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Research Article

Immunotherapy and Uterine Cancer

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Abstract

Uterine cancer is the most common gynecologic malignancy diagnosed among women in the United States. Globally, the incidence is highest in North America and lowest in South Central Asia. Current standard therapy for uterine cancer most commonly involves surgical removal of the uterus and surrounding tissues along with radiotherapy and chemotherapy depending on the stage of cancer. Sicne patients with advanced or recurrent endometrial cancer have a poor prognosis, there is an urgent need for developing new therapies. Recent developments in the understanding of the etiology and molecular characteritics of uterine cancer has made it possible to explore the role of immunotherapy in treating uterine cancer patients. Currently there are no FDA-approved immunotherapeutic agents available for the treatment of uterine cancer. This review discusses immunotherapy modalities that are under various phases of clinical trial investigations for the treatment of uterine cancer.

Keywords: *Uterine cancer; Adoptive cellular therapy; Immune checkpoint inhibitors therapeutic vaccination; Kinase inhibitors*

Abbrevations

ADC: Antibody-drug conjugate; ATP: Adenosine triphosphate; BCR-ABL: Breakpoint cluster Region-Abelson; CA-125: Cancer antigen 125; CCL: Chemokine ligand; CCR: Chemokine receptors; CEACAM5: Carcinoembryonic antigen-related cell adhesion molecule; CML: Chronic myeloid leukemia; COX: Cyclooxygenase; DC: Dendritic cell; Fc: Constant region; FGFRs: Fibroblast growth factor receptors; FKBP 12: FK Binding Protein-12; FLT-3: FMS-like tyrosine kinase 3: FVIIa: Factor VIIa; FX: Factor X; GM-CSF: Granulocyte-macrophage colony stimulating factor; HER2: Human epidermal growth factor receptor 2; IDO: Indoleamine 2,3-dioxygenase; IgG1: Immunoglobulin G1; IL: Interleukin; KLH: Keyhole Limpet Haemocyanin; K-ras: Kirsten rat sarcoma; MEK/MAPK/ERK: Mitogen-Activated Protein Kinase Kinase/Extracellular; MET: Hepatocyte growth factor receptor; MMAE: Monomethyl auristatin E; mRNA: messenger Ribonucleic acid; MSI: Microsatellite instability; mTOR: Mammalian target of rapamycin; PDGFRb: Platelet derived growth factor receptor b; PI3K: Phosphatidylinositol-3-kinase; PTEN: Phosphatase and Tensin Homolog; RAF: Rapidly Accelerated Fibrosarcoma; RET: Rearranged during transfection; RTK: Receptor tyrosine kinase; SFKs: Src-family protein tyrosine kinases; STAT3: Signal transducer and activator of transcription 3; TAAs: Tumor associated antigens; TF: Tissue factor; TIE-2: TEK tyrosine kinase, endothelial; TILs: Tumor infiltrating lymphocytes; TK: Tyrosine kinases; Treg: regulatory T cells; TRKB: Tropomyosin-related kinase B; TRKB: Tropomyosin-related kinase B; VEGFR: Vascular endothelial growth factor receptor; WT1: Wilms' Tumor Gene 1

Introduction/Epidemiology

Uterine cancer is the seventh most common malignant disorder and the most frequent pelvic gynecological cancer worldwide [1,2]. Most often, uterine cancer starts in the endometrium, the inner lining of the uterus (womb). This type of uterine cancer is called endometrial carcinoma and it makes up more than 95% of all the uterine cancers. Carcinosarcoma is another type of cancer that can start in the endometrium. Uterine sarcoma is a type of cancer that can develop in the muscle or connective tissues of the uterus [3].

In the United States, uterine cancer is the most common cancer of the female reproductive organs. According to the American Cancer Society in the year 2014, it was estimated that about 52,630 new cases of uterine cancer were diagnosed. Additionally, in the same year, about 8,590 women died from uterine cancer [4].

