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Review Article

IMMUNOTHERAPY IN ENDOMETRIAL CANCER

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ABSTRACT

Endometrial carcinoma is the most prevalent gynecologic malignancy in many countries, with a rising incidence and mortality in the last decades. Despite that, discovery of new therapies has shown little progress in recent years. Currently, immunotherapy is considered the oncologic milestone in the treatment of several tumors, and there is evidence to present a reasonable response in endometrial cancer mainly in a subgroup with immune microenvironment amplified and a high mutation rate. To date, several trials have been conducted exploring the role of Adoptive Cellular Therapy, Bispecific T-Cell Engager antibodies, immune-modulating agents and other Immunotherapy targets in patients with endometrium cancer with promising results. This review focuses on the evolving paradigm of immunotherapy in the treatment of endometrial cancer, describing the biologic basis, the importance of the molecular classification and the main modalities of immunotherapy studied until now. Immunotherapy represents an encouraging therapeutic in the treatment of endometrial cancer. Additional investigation is required to identify immune targets and predictors of response, allowing for the selection of patients most likely to benefit from immunological treatment.

Keywords: Endometrial neoplasms, Immunotherapy, Vaccines, CAR T-Cell, T-Cell-Engaging antibody, Immune checkpoint.

INTRODUCTION

Endometrial cancer (EC) is currently the most common gynecologic malignancy in developed countries and the second in low- and middle-income countries. Worldwide, more than 320,000 women per year are diagnosed with EC (Torre, *et al.*, 2012). While the majority of the patients are diagnosed at an early stage, approximately 27% have positive regional organs, lymph nodes or distant metastases at diagnosis (http://seer.cancer.gov/statfacts/html/corp.html). Patients with advanced disease or recurrent EC have very limited treatment options and a poor prognosis, and there is an urgent need for new therapies in this clinical context.

EC is a complex and heterogeneous disease from epidemiologic, pathological, molecular and clinical points of view. Recently, the Cancer Genome Atlas (TCGA) defined four clinically distinct EC types based on their overall mutational charge, specific p53, POLE and PTEN mutations, microsatellite instability (MSI), and histology (Cancer Genome Atlas Research Network, 2013). The current classification reflects both histopathologic and genomic features, which may help to tailor treatment. POLE mutant and MSI-high subtypes present a robust immune response. Tumor infiltrating lymphocytes (TIL) and peri-tumoral lymphocytes usually overexpresses PD-1 and PD-L1 in POLE and MSI tumors, what may explain their better prognosis compared to low and high copy number subtypes, aside from creating a rationale for immunotherapy development.

This review focuses on the role of immunotherapy in EC, analyzing its rationale and the available clinical data, and discussing hurdles and perspectives in this scenario.

RATIONALE OF IMMUNOTHERAPY IN ENDOMETRIAL CANCER

The innate and adaptive immune system at the female reproductive tract is a complex that is governed by the hormonal status modified according to the menstrual cycle. Hormonal fluctuations and interactions with immune system result in a protection environment against the invasion of pathogens and disease prevention while creating a favorable environment for embryonic implantation and fetal development (Vanderstraeten, *et al.*, 2015 and Wira, *et al.*, 2014). Obesity, which is related to an increased risk of developing EC, is considered to be a chronic inflammatory state, causing increased release of pro-inflammatory cytokines such as IL-6 and C-reactive protein (CRP) (Visser, *et al.*, 1999). In addition to the effect of the risk factors described in the immune system, the vast majority of EC cases are diagnosed in post-menopausal women and often in elderly patients. Age has a significant influence on the immune system, causing an overall decrease in immune-related functions and results in a dormant pro-inflammatory state (Pfister, *et al.*, 2008).

