical cancer have been reported. These include genetically modified CEA expressing yeast, “naked DNA” constructs encoding E6–E7 [164–166] and dendritic cell vaccines [167–169]. However, most of these are either in early clinical development or have yet to demonstrate significant clinical responses.

B. Immune checkpoint inhibitors—Recent studies have provided support for a potential role for immune checkpoint inhibitors in the development and spread of cervical cancer. PDL1 expression was observed in 95% of CIN and 80% of squamous cell carcinomas, but undetectable in normal cervical epithelial cells [170]. Furthermore, lymph nodes harboring metastatic cervical cancer were found to be characterized by high levels of PDL1+ APCs and FOXP3+ regulatory T cells (Tregs) [171]. The PD-1: PD-L1 pathway has also been implicated in mediating immune-resistance in HPV-associated head and neck squamous cell cancers [172]. Hence, there is accumulating evidence suggesting a potential therapeutic benefit for checkpoint inhibitors in cervical and other HPV related cancers.

In cervical cancer, CTLA4 directed therapy with ipilimumab after chemoradiation is in Phase I clinical trial evaluation (NCT01711515) in patients with locally advanced or metastatic cervical cancer. In addition several other trials using agents targeting the PDL1-PD1 pathway (including a phase II GOG/NRG sponsored study (NCT02257528)) are targeting patients with advanced or recurrent cervical and head and neck cancers (clinicaltrials.gov).

C. Adoptive T cell therapies—HPV-reactive T cells can be be isolated and expanded from patients' peripheral blood and tumor tissue [173, 174]. Stevanovic and colleagues recently showed that adoptive cell therapy using tumor infiltrating lymphocytes (TIL) resulted in two partial and one complete responses among the nine patients with heavily treated recurrent metastatic cervical cancer included in this cases series [173]. Of note, HPV reactivity of TIL correlated positively with clinical response, although the small number of cases precludes any definitive conclusions.

Adoptive cell therapy is one of the most rapidly evolving fields among immunotherapies, and there is significant research aimed at designing antigen specific engineered T cell receptors (TCRs) and chimeric antigen receptors (CARs). An NCI sponsored trial of adoptive cell therapy using an E6 targeting TCR (NCT02280811) is currently accruing.

IV. Immunotherapy of other Gynecologic Cancers

There is a relative paucity of data on potential immunotherapeutic targets in rarer gynecologic cancers such as sarcomas, GTN, low grade serous ovarian cancer, and malignant sex-cord stromal ovarian tumors. However, the basic immunotherapy concepts of enhancing immune recognition and activation and blocking immune-inhibitory pathways are likely to apply to these tumors as well.

Conclusions

The advances in understanding of genetics, tumor microenvironment, and interaction of tumors with the immune system in gynecologic malignancies provide compelling evidence that these cancers are not immunologically inert and generate a strong rationale for immunotherapeutic approaches. While many of such approaches have demonstrated significant promise in different tumor types, including gynecologic cancers, the benefit afforded by these treatments has so far been limited to only a subset of patients. Such challenges in immunotherapy logically call for identification of targetable markers

predicting better response and development of rational combinatorial approaches. Data from preclinical studies indicate that combinatorial modalities targeting different parts of the immune response (e.g. vaccines and immune checkpoint blockade) result in improved therapeutic efficacy and early clinical studies indeed indicate that such approaches can indeed be more effective. Combined immune checkpoint blockade such as CTLA-4/PD-1 blockade has already demonstrated evidence of superior activity in metastatic melanoma and certainly warrants evaluation in gynecologic cancers. One must take these findings with a word of caution, however, as the side effect profile in patients with advanced gynecologic cancers may be different and might not justify the potential benefits. Furthermore, the significant toxicities reported from the combination regimens such combined CTLA-4/PD-1 blockade would make it challenging to build further treatment combinations based on this platform [104]. To address these problems it is becoming increasingly evident that the efficacy of specific therapies and combinations will likely not be universal and that the choice of a treatment modality may need to be tailored to fit the needs of each individual patient. Through biomarker-guided clinical trials, we'll be able to better understand the mechanisms of response and resistance to immunotherapy and develop treatment strategies that will extend the benefit from immunotherapy to a broader range of patients and tumor types.

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