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Review article

Immunotherapy and Cervical Cancer

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Abstract

Cervical cancer is a leading cause of death worldwide, as per statistical analysis, it is the seventh most common cancer. Majority of the cervical cancers are caused by persistent infections with specific types of the human papillomavirus (HPV). HPV-infected cells produce specific proteins, or antigens that can be recognized by T cells, which are immune cells that play a critical role in the body's response to infectious agents and infected cells. As there are specific targets for development of cervical cancer immunotherapy is emerging as promising treatment for cervical cancer. In this paper we will discuss the target molecules involved in the carcinogenesis and various immunotherapies that are approved and that under clinical trials.

Keywords: Cervical Cancer; Immunotherapy; Immunosuppression; Kinase Inhibitors; Cytokines; Monoclonal Antibodies; Vaccines; HPV

Introduction

Cervical cancer is a cancer originating from the cervix. Cervix is the lower part of uterus in the human female reproductive system. Cervical cancer is one of the leading causes of death worldwide. According to the American Cancer Society, in the year 2014, more than 12,360 new cases of invasive cervical cancer were diagnosed [1]. Additionally, in the same year, 4,020 [1] cases of death due to cervical cancer were reported. As per the statistical analysis, it is the seventh most common cancer worldwide [2]. Eastern Africa (42.7), Melanesia (33.3), Southern (31.5) and Middle (30.6) Africa are observed as high-risk regions [2].

Cervical cancer represents 85% [2] of all the gynecologic cancers with an age-standardized (AS) incidence of 30 per 100,000 [3] and mortality rate of 7.5% [2]. According to ethnicity, AS rate is higher in white females (8.2 to 8.7 per 100,000) as compared to black (6.3 to 11.2 per 100,000) and Asian females (3.6 to 6.5 per 100,000) [3], although, a decrease in mortality rate was observed in last 30 years. There is higher incidence observed in two specific age groups of 30-34 (20 per 100,000) and 80-84 (13 per 100,000) [4,5].

Availability of the newer technologies in diagnosis and screening at regular intervals helps in early detection of cervical cancer. Diagnostic technology includes a primary requirement, for management of disease.

Etiology/ predisposing factor

Etiology of cervical cancer includes, but not limited to human papillomavirus (HPV), smoking, history of multiple pregnancies, sexual activity, immune deficiency, socioeconomic status, Diethylstilbestrol (DES) and use of oral contraceptives. These risks are directly linked to the cervical carcinoma. A family history of cervical cancer and history of sexually transmitted infections are possible risk factors, which cannot be directly related to cervical cancer progression. There are few other factors, which are still under investigation and cannot be directly linked to progression of disease.

Pathophysiology/ Molecular basis

Cervical cancer is a condition in which abnormal growth of cells starts in the cervix cells and invades into other parts of the body [6].

Thr most common cause of cervical cancer is Human Papillomavirus (HPV), which is a DNA virus from the papillomavirus family. HPVs establish productive infections mainly through keratinocytes of the skin or mucous membranes. Most HPV infections are subclinical and will cause no physical symptoms; however, in some people subclinical infections will become clinical and may cause benign papillomas (such as warts or squamous cell papilloma), premalignant lesions that will drive to cancers of the cervix, vulva, vagina, penis, oropharynx and anus [7].

The most common way of transmitting the HPV is through sexual contact causing the genital infections , there are other less common ways like through blood , surgery , hands and perinatal.

There are two categories of HPV virus based on their ability to promote cervical cancer, high risk and low risk. High-risk HPV types are distinguished from low-risk HPV types by the structure and function of the E6 and E7 products. In high-grade intraepithelial neoplasias and invasive cancers, HPV-DNA is generally integrated into the host genome. Integration of HPV-DNA deletes the E2 region, resulting in loss of its expression [8]. This interferes with the function of E2, which normally downregulates the transcription of the E6 and E7 genes, and leads to an increased expression of E6 and E7 genes. The E6 and E7 gene products deregulate the host cell growth cycle by binding to and inactivating two tumor suppressor proteins i.e. tumor suppressor protein (p53) and the retinoblastoma gene product (pRb). The HPV E6 gene product binds to p53 and targets it for rapid degradation [9].

