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Original Article

A Descriptive Analytical Research on Diagnostic and Prognostic Immunohistochemical p-16/ki67 Staining and Colposcopy Imaging, Cancer Pharmacotherapeutics, Immunotherapeutics, and co-therapeutic Modalities in Cervical Malignancy: A Medical Book

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Abstract

The diagnosis, imaging, and prognosis of cervical malignancy and the pre-cancer can be performed with human papilloma virus (HPV) DNA testing and p-16/Ki67 immunohistochemical staining, other than the Papanicolaou test, and the subsequent colposcopy. HPV-associated cancers are typical epithelial malignancies that are difficult to treat when metastatic. 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 cancer and metastatic disease treatment. Immunotherapy with PD-1–targeted agents has shown clinical activity in genitourinary and oropharyngeal cancers. This descriptive analytical research study explores cervical malignancy, and the different aspects of diagnostic p-16/Ki67 immunostaining, colposcopy imaging, cancer pharmacotherapeutics, onco-immuno-therapeutics and co-therapeutic modalities for a comprehensive cervical cancer treatment.

Key words: Immunohistochemistry, Colposcopy, Cancer Pharmacotherapeutics, Immunotherapeutics, Bevacizumab, Ipilimumab, Cemiplimab, Pembrolizumab, Preventive Human papilloma virus 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 the lower income countries. The diagnosis, imaging, and prognosis of

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cervical malignancy and the pre-cancer can be performed with human papilloma virus (HPV) DNA testing and p-16/Ki67 immunohistochemical staining, other than the Papanicolaou test, and the subsequent colposcopy. HPV-associated cancers are typical epithelial malignancies that are difficult to treat when metastatic. 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 cancer and metastatic disease treatment. Immunotherapy with PD-1–targeted agents has shown clinical activity in genitourinary and oropharyngeal cancers.

Objective

The objective of this descriptive analytical research study was to explore cervical malignancy, and the different aspects of diagnostic colposcopy, cancer pharmacotherapeutics, onco-immuno-therapeutics, and co-therapeutic modalities for a comprehensive cervical cancer treatment.

METHODOLOGIES, RESULTS, AND DISCUSSION

A Descriptive Analytical Research Study

p16/Ki-67 immunostaining to detect cervical cancer precursors among colposcopy referrals

Cytology-based screening has limited sensitivity to detect prevalent cervical precancers. HPV DNA testing is highly sensitive and provides a high, long-term reassurance of the low risk of cervical cancer. The specificity of HPV DNA testing is limited, requiring more disease-specific markers for efficient screening approaches. In one study, liquid-based cytology samples were collected from 625 women referred to colposcopy. A slide was stained using the CIN tec plus cytology assay. Pap cytology and HPV genotyping were conducted from the same vial. Clinical performance characteristics were calculated for all women, stratified by age, and for women referred with a low-grade squamous intraepithelial lesion (LSIL) Pap. In this study, p16/Ki-67 positivity increased with histologic severity, from 26.8% in normal histology, 46.5% in CIN1, and 82.8% in CIN2 to 92.8% in CIN3. Among women with CIN3, p16/Ki-67 positivity increased from 77.8% for women younger than 30 years without HPV16 to 100% for women 30 years and older with HPV16. The sensitivity and specificity to detect CIN3 were 93.2% and 46.1%, respectively, and increased to 97.2% and 60.0% among women 30 years and older. In women with high-risk (HR)-HPV–positive atypical squamous cells of undetermined significance (ASC-US) and LSIL, sensitivity and specificity for detection of CIN3 were 90.6% and 48.6%, respectively. This study concluded that p16/Ki-67 testing could reduce referral to colposcopy by almost half while detecting the most severe cases of CIN3. The high sensitivity of p16/Ki-67 with significantly improved specificity compared with HPV testing makes p16/Ki-67 a viable option for LSIL triage.

Cervical Pap smear screening has led to a substantial reduction of cervical cancer incidence in countries with established screening programs. However, Pap cytology has limited reproducibility, and a single Pap test has limited sensitivity to detect cervical precancer. HPV DNA testing is highly sensitive and provides a high, long-term reassurance of low risk of cervical cancer among women testing negative, permitting safe extension of screening intervals. Recently, more disease-specific molecular markers of cervical cancer have been recognized that may provide a combination of high sensitivity and high specificity for detecting cervical precancer. Most of these markers have been identified on the basis of our understanding of HPV related carcinogenesis. The progression from HPV infection to cervical precancer is characterized by a substantial change in the viral gene expression, from a transient infection characterized by expression of structural genes to a transforming infection with strong expression of viral oncogenes that interfere with host cell-cycle control. The expression of several host genes is affected by the oncogene products of HPV, including those involved in cellular proliferation, such as Ki-67, and cell-cycle control, such as p16. Immunostaining for p16 has been determined to be an effective biomarker of cervical disease in histology and cytology specimens. It is widely used to improve the reproducibility of cervical biopsy interpretations. In cytology, p16 can improve the accuracy for detecting cervical precancer compared with conventional cytology. Recently, a double-label immunostain for p16 and Ki-67 was developed that allows recognition of abnormal cells simply based on co-staining of the two markers in the same cell, potentially obviating the need for morphologic interpretation.

