UNIT NO. 4

HUMAN PAPILLOMA VIRUS (HPV) & CERVICAL CANCER

Dr Tay Eng Hseon

ABSTRACT

The confirmation of the central etiologic role of genital human papilloma virus (HPV) in cervical carcinogenesis led clinicians to use HPV testing as an adjunctive test to the Pap test and investigators to explore its role as a primary screening method. Studies on HPV vaccines, using viral-like particles (VLPs), are also underway, with the anticipated perceived potential of eradicating a large proportion of the cervical cancer incidence in the latter part of this century. It will immunise subjects against HPVs 16 &18, which together causes about 70% of cervical cancer and HPV 6 & 11, which cause about 90% of genital warts. A therapeutic vaccine is still experimental, largely targeting at the treatment of cervical intra-epithelial neoplasia (CIN).

INTRODUCTION

1. The confirmation of the central etiologic role of genital human papilloma virus (HPV) in cervical carcinogenesis led clinicians to use HPV testing as an adjunctive test to the Pap test and investigators to explore its role as a primary screening method.
2. Studies on HPV vaccines are also underway, with the anticipated perceived potential of eradicating a large proportion of the cervical cancer incidence in the latter part of this century.

HPV CAUSES CERVICAL CANCER – WHERE IS THE EVIDENCE?

1. In 1995, the International Biologic Study on Cervical Cancer (IBSCC) Study Group confirmed the role of genital HPVs as the central etiologic factor in cervical cancer worldwide. In this study, polymerase chain reaction (PCR) assays detected HPV DNA in 93% of cervical cancers specimens collected from 22 different countries[1].
2. Earlier laboratory work had demonstrated that the E6 & E7 proteins of oncogenic HPV genomes bind to tumour suppressor gene products, p53 and Retinoblastoma (Rb) factors, which provided a plausible mechanism for HPV-induced cervical neoplasm, hence lending support to its causal role[2,3].
3. However, believing the results of the IBSCC study (93%) to be an underestimate, Walboomers et al reanalysed the 7% HPV-negative cases for HPV serum antibodies and HPV DNA. This study used a more stringent procedure to ensure the presence of carcinoma cells within the materials used for PCR. In addition, three different PCR assays targeting different open reading frames were used. Combining the data from the latter and the previous study and excluding inadequate specimens, the authors calculated the worldwide HPV prevalence in cervical carcinomas to be 99.7%. This finding of the presence of HPV in virtually all cervical cancers is the highest world-wide attributable fraction so far reported for a specific cause of any major human cancer[4].

HPV AND HUMAN INFECTION

1. There are more than 100 types of HPVs. Approximately 35 of them causes anogenital infection, of which slightly more than a dozen are considered to have high oncogenic risk.
2. Over 50% of sexually active adults will become infected with HPV during their lifetime. In general, about 10-20% of sexually active women are infected with the high oncogenic strains of the HPV.
3. In particular, HPV 16 and 18 causes about 70% of the high grade cervical dysplasia and cervical cancer, whereas HPV 6 and 11 causes >90% of genital warts.
4. As with many viral diseases, infection with HPV will stay with the human host until it is eliminated by the host immune system. As such, HPV infection in many young ladies is usually transient and most will be eliminated by the age of 40-50 years old.
5. However, certain women succumb to the oncogenic potential of some of these viruses and develop cervical cancer. Smokers and immuno-suppressed patients (e.g. HIV patients. Autoimmune diseases, etc.) are particularly prone to carcinogenic transformation.
6. HPV 16 is most commonly linked with cervical cancer; found in 50% of cervical cancers. HPV 18 causes about 20% and the other HPV types cause the rest. Still other types of HPV cause anogenital warts, which are non-cancerous but can be extensive and difficult to treat.

WHY A VACCINE FOR THE PROPHYLAXIS OF CERVICAL CANCER?

1. Most deaths from cervical cancers occur in countries where women do not have regular Pap tests. However, an effective Pap smear screening programme requires a large amount time and effort to set up and maintain.
2. Therefore, a viral vaccine against common and high-risk HPV is certainly an attractive method of eradicating cervical cancers. Vaccination is less complicated and may be more practical in many parts of the world.