Low-risk HPV E6 proteins do not bind p53 at detectable levels and have no effect on p53 stability in vitro. The E7 protein from low-risk HPV types binds pRb with decreased affinity. Next, the E5 gene product induces an increase in mitogen-activated protein kinase activity, thereby enhancing cellular responses to growth and differentiation factors [10]. The inactivation of p53 and pRb proteins increases proliferation rate and genomic instability and leads to transformed cancerous cells [11].

Cervical cancers are majorly divided into four types depending upon the origin and histological subtypes: (refer to Table 1) [12,13]

Types of cervical cancer	Originated from	Percentage of cases
Squamous cell carcinoma	Metaplastic squamous epithelium located between the original and new squamocolumnar junctions, the transformation zone	80% - 90%
Adenocarcinoma	Glandular cells	10% - 20 %
Adenosqaumous carcinomas	Cell lining of cervix and gland cell	Rare or 2%
Small cell and neuroendocrine carcinoma	Neuroectodermal cells like argyrophilic, neuroendocrine, melanocytic cells	Rare

Table 1. Types of cervical cancer

Epigenetic Alterations

It is important to consider the epigenetic changes that occur in the viral genome and influence the virus-driven carcinogenic process as well as epigenetic changes in the host genome.

Alteration		Meaning
HPV related	Methylation of HPV-E2 binding sites	De-repression of E6 and E7 HPV oncoproeteins
	Methyation at HPV-E6 and E7 LCR	Cause or consequence of E6/E7 over-expression
	E6 and/or E7 interaction with DNMTs	Silencing of cellular tumor suppressor genes
	Interaction between E7 with HDACs	Aid in cell transformation
	Interaction between E6 with HATs	Aid in cell transformation
Host cell-related	Regional DNA hypermethylation	Silencing of tumor suppressor genes
	Global DNA hypomethylation	Genomic instability, oncogene over-expression
	Abnormal pattern of chromatin	Unknown
	Loss of imprinting at H19/IGF2 loci	Tumor progression
	H3 hyper-phosphorylation & acetylation	Associated with carcinogenesis Progression

Table 2. Main epigenetic alterations in cervical cancer [14]

Immunotherapy

The treatment protocols to stimulate immunity against cervical cancer are done by using: vaccine based immunotherapy, monoclonal antibodies, and adoptive cell therapy.

A. Vaccines:

Though cancer preventive vaccines were approved by the FDA, there are no vaccines approved for treatment of cervical cancer.

1. PNGVL4a-Sig/E7 (detox) /HSP70 DNA vaccine: An antigen-specific DNA cancer vaccine consisting of the coding sequences of a signal peptide (pNGVL4a-Sig), a detox form of the human papillomavirus type 16 (HPV-16) antigen E7, and the heat shock protein 70 (HSP70).

2. ADXS11-001 (Lm-LLO-E7): A cancer vaccine containing a live-attenuated strain of the bacterium Listeria monocytogenes (Lm), encoding human papillomavirus (HPV) type 16 E7 fused to a non-hemolytic listeriolysin O protein with potential immunostimulatory and antineoplastic activities.

3. Survivin peptide vaccine: A peptide vaccine comprised of synthetic HLA-A1, -A2 and -B35 restricted survivin epitopes combined with the adjuvant Montanide ISA-51 with potential antineoplastic activity.