In 2013 the Cancer Genome Atlas Research Network (TCGA) published a comprehensive genomic and transcriptomic analysis of EC, presenting a new classification of the disease based on genetic features. EC was divided into four subgroups based on genetic

aspect, rather than the two traditionally identified. In the molecular classification two types of EC, the polymerase epsilon-ultramutated (POLE) and the microsatellite instability (MSI)-hypermutated, seem to present an immune microenvironment amplified and a high mutation rate (Cancer Genome Atlas Research Network, 2013). POLE-mutated and MSI-high ECs are associated with high neoantigen loads and number of TILs, which is counterbalanced by overexpression of PD-1 and PD-L1 (Howitt, *et al.*, 2015). This might explain why POLE-mutated tumors, exhibiting more malignant histologic characteristics paradoxically have a good prognosis, as TILs might be reacting to abundant tumor neoantigens, thus preventing disease dissemination and controlling the disease at the tumor site (Bellone, *et al.*, 2015).

In other types of tumor, there is evidence that high mutational burden is associated with increased objective response, progression-free survival (PFS) and lasting clinical benefit in the treatment with the PD-1 blockade (Coosemans, *et al.*, 2008), suggesting a rational of a better benefit of immunotherapy in the subgroups of endometrial cancer POLE-mutated and MSI-high tumors.

VACCINES

When it comes to active immunotherapy, vaccines are the first thing that comes to mind, aiming to induce immunological memory. The product of Wilms tumor gene 1 (WT1) has been considered a potential target for vaccine studies in EC. Located on chromosome 11, the WT1encodes a transcription factor that contributes to the carcinogenesis of uterine sarcomas, and its expression was further analyzed in EC (Coosemans, *et al.*, 2008). Overall, 72% (26/36) of tumors stained positive for WT1. RT-PCR results showed WT1 positivity in 75% (24/32) of samples. Comparing the staining patterns of the 3 different biopsied sites, tumor heterogeneity was demonstrated in the majority (72%) of samples. The safety and clinical response of a weekly WT1 peptide vaccine (Human Leucocyte Antigen (HLA)-A2402-restricted, modified 9-mer WT1 peptide emulsified with Montanide ISA51 adjuvant) were investigated in a phase I trial (Ohno, *et al.*, 2009). Although a modest, uncontrolled, nonrandomized trial, this study demonstrated that the WT1 vaccine therapy seems to be safe and present clinical response in the patients with gynecological cancer. The disease control rate (DCR) in the initial 3 months was 25% (stable disease [SD] in 3 patients, progressive disease [PD] in 9 patients).

Vaccination was tested in another study (Coosemans, *et al.*, 2013), which included 6 pre-treated patients with uterine cancer who received four weekly vaccines of autologous dendritic cells (DCs) electroporated with WT1 mRNA. Three out of four HLA-A2-positive patients showed an oncological response; an enrichment of WT1-specific T-cells was observed in two of them. Two HLA-A2-negative patients did not show an oncological or an immunological response. One allergic reaction was observed. An HLA-A2.1-positive 46-year-old woman with end-stage serous EC that received 4 weekly injections of WT1-RNA-

loaded dendritic cells had a decrease in CA 125 and WT1-specific T-cells increased 2.5-fold after 2 injections (Coosemans, *et al.,* 2010).However, the patient, suffering from a diffuse disease which became progressive again, died 8 months later.

In the search for other antigens to vaccines, testis cancer (CT) antigens have been identified, expressed exclusively in male germ cells and placental tissue in healthy adults but ectopically in tumor cells of multiple types of human cancer. The limited nature of their expression leads to high tumor-specificity and immunogenicity (Gjerstorff, *et al.,* 2015). Several CT antigens have been identified in EC, including NYESO-1, MAGE-A4 (Resnick, *et al.,* 2002), KU-CT-1 (Okada, *et al.,* 2006) and SSX-4 (Hasegawa, *et al.,* 2004). Recently, MAGE-A4 and NYESO-1 expression were tested by immunohistochemistry in 3668 samples, and the first was more frequently expressed in the majority of malignancies, including EC (26.3%/1.3%) (Kerkar, *et al.,* 2016). An open-label cohort study tested a recombinant vaccinia-NYESO-1 and a recombinant fowlpox-NY-ESO-1(Jäger, *et al.,* 2006). Thirty-six patients were included and the only patient with EC was one of the three to demonstrate NY-ESO-1 seroconversion and a CD8+ and CD4+ T-cell response. Expression of other five tumor-associated antigens (TAA) (BORIS, MUC1, hTERT, MAGE-A3 and Sp17) was validated in uterine tumor samples in another study, with MUC1 and hTERT been considered as most suitable targets for use in immunotherapeutic regimens, based on expression levels and T-cell immunogenicity (Vanderstraeten, *et al.,* 2016).

