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Cervical Cancer- A Review

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Abstract
Cervical cancer is the third most leading cancer among women, is more prevalent in rural population. The rate and incidence of cervical cancer has declined due to HPV vaccination, screening and education. At present quadrivalent vaccine GARDASIL and bivalent vaccine CERVARIX are available in many countries where as in US the only available vaccine is GRADASIL-9 due to its more efficiency than quadrivalent and bivalent vaccine. Surgery and radiation are considered are best treatment for cervical cancer either individually or in combination. New immunotherapy has also discovered for treatment of cervical cancer.

Introduction

World-wide, cervical is considered as third most leading cancer among women in terms of new cases per year. The predominance (85%) of cervical cancer burden is in developing or less developed countries[1]. The incidence rate and death rate of cervical cancer in well developed countries has gradually declined due to cancer screening programs and Human Papillomavirus [HPV] vaccination programs sponsored by huge government budgets[2]. Today there is a superior understanding of natural history of human papilloma virus (HPV) infection and cervical carcinoma. Approximately all cases of cervical carcinoma are accompanied by chronic infection by carcinogenic HPV genotypes, which leads to progression of precancer in epithelium of cervix[3]. HPV types are classified into high risk and low risk types based on their biological properties and oncogenic potential[4].

Epidemology

Globally, cervical cancer is considered as third most common cancer among women[1]. To an extent of 5,60,505 new cases and 2,84,923 deaths occurred in 2015. With the determinant majority of around 85% cervical cancer cases and 87% of cervical cancer deaths occur in developing areas[5]. One of the major problems faced by Indian women is cervical cancer. In India about 1,20,000 women develop cervical cancer disease per year. India contributes 15.2% of the total cervical cancer deaths in world, cervical cancer deaths are more in rural areas when compared to urban population[6].

Prevention

Cervical cancer is caused by human papilloma virus, preventing HPV infection is necessary to prevent cervical cancer. It can be achieved either by vaccination or by complete abstinence from sexual activity[7].

Two vaccines are available intended to prevent this disease. They are quadrivalent vaccine GARDASIL and a bivalent vaccine CERVARIX, quadrivalent vaccine prevents against HPV 16, 11,16 and 18 and bivalent vaccine prevents against HPV 16 and 18. These vaccines are available and marketed in many countries considering as a prophylactic measure of HPV related diseases[5].

Both the HPV related antibodies decrease the incidence of premalignant chances of cervix and perineum all over by 93 percent and 62 percent individually[8].

Most often HPV vaccination is given to age 9 to 26 while the vaccination is potent if administered before the contamination take place. The immunization came into view to be efficacious no less than 4 to 6 years[8].

The bivalent vaccine (CERVARIX) and the quadrivalent vaccine (GRADASIL) were discontinued in United States in 2016 and 2017 respectively. At present GRADASIL9 is only vaccine available in United States, which targets HPV types 6,11,16,18 along with 31,33,45,55,58 - these causes 90 percent of cervical cases and most cases of genital warts[9].

Barrier Protection

Protection and use of spermicidal gel during sex reduces the risk of malignant chances of cervix. In addition, condoms are supportive in treating conceivable premalignant changes of cervix[8].

Screening For Early Detection of Cervical Cancer

Screening of asymptomatic women is done for prior diagnosis of cervical cancer, with an intention of identifying and treating the precancerous lesions of the cervix as an essential step to control cervical cancer[5].

Various screening options like cytology, testing for high risk HPV and visual based screening methods have been inspected and implemented in various regions ubiquitously[5].

Unique Characters of HPV to Interact with Host Immune System

The unique interaction of HPV with host immune system is achieved by three basic properties of HPV. As there is no viraemic phase, immune cells present in the circulation cannot approach the virus easily. The early infection is present on the basement membrane, where Langerhans cells are abundant cells present, especially in the apical layers of mucosa. The HPV does not elicit major damage to host cells, like lysis of the infected cell, minimises the inflammation and subsequent signalling allows the virus to duplicate silently. The expression off oncogenes is at too low levels throughout its initial life cycle. Highly immuneogenic substance like L1 and L2 capsid proteins are synthesised only in outer layers of the epithelium[10].

Pathway from HPV Infection to Carcinogenisis

HPV is a non-enveloped, circular, double stranded DNA virus approximately 8 kb in size that infects basal keratinocytes. Their genomes encode eight genes from E1, E2, E4, E5, E6, E7, L1, and L2 Open Reading Frame (ORF)[11].

A variety of cutaneous or mucous benign or malignant lesions can be caused by HPV. In most cases the infection is non symptomatic and can be solved rapidly by participation of host immune system[12].

While in some cases, the infection can be latent and reactive under some conditions like immune suppression. Typically, HPV types 16 and 18 are involved, in progression of lesions into invasive cancer[12].

Cervical intra epithelial neoplasia (CIN) is precancerous lesion which is precursor for cervical cancer. CIN is classified as CIN-1, CIN-2 and CIN-3 based on their degree of dysplasia, named as mild, moderate and severe. These lesions are non-symptomatic and many of them get progressed into invasive cancer in certain extent of time[12].

The most important proteins play role in malignant transformation of HPV related lesions are E6 and E7 proteins[12]. The function of HPV-16 E6 is to disintegrate the tumour suppressor protein p53 by the proteasome pathway. The

tumour suppressor protein p53 gets activated during either stress condition or if DNA damage occurs, there by positively regulates expression of gene involved in apoptosis. E6 interacts with a 100 k Da cellular protein, E6AP (E6 associated protein), which act as ubiquitin protein ligase (E3)[13].