Drug	Clinical trial identifier no.	Phase	Study design	Target
pNGVL4a-Sig/E7 (detox) /HSP70 DNA vaccine	NCT00121173	Phase I, Phase II	Non-Randomized, Safety/Efficacy Study, Open Label	Kill abnormal cells in the cervix
PNGVL4a-Sig/E7 (detox) /HSP70 DNA vaccine	NCT00788164	Phase I	Non-Randomized, Safety/Efficacy Study, Open Label	Stop tumor cells from growing
pNGVL4a-Sig/E7 (detox) /HSP70 DNA vaccine	NCT00988559	Phase I	Non-Randomized, Safety/Efficacy Study, Open Label	Stop tumor cells from growing
ADXS11-001	NCT02291055	Phase I, Phase II	Randomized, Safety/Efficacy Study, Open Label	E7 substance
Attenuated Live Listeria Encoding HPV 16 E7 Vaccine ADXS11-001	NCT01266460	Phase II	Safety/Efficacy Study, Open Label	E7 substance
ADXS11-001 (Lm-LLO-E7)	NCT01116245	Phase II	Randomized, Safety/Efficacy Study, Single blind	E7 substance
Survivin peptide vaccine	NCT00108875	Phase I, Phase II	Non-Randomized, Safety/Efficacy Study, Open Label	Target tumor cells
ISA101	NCT02128126	Phase I, Phase II	Safety/Efficacy Study, Open Label	Target HPV16
ADXS11-001	NCT02164461	Phase I, Phase II	Non-Randomized, Safety/Efficacy Study, Open Label	Target HPV+
VGX-3100 and INO-9012 DNA vaccine	NCT02172911	Phase I, Phase II	Safety/Efficacy Study, Open Label	HPV-16 or 18-positive
E6 TCR	NCT02280811	Phase I, Phase II	Safety/Efficacy Study, Open Label	HPV-16 E6 for HPV-Associated Cancers
HPV16 E7 peptide-pulsed autologous DCs	NCT00155766	Phase I	Non-Randomized, Safety/Efficacy Study, Open Label	Inhibit growth of implanted tumor cells
MVX-ONCO-1	NCT02193503	Phase I	Safety/Efficacy Study, Open Label	Target tumor cells

Table 3. Non-FDA approved vaccines [15-27]

4. ISA101: A therapeutic peptide vaccine consisting of thirteen synthetic long peptides (SLPs), which are 25-35 amino acids in size, derived from the human papillomavirus (HPV) type 16 oncoproteins E6 and E7, with potential immunostimulating and antitumor activities.

5. VGX-3100 and INO-9012 DNA vaccine: VGX-3100 is a DNA vaccine consisting of plasmids, encoding the E6 and E7 genes of human papilloma virus (HPV) subtypes 16 and 18, respectively, with potential immunostimulating and antineoplastic activities.

INO-9012 is a plasmid DNA vaccine encoding the human pro-inflammatory cytokine interleukin-12 (IL-12) with potential immunoactivating activity.

6. E6 TCR: A synthetic peptide sequence of human papillomavirus (HPV) type 16 oncoprotein E6. The E6 oncoprotein is implicated in the tumorigenesis of cervical carcinoma. Vaccination with HPV 16 E6 peptide may stimulate the host immune system to mount a cytotoxic T lymphocyte (CTL) response against cells expressing the E6 oncoprotein, resulting in tumor cell lysis.

7. HPV16 E7 peptide-pulsed autologous DCs: A synthetic peptide sequence of human papillomavirus (HPV) E7 nuclear protein, which is used to produce vaccines against HPV infection and HPV-related neoplasms.

8. MVX-ONCO-1: A phase I clinical trial to assess safety and tolerability of 6 vaccine doses of MVX-ONCO-1, administered sub-cutaneous (injections and capsules implantations) in patients with advanced metastatic solid tumor that are not amenable to any standard therapy.

B. HPV-targeted adoptive T cell therapy [28]:

Tumor infiltrating lymphocytes: A preparation of cells, consisting of autologous tumor infiltrating lymphocytes, that is manipulated in vitro and, upon administration in vivo, re-infiltrate the tumor to initiate tumor cell lysis. In vitro, therapeutic tumor-infiltrating lymphocytes (TILs) are isolated from tumor tissue and cultured with lymphokines, such as interleukin-2; the therapeutic TILs are then infused into the patient, where, after re-infiltration of the tumor, they may induce lysis of tumor cells and tumor regression. The use of therapeutic TILs is considered a form of adoptive immunotherapy.