Active immunotherapy has been tested not only in the advanced disease scenario but also in adjuvant therapy. In this context, a folate binding protein(FBP) derived peptide vaccine was tested, in a phase I/IIa trial including 51 patients (Jackson, *et al.,* 2017). The trial reveals that E39+GM-CSF (the vaccine in question) was well-tolerated and elicits a strong, dose-dependent in vivo immune response. Early efficacy results are promising in the 1000mcg dose cohort. This study proves the safety and establishes the dose of E39 for a larger prospective, randomized, controlled trial in HLA-A2+ endometrial and ovarian cancer patients to prevent recurrence.

ADOPTIVE CELLULAR THERAPY

The adoptive cellular therapy involves the administration of immune system components which offer immediate but short-term protection. This includes the generation of tumor-reactive T-cells that are genetically engineered to express recombinant or chimeric T-cell receptors directed against common TAAs (CAR T-cells) (Longoria, *et al.,* 2015), technology not yet tested in EC. Another type of adoptive cellular therapy, consisting of intraperitoneal transfer of lymphokine-activated killer (LAK) cells with IL-2 has been tested in a phase I trial that included 1 EC patient with abdominal metastases (Steis, *et al.,* 1990). Although 30% of patients had a documented partial response (PR), this was not observed in the patient with EC and toxicity profile of the treatment was unfavorable. Santin and

colleagues (Santin, *et al.,* 2000) reported results of infusion of peripheral blood T-cells stimulated with tumor lysate-pulsed autologous dendritic cells in a 65-year-old patient with chemoresistant EC and liver metastasis. The treatment consisted of 3 infusions every 3 to 4 weeks and stabilization of the liver metastasis was achieved (due to cytotoxic T-cell response). The same author observed a tumor specific, cytotoxic T-cell response in vitro through vaccination with tumor lysate-pulsed autologous dendritic cells in 3 patients with serous uterine carcinoma (USC) (Santin, *et al.,* 2002).

BISPECIFIC T-CELL ENGAGER (BITE) ANTIBODIES

Also in the passive immunotherapy setting, bispecific T-cell engager (BiTE) antibodies are being studied in EC (Wickramasinghe, *et al.,* 2013). The most promising agent of this class for the treatment of uterine cancer is solitomab, a novel bispecific single-chain antibody construct which targets epithelial-cell-adhesion-molecule (EpCAM) on tumor cells and also contains a CD3 binding region. The expression levels of EpCAM and the *in vitro* activity of solitomab against primary USC cell lines *in vitro* and *ex-vivo* in the ascites of USC patients was evaluated recently by Bellone and colleagues (Bellone, *et al.,* 2016). Surface expression of EpCAM was found in 85.7% (12 out of 14) of the USC cell lines tested by flow cytometry. EpCAM positive cell lines presented resistance to NK or T-cell-mediated killing after exposure to peripheral blood lymphocytes (PBL) in 4-hour chromium- release assays (mean killing ± SEM, 2.7 ± 3.1% after incubation of EpCAM positive cell lines with control BiTE®). In contrast, after incubation with solitomab, EpCAM positive USC cells became highly sensitive to T-cell cytotoxicity (mean killing ± SEM of 25.7 ± 4.5%; $P<0.0001$) by PBL. *Ex vivo* incubation of autologous tumor-associated lymphocytes (TAL) with EpCAM expressing malignant cells in ascites with solitomab, resulted in a remarkable increase in T-cell proliferation in both CD4+ and CD8+ T-cells, increment in T-cell activation markers (i.e., CD25 and HLA-DR), and a decrease in number of viable USC cells in ascites ($P<0.001$). Table 1 compiles the ongoing studies with active immunotherapy in EC.