In a large U.S.-based colposcopy referral population with excellent disease ascertainment, it was shown that cytologic staining for p16/Ki-67 has comparable sensitivity, but significantly higher specificity than HPV DNA testing, potentially reducing colposcopy referral by half. It was shown that p16/Ki-67 does best at detecting precancers with the highest risk of progression to cancer, namely, those related to HPV16 among women 30 years and older. These data from a large, independent study suggest that p16/

Ki-67 can be an important component of new HPV-based screening strategies.

Oncological Diagnostic Applications of Colposcopy

Colposcopy is a diagnostic procedure performed to evaluate women with an abnormal Papanicolaou (Pap) test, women with visual inspection with acetic acid, women positive for high-risk human papillomavirus (HPV) DNA, or with a suspicious appearing cervix even if the Pap test is normal. Women with LSIL and HPV-positive ASC-US are uniformly referred to colposcopy. All women with an LSIL referral Pap and an HPV-positive ASC-US referral Pap are usually evaluated by colposcopy and biopsy, for an analysis of the performance of p16/Ki-67 for triage of these cytology categories. Colposcopy is also performed as a post-treatment follow-up of intraepithelial and invasive carcinoma. Colposcopy is a procedure in which a lighted, magnifying instrument called a colposcope is used to examine the cervix, vagina, and vulva. It is a diagnostic procedure performed to evaluate abnormal cytology results from a screening Pap test. It is well known that colposcopy has significant variability and poor reliability between colposcopists. The ASCCP (American Society for Colposcopy and Cervical Pathology) published colposcopy standards in 2017 to address these concerns related to colposcopy. Colposcopy is a procedure in which a lighted, magnifying instrument called a colposcope is used to examine the cervix, vagina, and vulva. It is a diagnostic procedure performed to evaluate abnormal cytology results from a screening Pap test.

The indications for colposcopy include evaluation of women with an abnormal Pap test to localize the lesion, to map out the extent of the lesion, to select the biopsy site or sites; women positive for high-risk HPV DNA; visual inspection with acetic acid positive women, suspicious appearing cervix, postcoital or postmenopausal bleeding, even if the Pap smear is normal; unexplained abnormal lower genital tract bleeding; persistent inflammatory or unsatisfactory cervical cytology despite appropriate treatment, especially with high-risk factors for carcinoma cervix; persistent abnormal vaginal discharge or pruritus vulvae; for the identification and management of subclinical papillomavirus infection; patients with history of *in utero* diethylstilbestrol (DES) exposure; for the conservative management of intraepithelial neoplasia; identification and management of vaginal extension of cervical neoplasia; and for post-treatment follow-up after treatment of intraepithelial and invasive carcinoma and post-irradiation follow-up.

The ASCCP (American Society for Colposcopy and Cervical Pathology) has published standardization guidelines for the performance of colposcopy. The ASCCP makes recommendations for extensive and minimum requirements for a colposcopy. The colposcopist should examine the vulva, vagina, and cervix grossly in the natural state and also after the application of 5% acetic acid. The entire cervix and squamocolumnar junction must be visualized for adequacy. Both white light and a red-free (blue or green) filter should be applied to the visual field to identify any lesion.

Directed biopsies of lesions should be taken of each abnormal finding. Documentation in a minimum of text format should comment on the visibility extent, size, location, and description of each lesion (color, contour, border, and vascular changes), presence or absence of acetowhitening, complete or incomplete visibility of the squamocolumnar junction, documentation of biopsies and locations, if an endocervical curettage was performed, and finally the impression of the colposcopy (benign-normal, low grade, high grade, or cancer). Application of Monsel's solution or silver nitrate should be applied after the colposcopy is completed, and all biopsies are taken. Grade of cytological abnormality, colposcopic adequacy, visibility, and type of squamocolumnar junction should be documented. The location of lesion, size, and extent of lesion, endocervical, or vaginal extension of the lesion should also be clearly documented. Abnormal colposcopic findings should be described location wise in detail, and colposcopic impression should be made in terms of low grade or high-grade lesion along with Reid's or Swede score. Histopathologic diagnosis should never be made on colposcopy only. According to the 2011 IFCPC Nomenclature, the Swede score is used to score the colposcopic findings and to have uniformity in the reporting system. The total score is 10. Colposcopy is a diagnostic procedure done due to an abnormal cervical screening test or a visible lesion seen on the cervix during an examination. This diagnostic procedure assists with the formulation of a management plan based on the results of the biopsied pathology or lack of results. In general, all results can either be observed or treated and are based on evidence-based guidelines. Low-grade lesions can be followed up and managed according to ASCCP guideline algorithms. High-grade lesions are treated depending on the patient's age and fertility status. A patient that is pregnant will have their treatment deferred until after delivery unless there is a specific concern for an invasive lesion. Invasive lesions should be referred to an obstetrician and gynecologist and a gynecological oncologist for treatment options.