The E6/E6AP complex binds to p53 gene and results in ubiquitinated, gets targeted by proteasomes for degradation. As the major role of p53 is protection of integrity of genome buy promoting apoptosis or cell cycle arrest, cells with the expression of HPV16 E6 protein shows chromosomal instability, which increases the chance, that the HPV infected cells will evolve towards malignancy[13].

E7 is particularly found in the nucleus and the ability to bind with retinoblastoma (Rb) protein, and inactivates its function. The Rb protein has a key regulation in cell cycle. E7, modulates cell proliferation and promotes early cell entry into S-phase of the cell cycle. E7 also reacts with p21 and p27, important regulators of the cell cycle as well[12].

Generally, in such conditions p53 gene mediates apoptosis. But E6 inhibits the function of p53. In combination, the two proteins promotes/lead to extensive malignant invasive lesions. Besides by supressing E6and E7 genes, some malignant cells return to their previous benign phenotype[12].

Treatment of Cervical Cancer

At present three therapeutic modalities are used, they are surgery, radiotherapy, hormone chemotherapy. The first two modes surgery and radiotherapy are dominant both individually and in combination. Surgery is only therapeutic approach in preinvasive and microinvasive stage (stage Ia) of cervical carcinoma. Surgery and radiotherapy are used combinedly in Ib and IIa stages, radiation alone is used in IIb, IIIa, IIIb and Iva. In IVb, chemotherapy and locoregional radiotherapy are used[14].

It is accepted nearly in all oncology and radiology centres of world that combined therapy for cervical cancer is most efficacious. Intracavity brachytherapy and teleradiotherapy are combined. The first step is to destroy the malignant tissue at the cervix and its instant surroundings, while others are demolishing secondary deposits in the area of parametrium, regional and juxtra regional lymph nodes and other organs of small pelvis[14].

Role of Bile Acids in Treatment of Cervical Cancer

HS-1183, HS-1199, and HS-1200are synthetic derivatives of ursodeoxycholic acid and chenodeoxycholic acid used in treatment of cervical cancer. Further, increase in p21 WAF1/CIP1 by synthetic bile acids was dynamically accompanied with proliferating cell nuclear antigen (PCNA), which is needed for the process of DNA synthesis by DNA polymerase[14].

Treatment with natural products are suitable control of cervical cancer, which show reduced harmful effects.HS-1199, HS-1200, HS-1183 induced apoptosis in SiHa cells in a dose dependent mode. It is very essential that the synthetic derivatives of chenodeoxycholic acid and ursodeoxycholic acid are able to inhibit cell proliferation and inducing apoptosis in SiHa cells[14].

Immune Therapy in Cervical Cancer

Cytotoxic T-lymphocyte associated Antigen – 4 (CTLA-4), the first immune check point receptor, expressed on t-cells, capable of down regulation T-cell activation, to prevent over stimulation of the immune system. CTLA-4 has more affinity toward the B7 complex than CD28 targeting this immune check point can increase antitumor immunity. Preclinical findings encourage the production and clinical testing of fully humanised CTLA-4 antibodies. Example: ipilimumab[15].

Programmed cell death protein 1 (PD-1) is also animmune check point receptor, that can induce major immune resistance by supressing the activity of T-cell in peripheral tissue during the time of inflammatory response of infection. Pembrolizumab is a highly selective humanised monoclonal IgG-A kappa isotope antibody targeting PD-1[15].

Immune Therapy Besides Pembrolizumab in Cervical Cancer

Table 1 Selected ongoing trials of immune-checkpoint inhibitors in cervical cancer[15].

Agents	Targets	Phase	Indication
pembrolizumab	PD-1	II	Multiple types of advanced solid tumors
pembrolizumab	PD-1	II	Advanced cervical cancer, in combination with chemoradiation
Durvalumab Tremelimumab	PD-L1 CTLA-4	I	Advanced solid tumors, including advanced cervical cancer
Atezolizumab Carboplatin Cyclophosphamide	PD-L1	Ib	Advanced breast cancer and gynecologic cancer
Ipilimumab	CTLA-4	I	FIGO stage IB2/IIA with positive para-aortic lymph nodes; cervical cancer following chemoradiation
Nivolumab Ipilimumab	PD-1 CTLA-4	I/II	Neoadjuvant cohort and metastatic cohort in virus-associated cancers including HPV induced cervical cancer
Nivolumab	PD-1	II	HPV-16-positive incurable solid cancers, treatment naïve or in second line, including HPV-16-included cervical cancer
Atezolizumab Bevacizumab	PD-1	II	Persistent, recurrent or metastatic cervical cancer
Ipilimumab	CTLA-4	II	Metastatic or recurrent HPV-related cervical cancer
Nivolumab	PD-1	II	Persistent, recurrent or metastatic cervical cancer

Conclusion

Cervical cancer is third most leading cancer among women, causing roughly 200,000 deaths and 500,000 new cases per annum. The incidence of cervical cancer is more in developing population when compared to developed areas. This can be overcome by early detection and appropriate treatment to infected women and by creating awareness among people. HPV vaccination also plays a huge role in reducing incidence of cervical cancer.

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