The incidence of uterine cancer is highest in Northern America and lowest in South Central Asia [5]. Uterine cancer is rare in women under the age of 45. Most (about 3 out of 4) cases are found in women aged 55 and above. The average chance of a woman being diagnosed with this cancer during her lifetime is about one in 37. There are over 600,000 women that are survivors of this cancer. It is slightly more common in white women. However, more cases of deaths are recorded in black women [6]. It includes different types of histopathologic and genetic characteristics.

Etiology/Predisposing Factors [7,8]

Although the exact cause of uterine cancer is not known, some predisposing factors might increase the risk of uterine cancer in women:

1. Estrogen replacement therapy: Using estrogen alone, without progesterone, increases the risk of uterine cancer.
2. Being overweight or obese.
3. Reproductive and menstrual history: Women are at high risk of uterine cancer if at least one of the following happens: Have never had children, had their first menstrual period before the age of 12 years, went through menopause after the age of 55 years.
4. Taking tamoxifen: Women who have undergone tamoxifen therapy for 5 years or more have a higher risk of developing uterine cancer.
5. Polycystic ovarian syndrome: Women with polycystic ovaries and less periods, or none, are at higher risk of developing uterine cancer.
6. Endometrial hyperplasia: It is an overgrowth of normal cells at the uterine lining layer. It progresses to atypical endometrial hyperplasia, which is an overgrowth of abnormal cells. When it is untreated, approximately 1.6% of endometrial hyperplasias and 23% of atypical hyperplasias lead to uterine cancer.
7. Previous radiation therapy: Women, who have received high-dose radiation to the pelvis, are at higher risk of developing uterine cancer.
8. Diabetes: Diabetes may be a causing factor for uterine cancer.
9. Estrogen-secreting ovarian tumors: Women with estrogen-secreting ovarian tumors are at higher risk of developing uterine cancer, which may be due to the higher levels of estrogen.
10. Lynch syndrome (Hereditary non polyposis colorectal cancer): Women with Lynch syndrome tend to develop uterine cancer before the age of 45, which is much younger than women in the general population.

Pathophysiology/Molecular Basis

It has been anticipated that uterine cancer is of two types: estrogen dependent (type I) and estrogen independent (type II) [9]. Approximately 85% of endometrial cancers are of type I. These cancers have a tendency to occur in obese women and are typically preceded by complex atypical hyperplasia. Most commonly, it has low grade endometrioid histology and is limited to the uterus with minimal invasion. On the other hand, type II tumors are more liable to occur in thin and older patients with an atrophic endometrium. Usually, their histology is high grade serous or clear cell and show early metastasis in most of the patients [10-12]. Approximately half of all the endometrial cancer relapses occur in patients with type II tumors [12].

On the basis of a molecular level, differentiation between these two groups need to be made. For example, type I tumors commonly have phosphatase and tensin homolog (PTEN), Kirsten rat sarcoma (K-ras), and β-catenin mutations along with microsatellite instability (MSI). The probability of progesterone receptors to be found in these type I cancers is more. On the other hand, type II tumors have p53 mutations and human epidermal growth factor receptor 2 (HER2/neu) amplification [10,12].

Immunotherapy

The immunotherapy for uterine cancer includes vaccines, dendritic cell (DC) immunotherapy, immunomodulators and adoptive T cell therapy, monoclonal antibodies, kinase inhibitors, vascular endothelial growth factor (VEGFR) inhibitors and mammalian target of rapamycin (mTOR) inhibitors.

Vaccines

Non-FDA Approved Vaccines: MVX-ONCO-1 is a type of cancer vaccine that has recently been introduced as phase I clinical trial in patients with advanced solid tumors. It consists of a two-component system:

Vaccine: Administered by sub-cutaneous injection. This uses the patient's own irradiated cancer cells as vaccine antigens, with a key benefit of using the entire set of tumor antigens from the patient's cell.

Immune boosting agent: An immune boosting agent, granulocyte-macrophage colony stimulating factor (GM-CSF) is continuously delivered via encapsulated cells. The capsule, a smallhollow fibre, is placed underneath the skin at the same site as the vaccine injection.