Drug	Clinical trial identifier no.	Phase	Study design	Target
Tumor infiltrating lymphocytes	NCT01585428	Phase II	Non-Randomized, Safety/Efficacy Study, Open Label	Lysis of tumor

Table 4. Non-FDA approved adoptive drugs [29]

C. Monoclonal Antibodies:

a. FDA approved monoclonal antibodies:

1. Bevacizumab [30]:

Indication and uses: Bevacizumab has received FDA approval and it is a vascular endothelial growth factor-specific angiogenesis inhibitor indicated for the treatment of cervical cancer, in combination with paclitaxel and cisplatin or paclitaxel and topotecan in persistent, recurrent, or metastatic disease. Most common adverse events are epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, rectal hemorrhage, lacrimation disorder, back pain and exfoliative dermatitis. Warnings include gastrointestinal perforations, surgery and wound healing complications, and hemorrhage.

b. Non-FDA approved monoclonal antibodies: (List of MABs under clinical trials phase I-III is listed below in table 5).

1. Nimotuzumab: A humanized monoclonal antibody directed against the epidermal growth factor receptor (EGFR) with potential antineoplastic activity. Nimotuzumab binds to and inhibits EGFR, resulting in growth inhibition of tumor cells that overexpress EGFR.

2. Cetuximab: A recombinant, chimeric monoclonal antibody directed against the epidermal growth factor (EGFR) with antineoplastic activity. Cetuximab binds to the extracellular domain of the EGFR, thereby preventing the activation and subsequent dimerization of the receptor; the decrease in receptor activation and dimerization may result in an inhibition in signal transduction and anti-proliferative effects.

3. Panitumumab: A human monoclonal antibody produced in transgenic mice that attaches to the transmembrane epidermal growth factor (EGF) receptor. Panitumumab may inhibit autocrine EGF stimulation of tumor cells that express the EGF receptor, thereby inhibiting tumor cell proliferation.

Drug	Clinical trial identifier no.	Phase	Study design	Target
Nimotuzumab	NCT02095119	Phase I, Phase II	Safety/Efficacy Study, Open Label	EGFR
Nimotuzumab	NCT02083211	Phase III	Randomized. Efficacy study, Double blind	EGFR
Cetuximab	NCT00292955	Phase II	Randomized, Safety/Efficacy Study, Open Label	EGFR
Panitumumab	NCT01158248	Phase II	Open Label	EGF
Nimotuzumab	NCT01938105	Phase II	Safety/Efficacy Study, Open Label	EGFR

Table 5. Non-FDA approved monoclonal antibodies [31-35]

D. Checkpoint inhibitors:

(List of checkpoint inhibitors under clinical trials phase I-III is listed below in table 6).

1. Nivolumab: It binds to and blocks the activation of PD-1, an Ig superfamily transmembrane protein, by its ligands PD-L1 and PD-L2, resulting in the activation of T-cells and cell-mediated immune responses against tumor cells or pathogens.

2. Ipilimumab: A monoclonal antibody directed against cytotoxic T-lymphocyte-associated antigen-4 (CTLA4), an antigen that is expressed on activated T-cells and exhibits affinity for B7 co-stimulatory molecules.

3. MEDI4736: It is a monoclonal antibody directed against B7H1 (B7 homolog 1; programmed cell death ligand 1) with potential immunostimulating activity.

Drug	Clinical trial identifier no.	Phase	Study design	Target
Nivolumab	NCT02257528	Phase II	Safety/Efficacy Study, Open Label	PD-1
Ipilimumab	NCT01711515	Phase I	Safety Study, Open Label	CTLA4
Ipilimumab	NCT01693783	Phase II	Safety/Efficacy Study, Open Label	CTLA4
MEDI4736	NCT02291055	Phase I, Phase II	Randomized, Safety/Efficacy Study, Open Label	Advanced or Metastatic Cervical cancer

Table 6. Non-FDA approved checkpoint inhibitors [36-39]

E. Kinase inhibitors:

(List of kinase inhibitors under clinical trials phase I-III is listed below in table 7).

