THEME

Gynaecological malignancies

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HPV vaccination

A paradigm shift in public health

BACKGROUND

In 2006, the world's first quadrivalent human papillomavirus (HPV) vaccine (Gardasil) was made available to the Australian public. The quadrivalent HPV vaccine protects against cervical cancer, cervical abnormalities, and genital warts related to HPV types 6, 11, 16 and 18. General practitioners play a vital role in preventive medicine and as such should have a good understanding of the vaccine and its role in the primary prevention of cervical cancer and precancers.

OBJECTIVE

This article provides an overview of the HPV vaccine including efficacy and safety as it relates to its approved use in Australia.

DISCUSSION

The vaccine (Gardasil) is quadrivalent, providing protection against HPV types 6, 11, 16 and 18. These HPV types represent a significant burden on public health as they are responsible for 70% of cervical cancers, a substantial proportion of cervical abnormalities, and 90% of genital warts. The quadrivalent HPV vaccine (Gardasil) is indicated for females aged 9–26 years and males aged 9–15 years and should ideally be administered before the onset of sexual activity, however sexually active patients will also benefit.

The long awaited prophylactic human papillomavirus (HPV) vaccine became available in Australia in August 2006. Its introduction has been welcomed by health care professionals as a paradigm shift in public health. Up until now, detection of precancerous cervical lesions was central to preventing cervical cancer. With the availability of Gardasil, primary prevention of both precancerous and cancerous cervical lesions is possible. Together, screening and vaccination will potentially further reduce the burden of this disease. Australia is the third country worldwide to approve the vaccine following Food and Drug Administration approval in June 2006. Approval for marketing in Europe was granted in September 2006.

Although the incidence of cervical cancer in Australia is low, the incidence of precancerous abnormalities is considerable. In 2004, approximately 14 500 women were diagnosed with high grade abnormalities (on histology) requiring surgical treatment, and a further 16 500 women were diagnosed with low grade abnormalities (on histology) requiring further investigation and/or follow up. As well as the physical burden, these procedures and treatments are associated with psychological effects such as anxiety and stress.

In Australia, the Commonwealth Government will fund the vaccine for females aged 12–26 years from 2007. Gardasil will be put on the National Immunisation Program on an ongoing basis for girls aged 12–13 years to be delivered through schools. The government will also fund a 2 year catch up program for females aged 13–18 years in schools, and women aged 18–26 years to be delivered through general practitioners. The current cost on a private prescription for a course of immunisation with quadrivalent HPV vaccine (Gardasil) is $460 for three doses administered over 6 months.

The vaccine provides protection against HPV types 6, 11, 16 and 18. Human papillomavirus types 16 and 18 cause 70% of cervical cancer cases and approximately 50% of high grade cervical abnormalities, while HPV types 6 and 11 cause 90% of genital warts and 10% of low grade cervical abnormalities.[1] In females aged 9–26 years, the quadrivalent HPV vaccine (Gardasil) is indicated for the prevention of cervical, vulvar and vaginal cancer, precancerous or dysplastic lesions, genital warts, and infection caused by the vaccine HPV types. In males aged 9–15 years, the quadrivalent HPV vaccine (Gardasil) is indicated for the prevention of infection due to HPV types 6, 11, 16 and 18.[1] A bivalent vaccine (Cervarix) containing only HPV types 16 and 18 is likely to become available in Australia during 2007. Clinical trials have affirmed the immunogenicity and efficacy of the vaccine due

to HPV types 16 and 18, with further results from phase III trials expected in 2008.

Human papillomavirus

HPV overview

Human papillomavirus is now universally recognised as a necessary agent for the development of cervical cancer with HPV being present in 99.7% of cervical cancers.[2] The virus is also associated with over 90% of genital wart cases, approximately 70% of anal cancers, approximately 50% of penile cancer lesions, and approximately 20% of oropharyngeal cancers.[3,4] There are over 100 HPV subtypes including 40 anogenital types with some 15 high risk (oncogenic) types such as HPV 16, 18, 31 and 45 conferring cervical cancer risk. High risk HPV types are found in different proportions throughout the world, however HPV 16 and 18 are responsible for at least 70% of cervical cancers and 50% of high grade lesions worldwide.[5,6] Low risk subtypes such as 6 and 11 are involved in greater than 90% of genital warts and approximately 10% of low grade cervical abnormalities[3,7] (*Table 1*).