HUMAN IMMUNOCONJUGATE MOLECULE

Human immunocongugate molecule (hI-conI) is an antibody-like molecule target against tissue factor. This conjugate is composed of two human Factor VI as the targeting domain fused to human immunoglobulin G (IgG) Fc as an effector domain. It was tested in 16 samples of uterine serous papillary cancer (UPSC) that was pre-evaluated by immunohistochemistry for TF expression. This immunoconjugate showed strong cytotoxicity against USPC cell lines overexpressing TF and it may represent a novel therapeutic agent for targeting UPSC (Cocco, *et al.,* 2010).

TROPHOBLAST-CELL-SURFACE MARKER (TROP-2)

Trop-2 is a surface glycoprotein that was originally identified in human placental trophoblast and subsequently reported to be expressed by human carcinomas. The biological role of Trop-2 is still unclear, but its overexpression has been found to correlate with invasive behavior and poor prognosis in human carcinomas. The hRS7 is a humanized IgG1 monoclonal anti- body developed against Trop-2 and it has the ability in inducing antibody-dependent cellular cytotoxicity. In a study with USPC, cell lines were highly sensitivity to hRS7-mediated cytotoxicity in vitro and the authors concluded that hRS7 may represent a novel therapeutic agent for refractory USPC (Varughese, *et al.*, 2011).

SURVIVIN

Survivin is an antiapoptotic protein overexpressed in several tumors and it is an interesting target for immunotherapeutic strategies. In one analysis, the authors evaluated survivin immunogenicity by analyzing spontaneous B-cell and T-cell responses in patients. It was found spontaneous T-cell responses in 10/39 endometrial cancers that overexpressed surviving and they concluded that these data indicate that a survivin-specific immune response may be induced spontaneously and fortify the eligibility of survivin as an immunotherapeutic target (Vanderstraeten, *et al.*, 2015).

CHECKPOINT INHIBITORS

One mechanism by which cancer tissues limit the host immune response is via upregulation of PD-1 ligand (PD-L1) and its ligation to PD-1 on antigen-specific CD8+ T-cells, termed adaptive immune resistance. There is evidence that the PD-1 blockade induces responses by inhibiting the adaptive immune resistance process (Tumeh, *et al.*, 2014). Experience with those drugs in EC is scarce but promising.

The first study suggesting a benefit of treatment with anti-PD-1 in EC was a phase 2 study conducted to evaluate the clinical activity of pembrolizumab, an anti–PD1 immune checkpoint inhibitor, in 41 patients with metastatic carcinoma with or without mismatch-repair deficiency (Le, *et al.*, 2015). These patients with mismatch repair–deficient noncolorectal cancer, including 2 patients with EC, predicted clinical benefit of immune checkpoint blockade. A cohort expansion was presented and of the 8 patients with MSI EC, 4 presented PRs and 2 complete responses (CR) (Diaz, *et al.*, 2016).

The data of POLE and MSH6 Hyper-Mutated EC treated with anti-PD1 are limited to case reports demonstrating a remarkable and prolonged clinical response with nivolumab and pembrolizumab (Santin, *et al.*, 2016 and Mehnert, *et al.*, 2016). The immunotherapy seems to be promising for patients with MSI-high and POLE-mutated tumors, but when measured in all patients with metastatic EC, a modest response is noted. In a phase IB study, the KEYNOTE-028 trial (NCT02054806) recently published, the results were disappointing. Only 3 patients (1 POLE mutation, 1 MSI low and 1 MSI unknwn status) of the 24 treated

patients had a response (13% of the patients) (Ott, *et al.*, 2017). The clinical benefit of pembrolizumab for advanced EC is being further investigated in the phase 2 trial KEYNOTE-158 (NCT02628067).

Recently was presented at the 2017 American Society of Clinical Oncology the result of the Phase 1a study that evaluated the clinical activity, safety and biomarker results of atezolizumab (anti–PD-L1) in advanced/recurrent endometrial cancer. Patients were MSI-H (1/15), MSS (7/15) or MSI unknown (7/15). It was observed an ORR of 13% (2/15). One patient that responded was MSS and heavily infiltrated with tumor infiltrating lymphocytes (TIL's) and the other responder was hypermutated, MSI-H and moderately infiltrated with TILs. The authors concluded that atezolizumab showed durable clinical benefit in some patients (Fleming, *et al.*, 2017).