1. BKM-102 (Buparlisib): Buparlisib specifically inhibits class I PIK3 in the PI3K/AKT kinase- (or protein kinase B) signaling pathway in an ATP-competitive manner, thereby inhibiting the production of the secondary messenger phosphatidylinositol-3, 4, 5-trisphosphate and activation of the PI3K signaling pathway. This may result in inhibition of tumor cell growth and survival in susceptible tumor cell populations. Activation of the PI3K signaling pathway is frequently associated with tumorigenesis. Dysregulated PI3K signaling may contribute to tumor resistance to a variety of antineoplastic agents.

2. GSK1120212: An orally bioavailable 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, dual specificity threonine/tyrosine kinases 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.

3. Nintedanib: An orally bioavailable, indolinone-derived, receptor tyrosine kinase (RTK) inhibitor with potential antiangiogenic and antineoplastic activities. Multi-targeted tyrosine kinase inhibitor BIBF 1120, selectively binds to and inhibits vascular endothelial growth factor receptor (VEGFR), fibroblast growth factor receptor (FGFR) and platelet-derived growth factor receptor (PDGFR) tyrosine kinases, which may result in the induction of endothelial cell apoptosis; a reduction in tumor vasculature; and the inhibition of tumor cell proliferation and migration.

4. Pazopanib: The hydrochloride salt of a small molecule inhibitor of multiple protein tyrosine kinases with potential antineoplastic activity. Pazopanib selectively inhibits vascular endothelial growth factor receptors (VEGFR) -1, -2 and -3, c-kit and platelet derived growth factor receptor (PDGF-R), which may result in inhibition of angiogenesis in tumors in which these receptors are upregulated.

5. Sorafenib: Sorafenib blocks the enzyme RAF kinase, a critical component of the RAF/MEK/ERK signaling pathway that controls cell division and proliferation; in addition, sorafenib inhibits the VEGFR-2/PDGFR-beta signaling cascade, thereby blocking tumor angiogenesis.

Drug	Clinical trial identifier no.	Phase	Study design	Target
BKM-102	NCT01613677	Phase II	Safety/Efficacy Study, Open Label	PIK3
GSK1120212	NCT01958112	Phase II	Safety/Efficacy Study, Open Label	MEK 1, 2
Nintedanib	NCT02009579	Phase II	Randomized, Safety/Efficacy Study, Double blind	VEGFR
Pazopanib	NCT02348398	Phase I	Safety/Efficacy Study, Open Label	VEGFR)-1, -2 and -3, c-kit and platelet derived growth factor receptor (PDGF-R)
Sorafenib	NCT01932177	Phase I	Non-Randomized, Safety/Efficacy Study, Open label	RAF kinase

Table 7. Non-FDA approved kinase inhibitors [40-44]

Conclusion

The identification of oncogenic HPV as the primary etiological agent for cervical cancer and its precursor lesions leads the development of the control of cervical cancer and other HPV-associated malignancies. Clinical HPV vaccine trials provide a unique opportunity to identify the characteristics and mechanisms of the immune response that best correlates with clinical vaccine potency. Our success in treating cervical cancer is increasing and advancing with the knowledge of the function of the immune system. There has been a great development in the immunotherapy since past few years. The recent activities have increased our understanding of the tumor microenvironment, various immunotherapeutic modalities or combination therapy (like chemotherapy with immunotherapy). Additionally, the effects of such modalities in combination with immunotherapy in cancer patients are still exploratory phase. The complete perspective of immunotherapy treatment has still not been realized and/or utilized. Proper preclinical and clinical designs, serve as the important pillars in understanding the future of immunotherapy in treating cancer patients.

Abbreviations

HPV=Human papilloma virus, MABs=Monoclonal antibodies, FDA=Food and Drug Administration, mTOR= Mammalian Target of Rapamycin Immunotherapy, IFN=Interferon, IL=Interleukin, TK=Tyrosine kinase, CTLA4= Cytotoxic T-lymphocyte-associated antigen-4, VEGFR=Vascular endothelial growth factor receptor, FGFR=Fibroblast growth factor receptor, PDGFR= Platelet-derived growth factor receptor.

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