Natural history of HPV

Human papillomavirus is a nonenveloped double stranded circular DNA virus. The virus is highly infective with transmission rates of over 50% following exposure to a person with productive anogenital HPV infection.[8] The highest prevalence of HPV infection has been identified in sexually active women 25 years of age and younger.[9] Up to 80% of sexually active women and men will be exposed to at least one type of HPV in their lifetime.[10]

Infection with the anogenital types occurs largely through any type of genital contact. Condoms can reduce transmission, but do not prevent infection.[9,11] Human papillomavirus enters the body through micorabrasions in the anogenital skin and replicates in the basal epithelial cells. Infection is often subclinical but may present as condyloma (warts), cervical or anogenital abnormalities and cancers (*Figure 1*). Most women who contract HPV infection clear it spontaneously within a median of 8–14 months with persistence of a high risk HPV type only occurring in 3–10% of women. Low grade squamous epithelial lesions (LSIL) seen on Pap smears reflect acute infection with HPV and regression occurs in most cases. Much of the burden of this 'low grade disease' occurs in young women.[8] High grade squamous intraepithelial lesions (HSIL) as noted on Pap smears probably represent viral persistence and integration of HPV DNA and require treatment. Progression of these lesions and the development of invasive squamous carcinoma of the cervix can occur over time. In Australia, approximately 80% of these high grade cervical abnormalities (as detected on histology) occur in women under the age of 40 years.[12] Procedures to remove these lesions are associated with increased risk for adverse pregnancy outcomes.[13] The reduction in cervical cancer rates in Australia reflects an active Pap screening program and the surgical removal of high grade precancerous lesions.

Table 1. Effects of HPV infection

HPV type	Women	Men
16/18	• 70% of cervical cancer[5] • 50% of CIN 2/3[6] (HSIL) • 25% of CIN 1[7] (LSIL) • Most anal cancers[4]	• Most anal cancers[4] • Potentially prevention of infection (reduced transmission to women)
6/11	• 10% of CIN 1[7] • >90% of genital warts[3]	• Potentially prevention of infection (reduced transmission to women) • >90% of genital warts[3]

Vaccine development

Vaccination aims to produce neutralising antibodies capable of preventing infection by binding tightly to the surface of the virus and physically preventing the virus from docking with, and attaching to, a host cell. Human papillomavirus capsid structural proteins are the logical target for such antibodies, but HPV itself has been notoriously difficult to artificially culture. The landmark discovery of the 'late' capsid proteins 'L1' is widely recognised as leading to the development of the HPV vaccine. L1 assembles to form empty capsids, known as virus-like particles (VLPs) when expressed in yeast or other cells (*Figure 2*). Virus-like particles contain no infectious genetic material and because they are recombinant proteins have no oncogenic or disease causing potential, therefore being ideal for use as vaccines.[9]

The quadrivalent HPV vaccine (Gardasil) contains highly purified VLPs of the major capsid protein (L1) of the HPV types 6, 11, 16 and 18. The VLPs mimic the shell of the virus and are capable of generating potent antibody responses.[1] Australia can lay claim to a vital part of the HPV vaccine development story as it was 2006 Australian of the Year, Professor Ian Frazer, and Dr Jian Zhou, who worked as part of a research team at the University of Queensland to identify the VLPs.

Efficacy studies

Efficacy trials for the quadrivalent HPV vaccine (Gardasil) included two randomised, double blind, placebo controlled trials – FUTURE I and II. In these studies 5746 and 12 157 women aged 16 to 26 years respectively, were evaluated in 33 countries including Australia.[1] The clinical trials did not exclude women with evidence of HPV infection. Of the approximately 20 000 mostly sexually active women enrolled

in the phase II and III clinical trial program, 73% were naive to all four vaccine HPV types before vaccination.[1]

After a follow up of approximately 2 years (on average) among women who were naive to the relevant HPV types before vaccination, the efficacy of the quadrivalent HPV vaccine (Gardasil) was 100% for the prevention of HPV 16 or 18 related cervical intraepithelial neoplasia (CIN) grade 2 or worse or AIS (adenocarcinoma in situ), 95% efficacy for the prevention of CIN (any grade) caused by HPV 6, 11, 16 or 18 and 99% efficacy for the prevention of external genital lesions (genital warts and vulvar or vaginal intraepithelial lesions) due to the vaccine HPV types.[1,14] Evidence of efficacy was observed to commence during the vaccination period.