Figure 1 contains the timeline of the leading studies published so far and Table 1 compiles the ongoing studies with checkpoint inhibitors in EC.

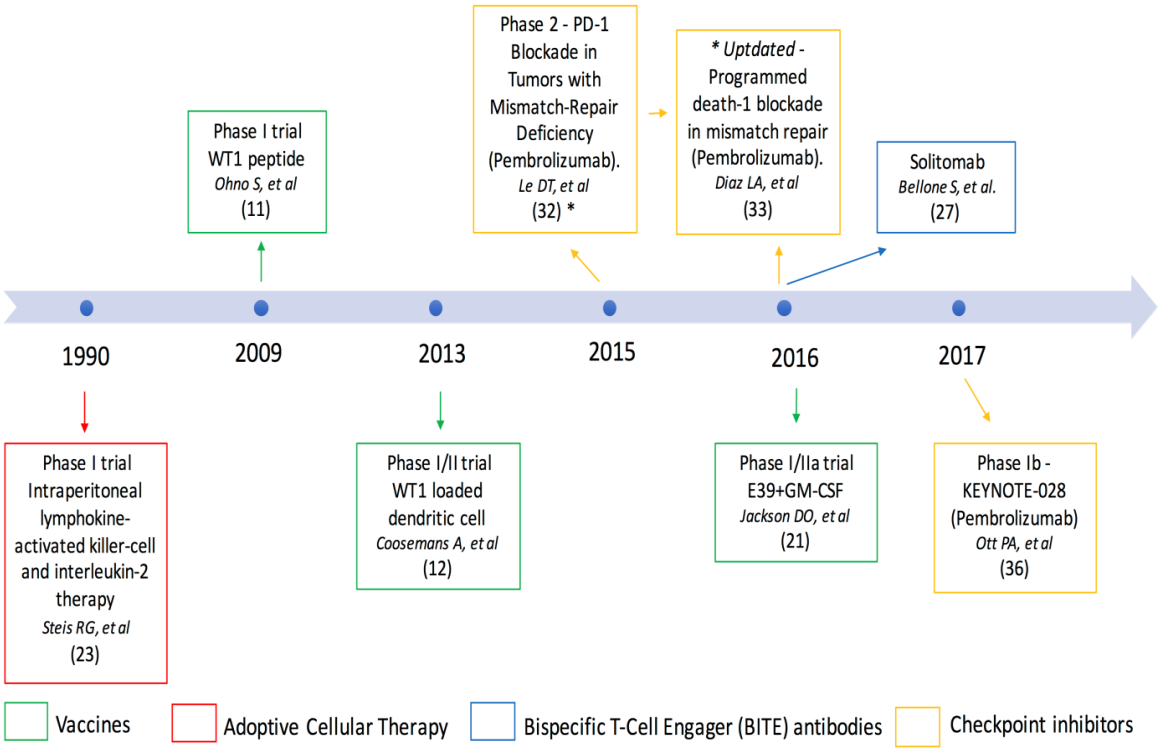

Figure 1: Timeline of the leading studies published so far on endometrial cancer immunotherapy.

Table 1: Ongoing studies with checkpoint inhibitors in endometrial cancer immunotherapy