Drugs	Clinical Trial Identifier no.	Phase	Study Design	Target
MVX-ONCO-1	NCT02193503	Phase I	Safety/Efficacy study, open label	Cancer cells

Table 1: *Non-FDA Approved Vaccines [13].*

Dendritic Cell (DC) Immunotherapy

DCs are a minor (<1%) subset of the white blood cell population. Immature dendritic cells have the capacity to capture and process antigens. When there is an interaction between chemokine receptor CCR7 and its ligands CCL19/CCL21, DC migrates to the lymph nodes, where the processed antigens are presented to T cells, thereby enhancing an immune response [14].

DC immunotherapy (Table-2) is most frequently based on DCs cultured in an *ex vivo* setting, starting from CD34+ precursor cells or CD14+monocytes. DC is loaded with (defined) tumor antigens at the immature state, which exist as synthetic peptides or messenger Ribonucleic acid (mRNA) [1].

The application of active immunotherapy in the treatment of uterine cancer has not been explored much. Yet, immunotherapeutic approaches hold promise for uterine cancer.

Cancer	No. of patients	Immunotherapy	References
Serous endometrial carcinoma	3	Injection of DCs loaded with whole tumor lysate	Santin A., *et al.* [15].
Uterine sarcoma	2	Injection of DCs loaded with the whole tumor lysate and KLH	Hernando JJ., *et al.* [16].
Serousendometrial Carcinoma	1	WT1-mRNA loaded DC immunotherapy	Coosemans A., *et al.* [17].
Leiomyosarcomas and serousendometrial Carcinoma	6	WT1-mRNA loaded DC immunotherapy	Coosemans A., *et al.* [18].

Table 2: *DC Immunotherapy in Uterine Cancer [15-18].*

Abbreviations: *KLH: Keyhole Limpet Hemocyanin; WT1: Wilms' tumor gene 1; DC: dendritic cell*

Immunomodulators

Tumor-induced immunosuppressive mechanisms activated in uterine tumors (Indoleamine 2,3-dioxygenase [IDO], COX-2 [cyclooxygenase-2], STAT3 [Signal transducer and activator of transcription 3], Treg [regulatory T cells]) can also be targeted by specific agents. The *in-vitro* treatment of endometrial cancer cells with curcumin, results in decreased interleukin (IL)-6 production and decreased IL-6 induced STAT3 phosphorylation and thus constitutes a promising new anti-cancer drug [19].

Another group of immunomodulatory drugs are thalidomide analogues, which possess immunomodulatory, anti-angiogenic, anti-inflammatory and anti-proliferative effects. Most immunomodulatory drugs are tested in hematological malignancies, but they might be beneficial in solid tumors like uterine cancer [20]. The parent drug thalidomide has been tested in uterine cancer, but showed limited or no efficacy; therefore it remains to be elucidated whether the optimized analogues will show enhanced effectiveness [21].

Adoptive T Cell Therapy

Adoptive T cell therapy is based on using immune cells that are grown outside the body of the cancer patient and re-infused in much larger numbers [22]. In order to increase the efficacy of this therapy, it can be combined with other treatments, such as chemotherapy or IL-2. Most data pertaining to adoptive T cell transfer has been obtained in melanoma [22]. Melanoma was chosen as a target because of the frequent observation of TILs (tumor infiltrating lymphocytes) and the presence of TAA (tumor associated antigens). It has also been tested in uterine tumors.

Monoclonal Antibodies

Non-FDA Approved Monoclonal Antibodies:

1.Bevacizumab: A recombinant humanized monoclonal antibody directed against the VEGFR, a pro-angiogenic cytokine. Bevacizumab binds to VEGF and inhibits VEGFR binding, thereby preventing the growth and maintenance of tumor blood vessels.

2.Trastuzumab: A recombinant humanized monoclonal antibody directed against the HER2.

3.SAR408701: An immunoconjugate consisting of anti-carcinoembryonic antigen related cell adhesion molecule 5 (CEACAM5), conjugated to a cytotoxic agent, with potential antineoplastic activity. Upon administration of anti-CEACAM5 antibody-drug conjugate SAR408701, the antibody moiety targets CEACAM5 on tumor cells. Upon antibody/antigen binding and internalization, the immunoconjugate releases the cytotoxic agent, which results in tumor cell death. CEACAM5, a member of the CEA family of proteins, plays a key role in cell migration, cell invasion, and cell adhesion and is overexpressed by a variety of cancer cell types.

