Research Article

An Observational Molecular Pharmacological Research Study on the Pharmacodynamic Rationale and Applications of the Pharmaco-Chemo-Immunotherapeutics of Cervical Pre-cancers and Malignancies

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ABSTRACT

Human papilloma virus (HPV) - associated cervical pre-cancers are very significant treatment points with improved prognosis, if managed immediately. Cervical cancers are typical epithelial malignancies that are difficult to treat when metastatic, with gradual prognostic worsening. Chemotherapy generally consists of combinations of cytotoxic agents, often administered in conjunction with a biological agent. These regimens have limited clinical activity and substantial toxicity, and better treatments are required. Immunotherapy works through different mechanisms than chemotherapy and has been a breakthrough for the treatment of certain malignancies. Targeting HPV oncoproteins with antigen-specific immunotherapy using therapeutic vaccines are under clinical trials for cervical pre-cancers, cervical cancer and metastatic disease treatment. Immunotherapy with PD-1–targeted agents has shown clinical activity in genitourinary and oropharyngeal cancers. The objective of this observational molecular pharmacological research study was to analyse the pharmacodynamic rationale and applications of the pharmaco-chemo-immunotherapeutics of cervical pre-cancers and malignancies. This observational molecular pharmacological research study extensively explored the cervical pre-cancers and cervical malignancies, and the different aspects of cancer pharmaco-chemotherapeutic, onco-immunotherapeutic, onco-radiotherapeutic, surgical oncological and synergistic therapeutic modalities for a comprehensive cervical oncological treatment.

Keywords: Molecular Pharmacology, Cancer Pharmaco-chemotherapeutics, Pharmaco-onco-immunotherapeutics, Bevacizumab, Ipilimumab, Cemiplimab, Pembrolizumab, Preventive HPV vaccines, GX-188E therapeutic DNA vaccine, Axalimogene filolisbac, Adoptive T-cell therapy.

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INTRODUCTION

According to GLOBOCAN 2018, cervical cancer is the fourth most commonly diagnosed tumor and the fourth cause of cancer death in females, worldwide, but ranks second in both incidence and mortality in developing countries. Human papilloma virus (HPV) - associated cervical pre-cancers are very significant treatment points, with improved prognosis, if managed immediately. Cervical cancers are typical epithelial malignancies that are difficult to treat when metastatic, with gradual prognostic worsening. Chemotherapy generally consists of combinations of cytotoxic agents, often administered in conjunction with a biological agent. These regimens have limited clinical activity and substantial toxicity, and better treatments are needed. Immunotherapy works through different mechanisms than chemotherapy and has been a breakthrough for the treatment of certain malignancies. Targeting HPV oncoproteins with antigen-specific immunotherapy using therapeutic vaccines are under clinical trials for cervical pre-cancers, cervical cancer and metastatic disease treatment. Immunotherapy with PD-1–targeted agents has shown clinical activity in genitourinary and oropharyngeal cancers.[1-15]

OBJECTIVE

The objective of this observational molecular pharmacological research study was to analyse the pharmacodynamic rationale and applications of the pharmaco-chemo-immunotherapeutics of cervical pre-cancers and malignancies, through exploring the cervical

pre-cancers and cervical malignancies, and the different aspects of cancer pharmacochemotherapeutic, onco-immunotherapeutic, onco-radiotherapeutic, surgical oncological and synergistic therapeutic modalities for a comprehensive cervical oncological treatment.

MATERIALS AND METHODS, RESULTS AND DISCUSSION

An Observational Molecular Pharmacological Research Study

This observational molecular pharmacological research study extensively explored the cervical pre-cancers and cervical malignancies, and the different aspects of cancer pharmacochemotherapeutic, onco-immunotherapeutic, onco-radiotherapeutic, surgical oncological and synergistic therapeutic modalities for a comprehensive cervical oncological treatment, and analysed the pharmacodynamic rationale and applications of the pharmaco-chemo-immunotherapeutics of cervical pre-cancers and malignancies, thus, elucidating the following research findings.

Human papillomavirus associated malignancies and therapeutics

HPV-associated cancers are common epithelial malignancies, that account for approximately 5% of all cancers worldwide. They occur at varied genitourinary and oropharyngeal anatomic sites. HPV-associated cervical pre-cancers are very significant treatment points, with improved prognosis, if managed immediately. Cervical cancers are difficult to treat when progresses to metastatic advanced-stage, with gradual prognostic worsening. Advanced-inoperable cervical cancer is a challenging entity due to increased percentage of loco-regional and distant recurrences. Recurrent cervical cancer not amenable to radical treatment, as well as metastatic disease, are difficult to cure, with a bad prognosis.

