

CERVICAL CANCER - A REVIEW**Dr. R. Vimalavathini***

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ABSTRACT

Cervical cancer is the fourth most common cases of cancer in women and is completely curable if detected at early stages. Cancer of the cervix is a significant public health problem globally. The role of human papillomavirus (HPV) virus in developing cervical cancer has been established. Cisplatin has been the single agent effective in treatment of cervical cancer. Numerous molecular targeting agents are also being evaluated. This study aims to review the recent advances in diagnosis and management of cervical cancer

KEYWORDS: Cervical Cancer, HPV.**INTRODUCTION**

Cervical cancer a multi-factorial disease is the fourth most commonly diagnosed cancer in world. In India cervical cancer alone accounts for 17% of the cancer deaths. With treatment, all stages consolidated five-year survival rate is around 72%. Genetic susceptibility, HPV infection, smoking; fibre deficient diet, long term use of oral contraceptives, women in their teens, early and multiple pregnancies, increases risk of cervical cancer.^[1] Poverty and ignorance negatively affects medical care and screening.^[2] Most of cervical cancer cases are due to persistent infection with high-risk HPV of type 16 and 18. The E6 and E7 gene products inactivate two tumor suppressor proteins, namely (p53) and the retinoblastoma gene product (pRb) and E5 gene product induces an increase in mitogen-activated protein kinase activity, thereby enhancing cellular responses to growth and differentiation factors. This results in continuous proliferation and delayed differentiation of the host cell. The long-term exposure to carcinogens causes tissue damage which induces cell proliferation, inflammation, angiogenesis, in order to repair the tissues damaged. But tissue repair is invariably

accompanied by the suppression of anti-tumor immunity, which contributes to the survival of the malignantly transformed cells.^[3]

Other pathological processes contributing to cancer are damage to the genetic apparatus of cells such as activated oncogenes and chromosome instability, methylation of viral and cellular DNA and telomerase activation,^[4] inflammation^[5] disruption of the immune system^[6], immune evasion by tumor cell,^[7] metastasis^[8] angiogenesis and oxidative - nitrosative stress. Mitochondrial oxidative stress, abnormal accumulation of specific mitochondrial metabolites and functional deficits in mitochondrial permeability transition affects DNA and signalling pathways.^[9]

Signs and symptoms

Cervical cancer is usually asymptomatic until the cancer cells begin to invade the surrounding tissues. Early symptoms include atypical periods, pelvic pain, pain during intercourse, vaginal discharge and oozing during sexual activity. High mortality rates are because 70% of cervical cancer cases in India are being diagnosed at an advanced stage.^[1] Metastasis involves uterine body, vaginal walls, parametrium, peritoneal cavity, bladder, or rectum, ovaries, ureters, rectum and bladder. Hematogenous dissemination is rare and occurs in lung, liver, bone and bowel.^[10]

Majority of recurrences occur within 18-24 months from time of diagnosis.^[11] Common sites of pelvic recurrence are cervix, uterus, vagina, parametria, bladder, ureters, rectum, and ovaries.^[12] Most frequent distant sites are paraaortic lymph nodes, lungs, and supraclavicular lymph nodes. Treatment for recurrent cervical cancer is based on type of primary therapy received, recurrence site (local, regional, and/ or distant), disease-free interval, symptoms.

Diagnosis

In advanced countries, the occurrence is relatively less due to concerted efforts in identifying precancerous lesions at an early stage. DNA testing for HPV, cytologic screening, visual inspection with acetic acid (VIA), together with HPV vaccines is some of the measures which have proved effective in reducing cervical cancer in susceptible women. Further indicative strategies are colposcopy, loop electrical excision procedure and conisation These are done if the biopsy affirms serious cervical intraepithelial neoplasia. Imaging modalities are exploited for dissemination and metastasis.^[13]