4.Abagovomab: A murine immunoglobulin G1 (IgG1) monoclonal anti-idiotype antibody, containing a variable antigen-binding region that functionally mimics the three-dimensional structure of a specific epitope on the ovarian cancer tumor-associated antigen CA-125, with potential antineoplastic activity.

5.HuMax-TF-ADC: An antibody-drug conjugate (ADC) comprised of a monoclonal antibody against human tissue factor (TF) covalently coupled, via a protease-cleavable peptide linker, to monomethyl auristatin E (MMAE), an auristatin derivative and potent microtubule disrupting agent, with potential antiangiogenic, anticoagulant and antineoplastic activities. Upon administration, anti-TF monoclonal antibody-MMAE conjugate binds to cell surface TF and is internalized. The antibody moiety prevents binding of TF to factor VIIa (FVIIa) and interferes with the activation of factor X (FX) into FXa. This may prevent thrombin formation and cancer-associated venous thromboembolism. It may also inhibit angiogenesis and tumor cell proliferation. After internalization of the agent, the MMAE moiety is released by proteolytic cleavage. It then binds to tubulin and inhibits its polymerization, which results in G2/M phase arrest and apoptosis. TF, a transmembrane protein and initiator of the coagulation cascade, is overexpressed in many tumor cells and tumor-resident endothelial cells. Expression of TF is correlated with metastasis, angiogenesis, tumor cell growth and tumor-associated thrombosis.

Drugs	Clinical trial identifier no.	Phase	Study design	Target
Bevacizumab	NCT00301964/ NCT00723255	Phase II	Safety/Efficacy study, open label	VEGF
Trastuzumab	NCT00006089	Phase II	Safety/Efficacy study, open label	HER2
SAR408701	NCT02187848	Phase I, Phase II	Non Randomized, Safety/ Efficacy study, open label	CEACAM5
Abagovomab	NCT00058435	Phase I	Randomized, open label	CA125
HuMax-TF-ADC	NCT02001623	Phase I	Non Randomized, Safety study, open label	Human TF

Table 3: *Non-FDA Approved Monoclonal Antibodies [23-28].*

Kinase Inhibitors

Non-FDA Approved Kinase Inhibitors

1.Sunitinib: The orally bioavailable malate salt of an indolinone-based tyrosine kinase inhibitor with potential antineoplastic activity. Sunitinib blocks the tyrosine kinase activities of VEGFR2, platelet derived growth factor receptor b (PDGFRb), and c-kit, thereby inhibiting angiogenesis and cell proliferation.

2.Sorafenib: A synthetic compound targeting growth signaling and angiogenesis. Sorafenib blocks the enzyme Rapidly Accelerated Fibrosarcoma (RAF) kinase, a critical component of the RAF/MEK/ERK (Mitogen-Activated Protein Kinase Kinase/Extracellular) signaling pathway that controls cell division and proliferation; in addition, sorafenib inhibits the VEGFR-2/PDGFR-beta signaling cascade, thereby blocking tumor angiogenesis.

3.Imatinib: A tyrosine kinase inhibitor with antineoplastic activity. Imatinib binds to an intracellular pocket located within tyrosine kinases (TK), thereby inhibiting adenosine triphosphate (ATP) binding and preventing phosphorylation. It also inhibits the subsequent activation of growth receptors and their downstream signal transduction pathways.

4.Pazopanib Hydrochloride: Pazopanib selectively inhibits VEGFR types 1, 2 and 3, c-kit and PDGF-R, which may result in inhibition of angiogenesis in tumors, in which these receptors are upregulated.

5.Cediranib: A tyrosine kinase inhibitor with antineoplastic activity. Competing with adenosine triphosphate, Cediranib binds to and inhibits all three VEGF-1,-2,-3 TK, thereby blocking VEGF-signaling, angiogenesis, and tumor cell growth.