The vaccine is best administered before the onset of sexual activity and therefore before potential infection with HPV, however, sexually active women also stand to benefit from vaccination. In women with previous HPV infection, as indicated by the presence of either antibodies or HPV DNA in samples at baseline, the vaccine was effective in preventing disease due to the remaining HPV types (to which they were naïve). Among women seropositive or DNA positive to one or more of the vaccine HPV types, the vaccine (Gardasil) was 100% effective against CIN 2 or worse or AIS due to the remaining HPV types. The vaccine was also highly effective against external genital lesions.[14]

Currently, efficacy data to 5 years is available from the phase II trials, where the combined incidence of HPV 6, 11, 16, and 18 related persistent infection or disease was reduced in vaccine recipients by 96%.[15]

The overall efficacy of quadrivalent HPV vaccine (Gardasil) will depend on the baseline prevalence of HPV infection and disease in the population vaccinated.[1] This is because the quadrivalent HPV vaccine has not been shown to protect against the consequences of all HPV types and will not protect against established disease caused by the HPV types contained in the vaccine.

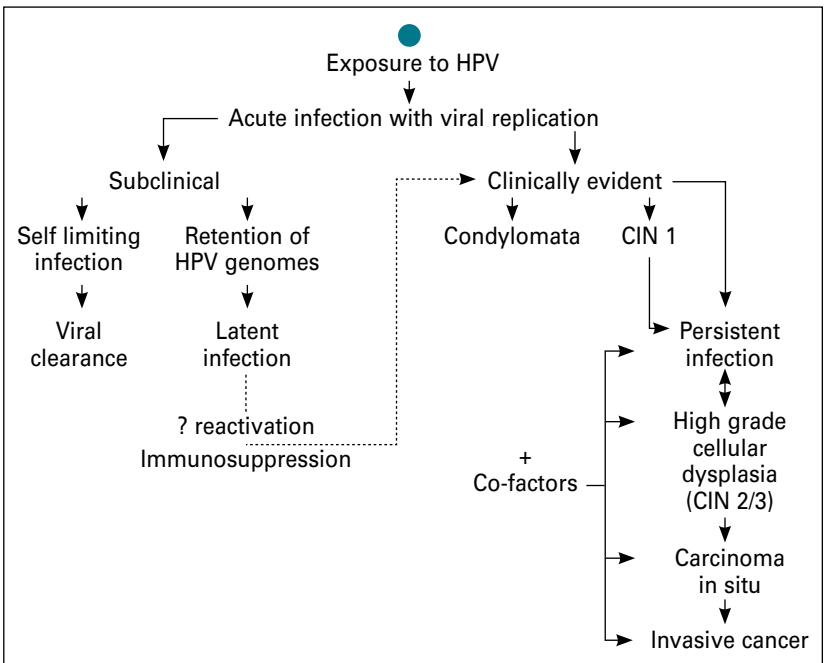

Figure 1. The natural history of HPV infection
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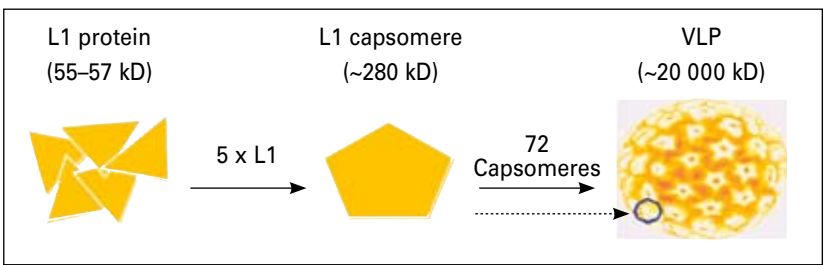

Figure 2. VLPs: breakthrough to HPV vaccine
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Immunogenicity

The quadrivalent HPV vaccine appears to be highly immunogenic. Over 99.5% of subjects became seropositive to all four HPV types by 1 month after the third dose. Antibody levels induced by the vaccine were substantially higher than those observed in women with evidence of natural HPV infection and a subsequent immune response.[1] Antibody levels in males aged 10–15 years and females were significantly superior to that observed in those aged 16–23 years. Immunogenicity data has been used to link efficacy in females 16–26 years to the younger populations.[1] Antibody response appears prolonged and evidence of an immune memory response has been observed.[16] Sentinel cohorts have been set up to evaluate long term efficacy well in advance of the general population. The need for booster vaccination is not yet established, although long term protection is anticipated. Other similar models such as hepatitis B vaccination,[17] give confidence for long term protection.