The general assessment is performed to determine whether there is adequacy or inadequacy for the reason (e.g., cervix obscured by inflammation, bleeding, and scar); to visualize the squamocolumnar junction and to determine whether

the visibility is completely visible, partially visible, or not visible; and also to visualize the transformation zone types 1, 2 and 3.

The colposcopy is performed to distinguish between normal and abnormal colposcopic cervical findings, which include the visualization of whether the original squamous epithelium is mature, columnar epithelium is atrophic or not, whether there is ectopy, metaplastic squamous epithelium, nabothian cysts, or crypt gland openings.

For visualizing abnormal colposcopic findings, the general characteristic features are looked into. The location of the lesion is observed, whether it is inside or outside the T-zone. The location of the lesion is also observed according to the clock position. The size of the lesion is examined, along with the number of cervical quadrants the lesion covers and size of the lesion in the percentage of the cervix. The grading of the lesion is done as follows: in grade 1, minor lesions, there would be thin aceto-white epithelium, irregular, geographic border, fine mosaic and fine punctation; in grade 2, major lesions, there would be dense aceto-white epithelium, rapid appearance of aceto-whitening, cuffed crypt (gland) openings, coarse mosaic, coarse punctuation, sharp border, inner border sign and ridge sign; in non-specific lesions, there would be leukoplakia (keratosis and hyperkeratosis), and erosion, Lugol's staining (Schiller's test) is done to observe whether the tissues are stained or non-stained. If the lesion is suspicious for invasion, there might be the presence of atypical vessels, or associated signs, such as, fragile vessels, irregular surface, exophytic lesion, necrosis, ulceration (necrotic), tumor, or gross neoplasm. Furthermore, miscellaneous findings might be seen in congenital transformation zone, condyloma, polyp (ectocervical or endocervical), inflammation, stenosis, congenital anomaly, post-treatment consequence, and endometriosis.

The scoring is done as follows:

Score	0	1	2
Aceto uptake	Zero or transparent	Shady, Milky (not transparent; not opaque)	Distinct, opaque white
Margins or surface	Diffuse	Sharp but irregular, jagged, 'geographical' satellites	Sharp and even, the difference in surface level, including 'cuffing'
Vessels	Fine, regular	Absent	Coarse or atypical
Lesion size	<5 mm	<5 mm 5–15 mm or 2 quadrants	>15 mm or 3–4 quadrants/ endocervical undefined
Iodine staining	Brown	Faintly or patchy yellow	Distinct yellow

Overall Swede Score

Overall Swede score	Colposcopic prediction of probable histology
0–4	Low grade/normal CIN 1
5–6	High grade/non-invasive cancer CIN 2+
7–10	High grade/suspected invasive cancer CIN 2+

Human Papillomavirus Associated Malignancies and Therapeutics

Human papillomavirus (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. Advanced-stage HPV-associated cancers are difficult to treat. Advanced-inoperable cervical cancer is a challenging entity due to increased percentage of locoregional and distant recurrences. Recurrent cervical cancer not amenable to radical treatment, as well as metastatic disease, is difficult to cure, with a bad prognosis.

Minimally invasive robotic surgery has become an effective surgical technique for the treatment of gynecologic malignancies, like cervical cancer. Minimally invasive surgery (MIS) is the standard approach to performance of several gynecologic procedures including hysterectomy, gynecologic 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, and 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-tumor 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 tumors, the efficacy of immune-checkpoint blockade therapy with antibodies directed against CTLA-4, PD-1, and PDL-1 in advanced gynecologic 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 and 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 tumors. Poor prognosis and early recurrence in cervical cancer have been associated with VEGF expression. Bevacizumab is a recombinant humanized 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, such as, 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 four amplification or HER2-overexpressed drugs in PDX significantly inhibited tumor growth compared with the control. A mTOR targeting drug, such as 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, such as 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, suhc as, 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 tumors, 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 tumor 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 tumor 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/tumor 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 through both Major Histocompatibility Complex Classes 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 tumor 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 tumor-infiltrating lymphocyte (TIL) cultures from fragments of a resected metastatic tumor 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. Tumor 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. Tumor-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, such as cell cycle inhibitors, histone deacetylases, cyclooxygenase-2 (COX-2), mammalian target of rapamycin (mTOR), heat shock protein (HSP), WEE1, NOTCH signaling, 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.[1-16]

CONCLUSION

Therefore, this descriptive analytical research on cervical malignancy, diagnostic colposcopy, cancer pharmacotherapeutics, immunotherapeutics and co-therapeutic modalities, well-delineates a detailed diagnostic colposcopy, cancer pharmacotherapeutics, immunotherapeutics, and co-therapeutic modalities. This study would certainly remain a landmark on the way toward future innovations in newer drug discovery and development of more appropriate, efficacious, safe, high quality, easily accessible, inexpensive, easily administered and comprehensively suitable drug, for a much better pharmacotherapy and immunotherapy of cervical malignancy, along with the other therapeutic modalities.

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