6.Cabozantinib: It is a small molecule receptor tyrosine kinase (RTK) inhibitor with potential antineoplastic activity. Cabozantinib strongly binds to and inhibits several RTKs, which are often overexpressed in a variety of cancer cell types, including hepatocyte growth factor receptor (MET), rearranged during transfection (RET), VEGFR types 1, 2 and 3, mast/stem cell growth factor (KIT), FMS-like tyrosine kinase 3 (FLT-3), TIE-2 (TEK tyrosine kinase, endothelial) and tropomyosin-related kinase B (TRKB).

7.Trametinib: It is an inhibitor of mitogen-activated protein kinase kinase (MEK MAPK/ERK kinase) with potential antineoplastic activity. Trametinib specifically binds to and inhibits MEK 1 and 2, resulting in an inhibition of growth factor-mediated cell signaling and cellular proliferation in various cancers. MEK 1 and 2, the dual specificity threonine/tyrosine kinases that are often upregulated in various cancer cell types, play a key role in the activation of the RAS/RAF/MEK/ERK signaling pathway that regulates cell growth.

8.CLR457: An orally bioavailable pan inhibitor of phosphatidylinositol-3-kinase (PI3K), with potential antineoplastic activity. Upon oral administration, pan-PI3K inhibitor CLR457 inhibits all of the PI3K kinase isoforms, which may result in apoptosis and growth inhibition in tumor cells overexpressing PI3K. Activation of the PI3K pathway promotes cell growth, survival, and resistance to both chemotherapy and radiotherapy.

9.Dasatinib: Dasatinib binds to and inhibits the growth-promoting activities of these kinases. Apparently because of its less stringent binding affinity for the Breakpoint cluster region-Abelson (BCR-ABL) kinase, dasatinib has been shown to overcome the resistance to imatinib of chronic myeloid leukemia (CML) cells harboring BCR-ABL kinase domain point mutations. SFKs (Src-family protein-tyrosine kinases) interact with a variety of cell-surface receptors and participate in intracellular signal transduction pathways; tumorigenic forms can occur through altered regulation or expression of the endogenous protein and through virally encoded kinase genes.

10.Ponatinib: It is a multitargeted RTK inhibitor with potential anti-angiogenic and anti-neoplastic activities. Ponatinib hydrochloride inhibits unmutated and all mutated forms of BCR-ABL, including T315I, the highly drug therapy-resistant missense mutation of BCR-ABL. This agent also inhibits other tyrosine kinases, including those associated with VEGFRs and fibroblast growth factor receptors (FGFRs); in addition, it inhibits the tyrosine kinase receptor TIE2 and FLT3. RTK inhibition by ponatinib hydrochloride may result in the inhibition of cellular proliferation and angiogenesis and may induce cell death. BCR-ABL is a fusion tyrosine kinase encoded by the Philadelphia chromosome.

11.INCB054828: An orally bioavailable inhibitor of the FGFR types 1, 2, and 3 (FGFR1/2/3), with potential antineoplastic activity. FGFR inhibitor INCB054828 binds to and inhibits FGFR1/2/3, which may result in the inhibition of FGFR1/2/3-related signal transduction pathways. This inhibits proliferation in FGFR1/2/3-overexpressing tumor cells. FGFR, a family of receptor tyrosine kinases upregulated in many tumor cell types, plays a key role in cellular proliferation, migration, and survival.

12.PKI-587: An agent targeting the PI3K and mTOR in the PI3K/mTOR signaling pathway, with potential antineoplastic activity. Upon intravenous administration, PI3K/mTOR kinase inhibitor PKI-587 inhibits both PI3K and mTOR kinases, which may result in apoptosis and growth inhibition of cancer cells overexpressing PI3K/mTOR. Activation of the PI3K/mTOR pathway promotes cell growth, survival, and resistance to chemotherapy and radiotherapy; mTOR, a serine/threonine kinase downstream of PI3K, may also be activated independent of PI3K.