Vaccination target group

The quadrivalent HPV vaccine (Gardasil) is registered for use in females 9–26 years of age and males aged 9–15 years.[1] Vaccination will benefit all patients within this age group with the greatest benefit being derived if administered before the onset of sexual activity. Even if a patient has been sexually active and infected with one of the four types in the quadrivalent HPV vaccine, they will still benefit from vaccination against the other three. In fact, in clinical studies of the women who had been infected with at least one vaccine HPV type, most were infected with only one type. Therefore sexually active women should not be discouraged or excluded from vaccination.

It is important to note, HPV vaccination is not a substitute for a Pap test and women should be instructed to continue with regular screening as not all oncogenic or high risk types are covered by the current vaccine. In addition, vaccination is not a treatment for existing HPV related disease – it is preventive of infection with four HPV types. Efficacy studies are ongoing in men and older women with data likely to be available in 2–3 years.

Protocol for vaccination

The quadrivalent HPV vaccine (Gardasil) is available as a prefilled syringe for ease of use. Each 0.5 mL dose contains approximately 225 µg of aluminium adjuvant. It should be administered intramuscularly in three doses of 0.5 mL, at 0, 2 and 6 months. However, in clinical studies efficacy has been demonstrated in individuals who have received all three doses within 1 year.[1]

If an alternative vaccination schedule is necessary, the second dose should be administered at least 1 month after the first dose and the third dose should be administered at least 3 months after the second dose.[1] Concomitant administration of quadrivalent HPV vaccine with hepatitis B vaccine has been demonstrated as safe and as immunogenic as when injections are given separately.[1]

Side effects and safety

In clinical trials, quadrivalent HPV vaccine (Gardasil) demonstrated a favourable safety profile when compared with placebo. Few subjects (0.2%) discontinued due to adverse experiences. Local symptoms such as injection site reactions (pain, swelling, erythema) were reported. The majority of patients (94.4%) who received Gardasil judged their injection site reaction to be mild or moderate in intensity. Fever has also been reported.[1]

Approximately 10% of participants in the FUTURE studies became pregnant and were instructed to defer completion of the vaccination regimen until resolution of the pregnancy. Outcomes of these pregnancies were comparable in subjects who received placebo and subjects who received the quadrivalent HPV vaccine (Gardasil). However, women should not electively vaccinate if pregnant. The quadrivalent HPV vaccine (Gardasil) has been designated Category B2 status in pregnancy. There is no contraindication to the use of the vaccine during lactation.[1] Normal precautions such as not vaccinating during a moderate to severe febrile illness and inquiry into hypersensitivity to yeast or other vaccine component(s) should be followed.[1]

Conclusion

Human papillomavirus vaccination presents a paradigm shift in the management of cervical cancer. Combined with cervical screening, vaccination will provide women with their best chance of protection against cervical cancer and cervical abnormalities. The quadrivalent HPV vaccine (Gardasil) is indicated for females aged 9–26 years and males aged 9–15 years and should ideally be administered before the onset of sexual activity, however sexually active individuals will also benefit. The vaccine will be funded in Australia for females aged 12–26 years from 2007 as part of the National Immunisation Program.

Summary of important points

- The quadrivalent HPV vaccine (Gardasil) protects against HPV types 6, 11, 16 and 18.
- HPV types 16 and 18 cause 70% of cervical cancer cases and 50% of high grade cervical abnormalities.
- HPV types 6 and 11 cause 90% of cases of genital warts and approximately 10% of low grade cervical abnormalities.
- Vaccination is indicated for females aged 9–26 and males aged 9–15 years.
- Best time to vaccinate: the sooner the better – ideally before onset of sexual activity, although sexually active women will also benefit.
- Women should continue with regular Pap tests as not all oncogenic or high risk types are covered by the vaccine.
- Vaccination is not a treatment for existing HPV related disease – it is preventive of infection with four HPV types.

Conflict of interest: Jenny May is a member of CSL Ltd's GARDASIL® Advisory Board.

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