TAY ENG HSEON, Chairman Medical Board, Kandang Kerbau Women's & Children's Hospital
Senior Consultant, Gynaecological Cancer Centre, Kandang Kerbau Women's & Children's Hospital

3. The concerns of vaccination, however, are its efficacy, duration of protection and safety.

PROPHYLACTIC HPV VACCINE DEVELOPMENT

HPV 16 - L1-E7 fusion protein expression is used to generate Chimeric Papillomavirus. Like Particles (CVLPs) of HPV 16. The immunisation of mice induces the production of antibodies that will neutralise L1 VLPs and E7-specific T cells in vitro and vaccinated animals were found to be protected against tumour growth following inoculation of HPV16-transformed cells. It was also noted that they have therapeutic effect on pre-existing tumours, therefore, CVLPs are deemed to be suitable for prevention and therapy of HPV infection[5].

Intranasal immunisation induces serum IgG production and vaginal IgA secretory antibodies were detected in the vagina. In addition both splenic & vaginal lymphocytes can be activated[6].

Live Recombinant Vacinia Virus expressing E6 E7 proteins of HPV 16 & 18 (TA-HPV) were tested in 8 patients with late stage cervical cancer. The patients vaccinated with a single dose TA-HPV. There were no significant clinical side-effects and 3 out of 8 patients developed HPV-specific response. HPV T-lymphocytes were detected in one of the 3 evaluable patients[7].

Highly purified virus-like particles of L1 capsid polypeptides are individually expressed by yeast host cells using an expression vector to drive the host cells. They are not a live virus & do not contain viral DNA. The VLPs are isolated from lysed yeast cells, purified, and adsorbed into adjuvants without preservatives.

ANIMAL STUDIES

Mice given research-grade vaccine material, resulted in robust individual serum antibody response to VLP.

Likewise, African Green Monkeys produced good antibody response in all animals tested. Safety studies in animals showed no major adverse reactions. There was no animal death, no adverse effect on body weight gain, no drug-related signs of irritation and unaffected microscopically. Therefore, paving the way to human studies.

PROOF OF CONCEPT

Investigational vaccines have been developed using viral-like particles (VLPs). It will immunise subjects against HPVs 16 &18, which together causes about 70% of cervical cancer and HPV 6 & 11, which cause about 90% of genital warts.

A controlled trial of a monovalent HPV type 16 vaccine has confirmed a high rate of seroconversion, with a 100-fold increase in the concentration of anti-HPV-16 antibodies. The same randomised controlled study showed that none of the 768 women in the HPV vaccine arm developed HPV-16 infection or HPV-16 CIN. But 41 of the 765 women in the placebo arm acquired HPV-16 infection and 9 developed HPV-16 CIN[8].

The efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women was tested in a randomised controlled trial[9]. In the according-to-protocol analyses, vaccine efficacy was 91.6% (95% CI 64.5-98.0) against incident infection and 100% against persistent infection (47.0-100) with HPV-16/18. In the intention-to-treat analyses, vaccine efficacy was 95.1% (63.5-99.3) against persistent cervical infection with HPV-16/18 and 92.9% (70.0-98.3) against cytological abnormalities associated with HPV-16/18 infection. The vaccine was generally safe, well tolerated, and highly immunogenic. The bivalent HPV vaccine was efficacious in prevention of incident and persistent cervical infections with HPV-16 and HPV-18, and associated cytological abnormalities and lesions[9].

Such vaccines will be applicable to both men and women. There has been no serious adverse experience (AE) in several preliminary protocols studied to-date. Most AEs were due to local injection sites reaction, which were encountered in both HPV vaccine and Placebo groups of subjects.

THERAPEUTIC VACCINE

A therapeutic vaccine is still experimental, largely targeting at the treatment of cervical intra-epithelial neoplasia (CIN).

Polynucleotide and recombinant viral vaccines encoding non-structural viral proteins show therapeutic and prophylactic efficacy in animal models and are candidate immunotherapies for established low-grade benign genital infections. Vaccines designed to elicit cytotoxic T-lymphocytes specific for the HPV oncoproteins E6 and E7 show immunogenicity and efficacy in transplantable tumour models in rodents. In Phase I and II trials these vaccines are immunogenic and safe but show limited efficacy[10].