Minimally invasive robotic surgery has become an effective surgical technique for the treatment of gynaecologic malignancies, like cervical cancer. Minimally invasive surgery (MIS) is the standard approach to performance of several gynaecologic procedures including hysterectomy, gynaecologic cancer staging procedures, myomectomy, pelvic organs prolapse repair and select adnexal procedures. Robotic-assisted surgery, a computer-based MIS approach has been adopted widely in the United States and several other countries.

As for the pharmacotherapeutic modalities of cervical cancer treatment, the approved immune-checkpoint inhibitors, the “first generation,” include monoclonal antibodies directed against PD-1 (pembrolizumab, nivolumab, cemiplimab); against PD-L1 (atezolizumab, avelumab, and durvalumab); and against protein CTLA-4 (ipilimumab). Combination chemotherapy and bevacizumab offers some clinical benefit, and anti-programmed death 1 receptor (PD-1) therapy has shown clinical activity, but these malignancies generally are incurable and better treatments are needed. Sequential ipilimumab after chemoradiotherapy is given in curative-intent treatment of patients with node-positive cervical cancer. Anti-tumour activity of cemiplimab as monotherapy or in combination with hypofractionated radiation therapy, is given in patients with recurrent or metastatic cervical cancer. Pembrolizumab and GX-188E therapeutic DNA vaccine are also emerging cervical cancer treatment options in patients with HPV-16-positive or HPV-18-positive advanced cervical cancer. Pembrolizumab, an IgG4-kappa humanized monoclonal antibody, against the programmed cell death protein 1 (PD-1) receptor, has been approved for the treatment of recurrent or metastatic cervical cancer. Although immune-checkpoint blockade therapy is rapidly altering the treatment landscape in solid tumours, the efficacy of immune-checkpoint blockade therapy with antibodies directed against CTLA-4, PD-1, and PDL-1 in advanced gynaecologic cancers has been limited. The exception has been the PD-1 inhibitor pembrolizumab in microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) advanced endometrial cancers, highlighted by the recent conditional approval of pembrolizumab in recurrent or metastatic PDL-1 positive cervical cancers and the accelerated approval of pembrolizumab and lenvatinib in microsatellite stable (MSS) or mismatch-repair proficient (pMMR) advanced endometrial cancer. GX-188E vaccination has been shown to induce human papillomavirus (HPV) E6-specific and E7-specific T-cell responses and cervical lesion regression in patients with cervical precancer. Preventive HPV vaccines and adoptive T-cell therapy, the systemic infusion of therapeutic T cells, are potential emerging cancer treatment modalities. Cellular therapy has shown to mediate the regression of HPV-associated cervical cancer, oropharyngeal cancer, and anal cancer, including durable, complete regression of cervical cancer.

The currently recommended standard of care treatment of cervical malignancy, according to the respective FIGO staging is that, for FIGO Stages IA1 and IA2, type II radical hysterectomy and pelvic lymph node dissection is suggested; for stages IB1 and IIA1, type III radical hysterectomy and pelvic lymph node dissection are suggested; for stages IB2 and IIA2, pelvic external beam radiation therapy, brachytherapy, and cisplatin based concurrent chemotherapy are suggested; for stages IIB and IVA, pelvic external beam radiation therapy, with brachytherapy and cisplatin-based concurrent chemotherapy, and with or without external beam radiation therapy to para-aortic nodes are suggested; and for stages IVB or recurrent disease not amenable to local therapy, paclitaxel, cisplatin and bevacizumab, or, paclitaxel and cisplatin, or, paclitaxel, topotecan and bevacizumab, or, paclitaxel and topotecan, or, paclitaxel and carboplatin, are suggested.

Targeted therapy in cervical cancer

Antiangiogenic therapy targeting the vascular endothelial growth factor (VEGF) and other pathways has improved

