



Cancer Research Network

Workshop Report: HPV and Cancer: Implications for Clinical Trials

On Thursday 15th November 2012, the National Cancer Research Institute (NCRI) Clinical Studies Groups (CSGs), partly supported by the NISCHR Register Research Group, hosted a workshop entitled 'HPV and Cancer: Implications for Clinical Trials' at the Academy of Medical Sciences in London. The workshop was attended by a multidisciplinary group of 48 members of the research community, including clinical and medical oncologists, surgeons, pathologists, translational scientists and researchers.

Introduction to the workshop

Professor Henry Kitchener (University of Manchester) opened the meeting, welcomed attendees to the workshop and explained aims for the day. The objectives for the meeting were as follows:

1. To review current knowledge and understanding of human papillomavirus (HPV) and any related therapies.
2. To identify key issues for clinical trials and translational research.
3. To discuss and agree the priorities for the next stage of clinical trials involving HPV and if possible, identify 1-2 specific trial ideas that could be taken forward.

Professor Kitchener expressed a hope that as a result of the information presented in the morning talks and the outputs of the discussions from the afternoon breakout sessions, a report could be produced on behalf of the attendees, detailing the group's consensus on the best way to move the field forward.

Session 1: HPV updates

Cancer Burden associated with HPV

Professor Peter Sasieni (Queen Mary University of London) began the morning with an introduction to HPV by describing the different types, explaining which types were linked to cancer and which cancer types were associated with HPV infection (cervical, oral, vaginal, vulval, penile and anal). Professor Sasieni identified cervical cancer as the greatest HPV-related cancer burden, noting that HPV DNA is found in the vast majority of cervical cancers and that HPV types 16 and 18 account for 70% of all cases. Infection by HPV is known to precede the onset of cancer and once cells are infected, HPV oncoproteins E6 and E7 knockout host tumour suppressors p53 and pRB, respectively. HPV vaccination has been shown to be successful in preventing precursor lesions. Professor Sasieni proceeded to describe the virus types associated with the other HPV-related cancers and concluded by presenting the incidence of HPV-related cancers in the UK and worldwide.

HPV Expression and Carcinogenesis

Dr John Doorbar (MRC National Institute for Medical Research) opened his presentation by showing the evolutionary tree for HPV and explaining that HPV is a well-adapted organism that does not always cause significant harm or illness. Dr Doorbar went on to discuss the segregation of HPV into alpha-, beta- and gamma genera, noting beta- and gamma-HPV have little pathological effect but alpha-HPV is further segregated into low risk (those not driving cell proliferation) and high risk (classed as direct carcinogens). The mechanism of infection by HPV was described and Dr Doorbar emphasised that the HPV virus does not drive neoplasia on its own, highlighting the significance of host basal layer infiltration by the virus and long term deregulation of gene expression that occurs during the progression of neoplasia to cancer in cervical cells.

Immunology of HPV

Professor Peter Stern (Paterson Institute for Cancer Research) reviewed the natural history of HPV infection and the HPV lifecycle in the cervix. The role of the host immune system in the clearance of the virus was discussed, with an emphasis on the dependency on the local cellular immunity. HPV has evolved to evade the immune system through a number of mechanisms, enabling a persistent infection, which is necessary, although not solely sufficient, for progression to cervical cancer. The prevention of HPV infection using a prophylactic vaccine has been observed, with the response mediated by neutralising antibodies. Professor Stern discussed the requirement for a vaccine to elicit an immune response greater than that produced naturally. He concluded by comparing the intensity of immune response elicited and efficacy of the two HPV vaccines currently available (Cervarix® and Gardasil®) and identified key issues to consider in further development of prophylactic vaccines.

Therapeutic Interventions

Professor Christian Ottensmeier (University of Southampton) introduced the concept of immunotherapy and gave examples of how the method has been effective in the treatment of other cancers, such as melanoma and lung cancer. The prospect of using HPV as a target for immunotherapy was discussed, with E6 and E7 suggested as the most promising potential antigens. Mechanisms of therapeutics in development were described, including viral vaccines, peptides, DNA vaccines and mRNA vaccines. Professor Ottensmeier highlighted the importance of the tumour microenvironment, explaining that myofibroblast levels conversely relate to T-cell levels and low myofibroblast and high T-cell levels indicate better prognosis. Professor Ottensmeier concluded by noting that HPV was a promising target despite uncertainty as to the best vaccine, emphasising the importance of developing clinical trials with the correct endpoints and stressing the inability of available prophylactic vaccines to treat an established HPV infection.