In a phase I/II clinical trial, the potential use of the MVA E2 recombinant vaccinia virus to treat cervical intraepithelial neoplasia CIN 1, CIN 2, and CIN 3 lesions associated with human papillomavirus (HPV) infection was evaluated. Seventy-eight women with CIN 1-, CIN 2-, and CIN 3-grade lesions were treated with either an MVA E2 recombinant virus vaccine or with cryosurgery. The results showed that therapeutic vaccination with MVA E2 vaccine was an excellent prospective means for stimulating the immune system and causing the regression of precancerous CIN 1, CIN 2, and CIN 3 lesions when the vaccine was given locally[11].

THE FUTURE

Vaccination for HPV in combination with screening can be a cost-effective health intervention, but it depends on maintaining effectiveness during the ages of peak oncogenic HPV incidence.

Identifying the optimal age for vaccination should be a top research priority.

However, successful prophylactic cervical cancer vaccines may not eliminate the requirement for a screening program, and the feasibility of HPV testing has not been demonstrated in the setting of a low-resource, developing country. Pap

testing will continue to be a relevant screening tool for the near future.

Vaccination against HPV infection could reduce the risk of infection and, most importantly, may decrease the incidence of cervical cancer.

REFERENCES

1. Bosch, Manos, Munoz, Sherman, Jansen, Moreno, Kurman and Shah. Prevalence of human papillomavirus in cervical cancer: A worldwide perspective. J Natl Cancer Inst 1995; 87:796-802.
2. Dyson, Howley, Munger, Harlow. The human papillomavirus 16 E7 oncoprotein is able to bind the retinoblastome gene product. Science 1989; 172:331-40.
3. Werness, Levine, Howley. Assoication of human papillomavirus type 16 and 18 E6 protein with p53. Science 1990; 248:76-9.
4. Walboomers JMM et al. Human Papilloma Virus is a necessary cause of invasive cervical cancer worldwide. J Pathol. 189: 12-19 (1999).
5. Chimeric Virus-Like Particles of the HPV Type 16 as a Prophylactic and Therapeutic Vaccine. Jochmus I et al. Arch Med Res 1999;Jul-Aug; 30(4):269-74.
6. Cytotoxic T Lymphocytes in Vaginal Draining Lymph Nodes. Dupuy C et al. J Virol 1999;Nov; 73(11):9063-71.
7. A recombinant vaccinia virus encoding HPV types 16 & 18, E6 & E7 proteins s immunotherapy for cervical cancer. Borysiewivz LK et al. Lancet 1996; 347:1523-7.
8. Koutsky LA et al. A Controlled Trial of a Human PapillomaVirus Type 16 Vaccine. NEJM. 2002; 347(21):164551.
9. Harper DM et al. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. Lancet. 2004 Nov 13; 364(9447):1757-65.
10. Stanley MA. Progress in prophylactic and therapeutic vaccines for human papillomavirus infection. Expert Rev Vaccines. 2003 Jun; 2(3):381-9.
11. Corona Gutierrez CM et al. Therapeutic vaccination with MVA E2 can eliminate precancerous lesions (CIN 1, CIN 2, and CIN 3) associated with infection by oncogenic human papillomavirus. Hum Gene Ther. 2004 May; 15(5):421-31.

LEARNING POINTS

1. **The confirmation of the central etiologic role of genital human papilloma virus (HPV) in cervical carcinogenesis led clinicians to use HPV testing as an adjunctive test to the Pap test and investigators to explore its role as a primary screening method.**
2. **Studies on HPV vaccines, using viral-like particles (VLPs), are also underway, with the anticipated perceived potential of eradicating a large proportion of the cervical cancer incidence in the latter part of this century. It will immunise subjects against HPVs 16 &18, which together causes about 70% of cervical cancer and HPV 6 & 11, which cause about 90% of genital warts.**
3. **A therapeutic vaccine is still experimental, largely targeting at the treatment of cervical intra-epithelial neoplasia (CIN).**
4. **Vaccination for HPV in combination with screening can be a cost-effective health intervention, but it depends on maintaining effectiveness during the ages of peak oncogenic HPV incidence.**
5. **Identifying the optimal age for vaccination should be a top research priority.**
6. **Successful prophylactic cervical cancer vaccines may not eliminate the requirement for a screening program, and the feasibility of HPV testing has not been demonstrated in the setting of a low-resource, developing country. Pap testing will continue to be a relevant screening tool for the near future.**
7. **Vaccination against HPV infection could reduce the risk of infection and, most importantly, may decrease the incidence of cervical cancer.**