Treatment

Treatment options are based on the stage of the cancer, the type of cancer, the patient's age and her reproductive phase. Treatment options include surgery, chemotherapy and radiation therapy. Carcinoma in situ is treated by cryosurgery, laser ablation, conisation and loop excision with lifelong follow-up. Early stages of cervical cancer are treated with hysterectomy with evacuation of the lymph hubs or radiation treatment, with or without chemotherapy. Total abdominal hysterectomy is advised in post reproductive age group and trachelectomy is advocated for women of reproductive phase. For advanced disease palliative therapy is mainstay.^[14]

Chemotherapy

Cisplatin is the most extensively studied and the most active single agent. Combination chemotherapy of cisplatin with paclitaxel or topotecan is recommended for recurrent or advanced cervical cancer. For patients with compromised renal function, carboplatin remains a reasonable option. In case of adenocarcinomas mitomycin C or the taxanes in combination with cisplatin is the standard of care. With increasing number of drugs myelosuppression and nephrotoxicity are the main side-effects. fosfamide regimens may, in addition cause encephalopathy.^[14]

Molecular targeted therapy

Novel Receptor tyrosine kinase (RTK) inhibitors, such as bevacizumab, sorafenib, imatinib, pazopanib, cediranib, are being evaluated since overexpression of the vascular endothelial growth factor are implicated in the development and progression of cervical cancer. EGFR inhibitors, such as gefitinib, erlotinib, cetuximab, lapatinib, trastuzumab, panitumumab, are being evaluated in cervical cancer since viral oncoproteins contribute to carcinogenesis by activating EGFR-Ras MAP kinase pathway. Celecoxib has shown some potential as medical treatment for cervical pre-invasive disease.

Src inhibitors, such as dasatinib, are being extensively studied for cervical cancer since preclinical studies reports suggests that HPV oncoproteins upregulates Src family kinases. Aberrant activation of mammalian target of rapamycin (mTOR) pathway may occur in cervical cancer and clinical trials with temsirolimus, alone or in combination with chemoradiation, are currently ongoing.

Demethylating agents, such as decitabine, may re-express tumor suppressor genes and are considered amongst the most innovative therapeutic strategies in cervical cancer. Tricostatin, Vorinostat and Valproic acid are HDAC inhibitor that can modulate tumor suppressor gene expression.

Veliparib, an oral PARP inhibitor has exhibited induction of apoptosis in cervical cancer. Antioxidant such as polyphenols Polyphenol also enhanced cisplatin chemosensitivity cervical cancer cells through apoptosis induction Antiviral agents namely lopinavir and cydofovir had favourable in vitro results.^[15]

Vaccination

Two vaccines namely Gardasil and Cervarix are recommended in females, to receive three doses of HPV vaccine at 11-12 years of age.^[16] Gardasil targets HPV 6, 11, 16 and 18 and Cervarix acts against types 16 and 18. Though HPV antibodies are commonly given to age 9 to 26 but the high cost of antibody is a matter of concern.^[2]

Shock, fear, self-blame, and anger are the most common emotions experienced by women diagnosed of cervical cancer and may experience loss in Quality of Life and sexual difficulties.^[17] Women diagnosed of cervical cancer require lot of counselling regarding psychosexual problems, social support patience and time to make them strong enough to deal with the disease and its treatment.^[18]

Cervical Cancer in Pregnant Women

Treatment depends mainly on gestational age, disease stage, histology and women's need. When preservation of pregnancy is not required, hysterectomy and chemo-radiotherapy are feasible options. When surgical treatment during pregnancy is not possible, chemotherapy can be given until fetal maturation, followed by radical hysterectomy in postpartum period.^[19]

CONCLUSION

Numerous studies have shown that women's awareness of the established link between HPV and cervical cancer, and the importance of cervical screening, is still lacking. Different techniques for counteractive action include: having few or no sexual accomplices and the utilization of condoms. Women must continue to become more aware of the factors contributing to the development of cervical cancer, get involved in screening programs and in creating public awareness.

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