outcomes in multiple solid tumours. Poor prognosis and early recurrence in cervical cancer has been associated with VEGF expression. Bevacizumab is a recombinant humanised monoclonal immunoglobulin (Ig)-G1 antibody directed against VEGF-A. By inactivating VEGF-A, it blocks signal transduction through VEGFR-1-associated and VEGFR-2-associated pathways. The other targeted therapies, under various phases of clinical trials, include tyrosine kinase inhibitors sunitinib, which inhibits VEGFR, PDGFR, c-KIT, and FLT-3, and pazopanib, which inhibits VGFR, PDGFR, and c-KIT. Brivanib, an inhibitor of VEGFR and FGFR, is also another targeted therapy modality of advanced cervical cancer, which is under clinical trial. Other VEGF/ VEGFR targeting drugs, like, nintedanib and cediranib are also investigational drugs. Cervical cancer expresses moderate to high levels of epidermal growth factor receptor (EGFR) protein. Several studies with EGFR-targeted therapies, gefitinib, erlotinib and cetuximab, are undergoing different phases of clinical trials. Different clinical trials were also conducted with lapatinib, a HER2 inhibitor, and pazopanib (combination of HER2 inhibitor with VEGFR inhibitor). A recent study of molecular profiling of cervical cancer samples and testing in patient-derived xenograft (PDX) models has demonstrated that co-administration of trastuzumab and lapatinib, the BCAR4, breast cancer anti-estrogen resistance 4 amplification or HER2-overexpressed drugs in PDX significantly inhibited tumour growth compared with the control. A mTOR targeting drug, like temsirolimus, and histone deacetylase (HDAC) targeting drug, like valproic acid, are also under investigational phase.

PD-1 (programmed cell death 1) and PD-L1 expression on cervical cancer infiltrating T cells and dendritic cells, respectively, has been reported to be associated with high risk HPV positivity and increasing cervical intraepithelial neoplasia grade. PD-1 is expressed by a high fraction of infiltrating CD8 T cells in cervical cancer, suggesting that blocking of PD-1, by the immune checkpoint inhibitors, like pembrolizumab and ipilimumab, might have therapeutic potential and is undergoing clinical trials. Nivolumab, a fully human antibody against PD-1, is also undergoing different clinical trials as a second-line treatment of cervical cancer. PARP inhibitors, like, olaparib and veliparib, are also being investigated for a potential anti-carcinomatous drug target. Poly (ADP-ribose) polymerase (PARP) is a constitutively expressed enzyme that is involved in base excision DNA repair as well as cell replication, transcription, differentiation and gene regulation, and its inhibition has been shown to be synthetic lethal with homologous recombination DNA repair defects. The PARP inhibitor veliparib was studied in combination with cytotoxic therapy in women with recurrent or persistent cervical cancer after receiving pelvic radiation, with or without cisplatin.

The immune checkpoint inhibitor approach is likely to provide higher benefit in earlier lines of treatment and perhaps in combination with other strategies such as chemotherapy and / or radiotherapy.

Immunotherapeutics of cervical carcinoma

The rationale for immunotherapy in cervical carcinoma (CC) is that, given that almost all CCs are human papillomavirus (HPV)-related tumours, CC could represent a paradigmatic example for the benefit obtained from immunotherapy. The immune system is often stimulated by non-human (viral) antigens, and for this reason it was possible to develop a vaccine as tumour prophylaxis. Several studies have confirmed that a large number of genomic alterations are found in CC patients, for example, in the following genes: KRAS, PIK3CA, TP53 and PTEN. This high mutational burden might be responsive to immunotherapy. HPV-integrated genes are often described in CCs.

In a pharmacogenomic study, it was identified that 384 integrated gene sites could influence T cell activation in the KEGG (Kyoto Encyclopedia of Genes and Genomes, https://www.genome.jp/kegg/) database, indicating the possibility of a strong correlation between HPV infection and immune surveillance. There is an interesting correlation between HPV-mediated immune tolerance and tumour development. The ability of HPV to promote a so-called “non-lytic life cycle” inactivates (or partially activates) dendritic cell migration to lymph nodes and consequently inhibits immune activation. At the same time, low expression of E6 and E7 HPV proteins reduces Langerhans cell activity, leading to an immune-tolerant status that can potentially promote CC development. With regard to immune checkpoints, high levels of CTLA4 and PD1/PD-L1 are often detected in CC patients, and PD1/PD-L1 are frequently expressed in dendritic cells in Cervical Intraepithelial Neoplasia (CIN) samples. PD1/PD-L1 expression has been shown to be present in 95% of intraepithelial lesions and around 80% of squamous carcinomas. Several studies on CC have demonstrated high expression levels of immune-suppressive cytokines, such as IL-10, confirming an interesting link between immune checkpoints and CC progression. Recently, it was shown that PD-L1 expression correlates with TILs, predicting response in CC patients treated with neoadjuvant chemotherapy.

One antibody–drug conjugate, tisotumab–vedotin, has been studied in cervical cancer patients.