Drugs	Clinical trial identifier no.	Phase	Study design	Target
Sunitinib	NCT00478426	Phase II	Efficacy study, open label	VEGFR2
Sorafenib	NCT00238121	Phase II	Safety/Efficacy study, open label	RAF kinase
Imatinib	NCT00506779	Phase II	Efficacy study, open label	TK inhibitor
Pazopanib Hydrochloride	NCT01247571	Phase II	Efficacy study, open label	VEGFR
Cediranib	NCT02340611	Phase II	Efficacy study, open label	VEGFR
Cabozantinib S-malate	NCT01935934	Phase II	Efficacy study, open label	RTK
Trametinib	NCT01935973	Phase II	Randomized, Safety/Efficacy study, open label	MEK 1 and 2
CLR457	NCT02189174	Phase I/II	Non Randomized, Safety/efficacy study, open label	Pan PI3K inhibitor
Dasatinib	NCT01440998	Phase I	Efficacy study, open label	BCR-ABL kinase
Ponatinib	NCT01888562	Phase I	Safety/Efficacy study, open label	RTK
INCB054828	NCT02393248	Phase I	Open label	FGFR type I, II and III
PKI-587	NCT02069158	Phase I	Safety/efficacy study, Single blind	Dual inhibitor of both PI3K and mTOR

Table 4: *Non-FDA Approved Kinase Inhibitors [29-40].*

VEGFR Inhibitors

Non-FDA Approved drugs

Ziv-aflibercept: A protein comprised of segments of the extracellular domains of human VEGFR types 1and 2 fused to the constant region (Fc) of human IgG1 with potential antiangiogenic activity.

Drugs	Clinical trial identifier no.	Phase	Study design	Target
Ziv-aflibercept	NCT00462826	Phase II	Safety/Efficacy study, open label	VEGF

Table 5: *Non-FDA Approved VEGFR Inhibitor [41].*

mTOR Inhibitor

Non-FDA Approved mTOR Inhibitors

1. Temsirolimus: It is an ester analog of rapamycin. It binds to and inhibits the mTOR, resulting in decreased expression of mRNAs, necessary for cell cycle progression and arresting cells in the G1 phase of the cell cycle.

2. AZD2014: It is an inhibitor of the mTOR and has potential anti-neoplastic activity. mTOR kinase inhibitor, AZD2014, inhibits the activity of mTOR, which may result in the induction of tumor cell apoptosis and a decrease in tumor cell proliferation. mTOR, a serine/threonine kinase that is upregulated in a variety of tumors, plays an important role downstream in the PI3K/Akt/mTOR signaling pathway.

3. Everolimus: A derivative of the natural macrocyclic lactone sirolimus with immunosuppressant and anti-angiogenic properties. In cells, everolimus binds to the immunophilin FK Binding Protein-12 (FKBP-12) to generate an immunosuppressive complex that binds to and inhibits the activation of the mTOR, a key regulatory kinase. Inhibition of mTOR activation results in the inhibition of T lymphocyte activation and proliferation associated with antigen and cytokine (IL-2, IL-4, and IL-15) stimulation and the inhibition of antibody production.

Drugs	Clinical trial identifier no.	Phase	Study design	Target
Temsirolimus	NCT00723255	Phase II	Safety/ Efficacy study, open label	Block enzymes needed for cell growth
AZD2014	NCT02208375	Phase I, Phase II	Non Randomized, Safety/ Efficacy study, open label	mTOR
Everolimus	NCT02188550	Phase II	Non Randomized, open label	FKBP-12
Everolimus	NCT02228681	Phase II	Randomized, Safety/ Efficacy study, open label	FKBP-12

Table 6: *Non FDA Approved mTOR Inhibitors [42-45].*

Conclusion

Uterine cancer is a very common malignancy affecting thousands of women worldwide, with the number of cases increasing annually. Our success in treating uterine cancer is increasing and advancing with the knowledge of the function of the immune system. Immunotherapy has been a promising development in the past few years. The recent activities have increased our understanding of the tumor microenvironment and various immunotherapeutic modalities alone or as a combination therapy (like chemotherapy with immunotherapy). Additionally, the effects of such modalities in combination with immunotherapy in cancer patients are still in an exploratory phase. The complete perspective of immunotherapy treatment has not been realized and/or utilized. Proper preclinical and clinical designs are the important pillars in understanding the future of immunotherapy in treating cancer patients.

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