

Scientific meeting - Short Report

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REPORT

The 22nd International Papillomavirus Conference and Clinical Workshop was held from April 30 to May 6, 2005, at the city of Vancouver, Canada. This is the most important international forum gathering, on a yearly basis, researchers and clinicians involved with research on Human Papilloma Virus (HPV) and therapeutic alternatives for the treatment of its associated diseases. Additionally, this meeting attracts a number of companies engaged in the promotion and marketing of diagnostic systems and therapeutic drugs or procedures for HPV and associated disorders.

The sessions taking place at this meeting focused mainly on the following topics, in relationship with HPVs:

- a) Mechanisms of malignant transformation
- b) Immunobiology of the HPVs
- c) Prophylactic and therapeutic vaccines
- d) Epidemiology
- e) Therapeutic trends and alternatives
- f) HPV proteins as therapeutic targets
- g) Proteomics and microarrays in HPV-associated diseases

A number of reports were presented in which microarrays were used in cervical (and other) cancers to analyze the transcriptome regulated by apoptosis-inducing cytostatics such as Paclitaxel. Likewise, these reports highlighted the advantages and limitations of Proteomics in the search for cancer biomarkers.

Some of the most innovative therapeutic strategies presented at the conference that are still at the discovery or research phase were:

- a) The development of a restriction enzyme specific for HPV DNA that is unable to cut the cellular DNA of the host
- b) The anti E7-E6 ribozyme system as a platform for the treatment of HPV-induced cancer
- c) Chemical inhibitors of the E1-E2 dimerization
- d) RNAi (interfering RNA), targeting E6 and E7 with specific oligonucleotides
- e) The identification of a protein inhibitor for Casein Kinase 2

A consensus was reached on the current, most effective trends for the treatment of high-degree lesions of the cervix, which include electrocauterization, cryotherapy, laser, LEEP and conisation. However, it was remarked that these physicochemical methods produce side effects which affect the quality of sexual life for women, especially before menopause.

The management of advanced cervical cancer (including microinfiltrating forms) is still mainly based on surgery, treatment with ionizing radiations, chemotherapy (as adjuvant) and their combinations, although there was an agreement on the fact that the main limitation of surgery is the damage it inflicts on the surrounding stroma, which plays a critical role in tumoral progression. A novel strategy was suggested,

based on the local use of chemotherapy on focal lesions. As for the treatment of genital warts, 5-Fluorouracil-based creams and an ointment named AS101, based on Ammonium-3-chloro dioxethylene, 0-0 tellurate as active principle, have joined the ranks of products with proven efficacy, although alpha-IFN inhibitors such as Imiquimod (Aldara) remain as market leaders with the highest effectiveness in the treatment of these lesions.

The results of a Phase-II study of Imiquimod in Cervical and Vulvar Intraepithelial Neoplasias were presented, yielding a 75% efficacy in the response to treatment. Similarly, preliminary data from a pilot trial for self-treatment of intraanal condylomata with 5% Imiquimod tampons were disclosed, resulting in acceptable levels of side effects and suggesting that the treatment is effective, although more trials are required to substantiate this conclusion.

Very interesting results were presented concerning the biology of HPV, like the first demonstration of the interaction of the virus with epithelial stem cells, the cellular receptors for HPV, the role played by telomerases in cancer, the function of regulatory cells in cervical cancer and the strategies for the enhancement of the immune response to HPV. Data on the molecular mechanisms underlying the pathogenicity of these viruses were presented as well.

Head and neck tumors received special attention during this meeting, since it is argued that HPV is present in more than 30% of these cases. A whole session was devoted to the relationship between HPV and AIDS as well, due to the fact that the advent of triple therapy for HIV-infected patients has extended their life expectancy, and therefore the incidences of anal and cervical dysplasias and cancer have concomitantly risen up to three-fold. This rise has been detected both in women and men, with a higher incidence of anal cancer in homosexual males. In general, it is said that HPV infections in these patients may lead to a worsening of their immunological status.

The development of prophylactic vaccines and their results was a widely debated topic. These vaccines are mostly VLP based on protein L1 (the major protein in the viral capsid). Merck developed a tetravalent HPV 16, 18, 6, 11 vaccine manufactured in yeast that uses aluminum hydroxide as adjuvant, for which the company is going to apply for FDA approval at the end of 2005, having a probable date of release to market on 2006. Glaxo-SmithKline, on the other side, has developed an HPV 16-18 vaccine produced in baculovirus that uses ASO4 as adjuvant, and will be seeking regulatory approval in Europe during 2006, with a probable date of release to market on year 2007. Both manufacturers claim that their vaccines have an efficacy higher than 90% against the persistence of the HPV genotypes included in the product,

which is therefore genotype-specific. The future market price for both vaccines is estimated to be high, due to the complexities of the manufacturing process involved in both cases and the need for maintenance of a cold chain for their delivery.

The meeting also touched on the topic of second-generation prophylactic vaccines, including those designed for oral administration or containing polypeptides derived from the E7 viral protein, with the aim of evaluating their therapeutic efficacy. Some emphasis was placed on the manufacture of VLP from L2 (minor viral coat protein), since the immune reaction against this protein usually cross-reacts among different HPV genotypes.

The preliminary data from Phase-II trials of therapeutic vaccines based on peptides, Hsp-E7 and vaccinia-E7E6 were also presented, although they are still not conclusive. Some very innovative results were presented dealing with the possibility of combining new tools with the aim of devising therapeutic

vaccines, such as the use of dendritic cell-based vaccines transfected with RNAi for the Bak and Bax proteins to ensure their survival, and the use of HBsAg-based VLP as a vector for the presentation of foreign CTL epitopes due to their capacity for induction of a strong humoral and cellular response, together with the fact that the HBsAg vaccine is already licensed worldwide against Hepatitis B. The strategy followed in this case was the deletion of endogenous epitopes, substituting them with one or more foreign epitopes (Specifically, CTL epitopes for the induction of a response against HPV and B epitopes against RSV). Results were also presented about the use of a DNA vaccine coding for a single chain trimer composed of a viral peptide, b2-microglobulin and the heavy chain from MHC-I.

In summary, a total of 1200 delegates from 50 countries attended the congress; and the venues for the next meetings (Czech Republic in 2006, China in 2007 and Sweden in 2008) were also disclosed