Immune Response Modifiers: Human Papilloma Virus and Beyond

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Speaker:	Prof. B. Berman
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In this lecture, the speaker presented an update on human papilloma virus (HPV) infection and its treatment using interferon and imiquimod.

Epidemiology

Human papilloma virus infection is an important and common infection. In 1997, it was estimated that 75% of American adults have genital warts or have serological evidence of HPV infection. Polymerase chain reaction in detecting HPV virus was positive in 46% of young females having routine pre-college gynaecological examination. The lifetime risk was calculated to be 79%.

Virology

Human papilloma virus has a molecular weight of 5,000,000 kda and contains 8,000 base pairs of circular double stranded DNA. The fact that it has no envelope means that it is resistant to drying and cryotherapy. Cryotherapy only eradicates HPV infection indirectly by destruction of the epidermal cell. An anti-HPV vaccine is in development and targets the "late region" of DNA known as L1-major nucleocapsid protein. In the "early region", viral E5 protein is responsible for epithelial cell proliferation, E6 protein binds to p53 tumor suppression gene, and E7 protein binds with tumor suppression gene Rb (Retinoblastoma). Both E6 and E7 proteins are always expressed in HPV-related cancer including cutaneous squamous cell carcinoma, cervical intraepithelial neoplasm, carcinoma of cervix and anal squamous cell carcinoma.

There are at present up to 80 different subtypes of HPV viruses. HPV types 1, 2, 3 and 7 are associated with plantar warts, common warts, plane warts and butcher's warts respectively. In epidermodysplasia verruciformis, sunlight is co-carcinogenic with HPV types 5 and 8. UVB converts trans-urocanic acid to cis-urocanic acid, which induces p53 gene mutation. Genital warts are associated with HPV types 6, 11, 16, 18, 31, 33 and 35. The use of aceto-whitening as a diagnostic test for genital warts is now declining in US as it only allows maceration at thickened stratum corneum and does not detect HPV giving a false positive rate of up to 50%. Latent HPV infection is detected by polymerase chain reaction.

HPV types 16, 18, 31, 33, 35 are associated with cervical carcinoma. As the anus shares the same histology with ectocervix, it is important to remember that peri-anal warts (HPV types 6, 11, 16) are associated with anal squamous cell carcinoma. A number of centers are now doing "PAP smear" for anal lesions looking for anal intraepithelial neoplasia (AIN).

Interferon (IFN)

First discovered in 1957, IFN is now established as an anti-viral agent with anti-proliferative and immuno-modulatory effects. It has the ability to up-regulate tumor suppressor gene p53, reduce oncogene (c-myc, -fos, h-ras) expressions and enhance apoptosis. In the treatment of genital wart, IFN has been shown to give cure rates of 54-70% requiring 9-16 injections over 3-8 weeks. Its side-effects include pain, fever, myalgia and headache.

Imiquimod

This immuno-modulator causes local induction of IFN, tumor necrosis factors, interleukin (IL)-1, IL-6 and IL-8. It binds to macrophages and promotes gene expressions of these immunological cytokines.

Treatment of genital warts

Currently FDA has approved the use of imiquimod, applying three times per week for eight hours, for

treating genital warts. Edwards showed that 5% imiquimod cream is an effective and safe self-administered therapy for external anogenital warts when applied three times a week overnight for up to 16 weeks. The recurrence rate is low. Using strict complete clearance as an end point, 54% of patients showed complete clearance over 16 weeks, while 81% of patients showed more than 50% clearance over the period. Side effects of topical imiquimod are mild and local erythema is the commonest. Over use of topical imiquimod may cause excess inflammatory response and erosions may occur. These erosions are characteristically painless and will resolve on stopping imiquimod. Other studies confirmed that imiquimod exerted its effect with detection of increased local immunological cytokines levels and a reduction of HPV viral load. Patients may prefer to have their genital wart removed immediately rather than waiting for imiquimod to take its effect. Two pilot studies assessed the safety of using imiquimod combined with local destructive therapy in treating genital warts. After local destruction with cryotherapy or electrocautery, imiquimod is immediately applied to the site to eradicate residual virus. Both studies showed that the median time to healing following wart ablation was unaffected. Thus, it appears to be safe to combine local destructive therapy and imiquimod.

Treatment of "off-label" conditions

Common and plantar warts

Clearance of common warts that were resistant to ablation and 5-florouracil had been seen in patients using topical imiquimod. It is possible that these patients, who were resistant to destructive modalities and had multiple recurrences, often benefit from immunotherapy. For treating plantar warts, the speaker suggested the use of topical salicylic ointment or retinoid in the morning followed by imiquimod in the evening. Co-administration of another topical agent with imiquimod is not recommended as it may affect the stability of the preparation and also lowers the effective concentration. Occlusive therapy with imiquimod under tegaderm for three days is also helpful and patient compliance is good.

Molluscum contagiosum

A safety study applying imiquimod to thirteen children (5 girls and 8 boys with a mean age of 7) with molluscum contagiosum every night for four weeks showed no systemic upset. Forty-two percent had no local side effect but 50% has mild inflammatory reactions.

Keloid excision sites

Previous studies showed that recurrence rates of keloid after excision in one year were 51% (excision alone), 58% (with intralesional steroid after excision) and 19% (with intralesional IFN at day of excision and 1 week later). IFN works by enhancing keloidal collagenase activity, reducing keloidal collagen and glycosaminoglycans synthesis and induce apoptosis. In a pilot study, use of imiquimod once per day at keloid excision site for two months had showed no recurrence six months after excision in eight of 13 patients.

Other conditions

Topical imiquimod has been shown to be effective in cases of alopecia areata by inducing "cytokine dermatitis". It has also been used to treat cases of superficial basal cell carcinoma and actinic keratosis. Currently, there are many other on-going researches studying other indications of imiquimod and imiquimod analogues.

Learning points:

In the treatment of genital wart, cryotherapy only eradicates HPV infection indirectly by destruction of the epidermal cell.