The immunotherapeutic modalities of cervical cancer treatment include the following:

a) Prophylactic

(i) Preventive HPV vaccines

b) Therapeutic

(i) GX-188E therapeutic DNA vaccine

(ii) Axalimogene filolisbac ADXS11-001

(iii) Adoptive T-cell therapy

Cervical cancer therapeutic vaccines aim to eradicate HPV-infected cells by stimulating cytotoxic T cells against the

viral/tumour antigens. The HPV E6 and E7 oncoproteins are expressed in HPV-associated cancers and are ideal targets for a therapeutic vaccine. Many live bacterial vectors have been explored in HPV therapeutic vaccines including *Listeria monocytogenes*, *Lactobacillus lactis*, *Lactobacillus plantarum*, *Salmonella enterica* and BCG. *Listeria monocytogenes* has the ability to replicate in the cytosol of antigen-presenting cells and infects monocytes and macrophages, allowing bacterial peptide antigens to be processed and presented *via* both Major Histocompatibility Complex class I and II pathways, generating potent CD8 and CD4 T cell–mediated immune responses. The sensitivity of *Listeria* to antibiotics allows the vector to be killed *in vivo* as required. The *Listeria*-based vaccine potency is further enhanced by encoding recombinant proteins composed of HPV E6 and E7 antigens fused to immunostimulatory molecules. Axalimogene filolisbac (ADXS11-001), a live, attenuated *Listeria monocytogenes* bacterial vector secreting HPV-16 E7 fused to listeriolysin O (LLO), is under investigation for treatment of HPV-associated malignancies including cervical cancer. A phase II study evaluated the safety and efficacy of ADXS11-001, administered with or without cisplatin, in patients with recurrent or refractory cervical cancer following prior chemotherapy and / or radiotherapy.

Therapeutic T cells, is an emerging cancer treatment modality that can induce complete tumour responses in some patients with B-cell malignancies or metastatic melanoma. A study was conducted to test whether adoptive T-Cell therapy could mediate the regression of HPV-associated epithelial cancers. A method was established in the study to generate independent tumour-infiltrating lymphocyte (TIL) cultures from fragments of a resected metastatic tumour deposit. Because HPV-associated cancers constitutively expressed the HPV E6 and E7 oncoproteins, immunologically foreign viral proteins that are attractive targets for immunotherapy and cultures with HPV-oncoprotein reactivity were selected preferentially for administration to patients. A completed clinical trial was presented with long-term follow-up, in which, 18 patients with metastatic cervical cancer and 11 patients with other cancers participated. The trial was a phase II design with two cohorts, cervical cancers and noncervical cancers. Cell infusion was preceded by a lymphocyte-depleting conditioning regimen and followed by systemic high-dose aldesleukin. Tumour responses occurred in 5 of 18 (28%) patients in the cervical cancer cohort and 2 of 11 (18%) patients in the noncervical cancer cohort. Two of the responses in cervical cancer were complete and the ongoing treatment continued for 67 and 53 months follow-up. Responses in the noncervical cancer cohort were in anal cancer and oropharyngeal cancer. The HPV reactivity of the infused T cells correlated with clinical response. Peripheral blood repopulation with HPV-reactive T cells also correlated with clinical response. These findings supported the concept that cellular therapy can mediate the regression of epithelial cancers, and they suggested the importance of predictive biomarkers and novel treatment platforms for more effective therapies.

In another similar study on the target antigens in two patients, complete responses were experienced in the clinical trial. Tumour-infiltrating lymphocyte therapy was administered to each patient, which targeted HPV antigens. However, the predominant target antigens were a cancer germline antigen in one patient and mutant neoantigens in another patient.

A number of biological agents modulating different signal transduction pathways are currently in clinical development, like cell cycle inhibitors, histone deacetylases, cyclooxygenase-2 (COX-2), mammalian target of rapamycin (mTOR), heat shock protein (HSP), WEE1, NOTCH signalling and others. With a better understanding of the central role of HPV infection in tumorigenesis of cervical cancer, more studies are evaluating the role of immune-directed therapies in cervical cancer, in adjuvant as well as metastatic settings.[1-15]

CONCLUSION

Therefore, this observational molecular pharmacological research on the cervical pre-cancers, cervical malignancies, cancer pharmacotherapeutic, onco-immunotherapeutic, onco-radiotherapeutic, surgical oncological and synergistic therapeutic modalities, well-delineated a detailed analysis of these multi-dimensional therapeutic modalities, while analysing the pharmacodynamic rationale and applications of the pharmaco-chemo-immunotherapeutics of cervical pre-cancers and malignancies.

This study would certainly lead to future newer drug and vaccine discoveries, for an improved pharmacotherapy and immunotherapy of the cervical pre-cancers and cervical malignancies.

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