DRUG	RECRUITMENT	SETTING	PHASE/ N	OUTCOME	NCT NUMBER
PEMBROLIZUMAB					
Pembrolizumab	Recruiting	Ultramutated and Hypermutated recurrent EC	Phase 2/ 25 pts	Response rate, safety, PFS, OS	NCT02899793
MK-3475	Recruiting	Stage III-IV EC	Phase 1/ 9 pts	Safety, PFS	NCT02630823
Pembrolizumab	Not yet recruiting	Advanced or recurrent EC	Phase 2/ 46 pts	Response rates, safety and tolerability	NCT02549209
IMGN 853 and Pembrolizumab	Recruiting	Advanced OC or EC	Phase 1/ 200 pts	Response rate, Safety, PFS, OS	NCT02606305
Pembrolizumab and Lenvatinib	Recruiting	Advanced solid tumors	Phase 1 and 2/ 250 pts	MTD, Response rate, safety, PFS, OS	NCT02501096
Pembrolizumab	Recruiting	Gynecologic tumors	Phase 1/ 15 pts	Change in immune infiltrates, safety	NCT02728830
Pembrolizumab and INCB039110 or INCB050465	Recruiting	Advanced solid tumors	Phase 1/140 pts	Evaluation of safety and tolerability	NCT02646748
MK-3475	Recruiting	Advanced solid tumors	Phase 2/ 1100 pts	Response rate	NCT02628067
Mirvetuximab Soravtansine in Comb. With Bevacizumab, Carboplatin, PLD or Pembrolizumab	Recruiting	Gynecologic tumors	Phase 1/ 200 pts	Safety and response rate	NCT02606305
MK-3475 and Epacadostat	Recruiting	Advanced solid tumors	Phase 1-2/463 pts	Objective response rate	NCT02178722
NIVOLUMAB					
Nivolumab plus Ipilimumab	Not yet recruiting	Advanced EC	Phase 2/ 60 pts	Response rate, PFS, OS	NCT02982486
Nivolumab	Recruiting	Advanced solid tumors	Phase 1 and 2/ 49 pts	Response rate, Safety,PFS, OS	NCT02423954
Nivolumab and Interferon	Recruiting	Advanced solid tumors	Phase 1/15 pts	Adverse events	NCT02614456
ATEZOLIZUMAB					
Atezolizumab	Recruiting	Gynecologic and Breast cancer	Phase 1/ 12 pts	Response rate, Safety	NCT02914470
Atezolizumab and GDC-0919	Recruiting	Advanced solid tumors	Phase 1/ 305 pts	MTD, Response rate, safety	NCT02471846

DURVALIMUMAB					
Durvaliumab and Tremelimumab	Recruiting	Persistent or recurrent EC	Phase 2/ 80 pts	Response rate	NCT03015129
AVELUMAB					
Avelumab	Recruiting	Persistent or recurrent EC	Phase 2/70 pts	Response rate, safety, PFS, OS	NCT02912572
BITE					
MCLA-128	Recruiting	Advanced solid tumors	Phase1-2/130 pts	Safety, tolerability, PK, response rate	NCT02912949
CAR-T					
Anti-meso-CArT cell	Recruiting	Advanced solid tumors	Phase 1/20 pts	Safety, tolerability, response rate, survival of CAT cell	NCT02580747
AUTOLOGOUS T CELL					
Tumor infiltrating lymphocytes	Recruiting	Advanced solid tumors	Phase 2/290pts	Response rate, safety, tolerability	NCT01174121
OTHER MECHANISMS					
VSV-hIFNbeta-NIS	Not yet recruiting	Advanced or recurrent EC	Phase 1/33 pts	Adverse events	NCT03120624
INCAGN01876(Anti-GITR antibody)	Recruiting	Advanced solid tumors	Phase 1-2/ 146 pts	Safety and tolerability	NCT02697591

EC: Endometrial Cancer; OC: Ovarian Cancer; Pts: Patients; PFS: Progression Free Survival; OS: Overall Survival; MTD: Maximum Tolerated Dose

CONCLUSION/FUTURE OF IMMUNOLOGY IN ENDOMETRIAL CANCER

The immune checkpoint inhibitors have ushered a new era in the treatment of cancer patients. Preclinical and promising clinical data supports the development of immunotherapy in gynecologic cancers.

Given the unmet clinical need in recurrent or metastatic EC, exploration of novel therapeutic approaches is warranted. Existing evidence suggests that EC, mainly POLE-mutated tumors, is sufficiently immunogenic to be a reasonable candidate for immunotherapy. More clinical trials are required in this field to bring new and potentially lifesaving treatments to more EC patients, and stratification by TCGA molecular classification is essential not to miss a benefit for a specific EC subtype.

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