Session 2: Disease-specific Updates

Anal Cancer

Dr Rob Glynne-Jones (Mount Vernon Centre for Cancer Treatment) began by noting the rarity of anal cancer (approximately 2 cases/100,000) and highlighting the incidence within the UK, adding that incidence of anal cancer amongst women is increasing. Anal cancer has a number of known associations including HPV, female gender, immune suppression, HIV status, number of sexual partners/anal intercourse in men and smoking. Dr Glynne-Jones noted HPV 16 is found in 60-80% of cases of anal cancer in Europe and either HPV 16 or 18 in 80-90% of cases. Anal HPV infections clear at a faster rate than cervical HPV infections, which could be explained by differences in epithelial tissue types. Dr Glynne-Jones described anal intraepithelial neoplasia (AIN), but cautioned that most hypotheses are extrapolated from MSM data. Data presented suggest a better prognosis for HPV 16-positive tumours than HPV 16-negative tumours, as indicated by improved time-to-failure and progression-free survival. Dr Glynne-Jones suggested overexpression of p16, a cell cycle regulator, could serve as a surrogate biomarker for anal cancers containing a HPV infection and presented data that illustrated most anal cancers cases in the UK are HPV 16-positive and p16-positive, both of which could serve as predictors of treatment sensitivity.

Gynaecological Cancer

Professor Henry Kitchener (University of Manchester) reviewed the history of HPV and gynaecological cancers, stressing that HPV is the main cause of cervical cancer and is implicated in approximately half of vulval cancer cases. HPV infection will clear in most cases but if it does not, the progression to cervical cancer can be 10-15 years from the initial onset of infection. Professor Kitchener suggested exploitation of the role of HPV in cervical cancer via both HPV vaccination and screening, explaining how cytological results could be stratified and triaged and testing for cure following treatment of cervical intraepithelial neoplasia (CIN) could improve efficacy and cost-effectiveness of the cervical screening programme. An approved pilot study for HPV screening was described in detail and Professor Kitchener identified potential issues for HPV screening, including the best protocol for women who are HPV-positive/cytology-negative and what information to provide to patients when this occurs. Vulval cancer was briefly discussed, noting most cases of vulval intraepithelial neoplasia (VIN) are HPV 16-positive, but VIN is difficult to treat and will require an effective therapeutic vaccine. Professor Kitchener concluded by stating that the role of HPV in cervical cancer has resulted in a national prophylactic vaccination programme and a replacement of cytology as the superior HPV screening method, but the high burden of cervical cancer in poorer, developing countries still presents a significant challenge.

Head and Neck Cancer

Professor Hisham Mehanna (University of Birmingham) began with data that illustrated the doubling of incidence of oropharyngeal cancer cases and the proportion of cases caused by HPV over the last 10 years. The geographical differences of HPV-positive oropharyngeal cancer were discussed, notably

highlighting the significantly higher number of cases in Western Europe as compared to the rest of the world. Professor Mehanna outlined differences between the characteristics of HPV-positive and negative head and neck squamous cell cancer (HNSCC), noting HPV-positive HNSCC is associated with oral sex and better prognosis whereas HPV-negative HNSCC is associated with smoking and excessive alcohol use and poorer prognosis. Professor Mehanna introduced the concept of three risk categories for oropharyngeal cancer: HPV-positive/non or low-smoker (low), HPV-positive/smoker (intermediate) and HPV-negative/smoker or non-smoker (high). De-ESCALaTE HPV, a clinical trial looking at the possibility of reducing toxicity in the low risk group, was described in detail. Failure in locoregional disease control is thought to be the primary reason behind a poorer prognosis for the intermediate and high risk groups and a new clinical trial with a multi-arm, multi-stage design entitled ComPARE was introduced. The trial will explore the best method to improve locoregional control in these risk groups. Professor Mehanna also described another trial looking at prognostic biomarkers and concluded the session by highlighting the significant challenges associated with head and neck cancer prevention, namely, the lack of a pre-cancerous lesion and thus, no viable method of screening for head and neck cancer.

Penile Cancer

Dr Jim Barber (Velindre Cancer Centre) addressed the rare incidence of penile cancer, estimating around 500 cases per year are diagnosed in the UK. Approximately half of all cases are related to HPV, and similar to other cancers, most HPV-positive cases are also positive for HPV16 and HPV18. Risk factors include smoking status, age, HIV status and circumcision. Dr Barber reviewed trends in pathological data for 148 cases of penile cancer, emphasising how difficult it is to find data on large cohorts of patients due to disease rarity. HPV vaccination for boys was mentioned, but the potential cost-effectiveness of vaccination was unclear. Dr Barber introduced a number of unanswered questions about the disease, including effect of HPV status on prognosis and the best treatment regime and concluded by describing a new clinical trial titled InPACT which will aim to determine if HPV status has any prognostic value for penile cancer and to find the best treatment for inguinal node metastases in penile cancer patients.

Psychological considerations

Professor Clare Wilkinson (Bangor University) began with a visual depicting the number of health care encounters a patient may experience before and after the introduction of HPV testing. It was emphasised that each of these encounters presents an opportunity to share information regarding HPV and the way in which this information is conveyed is critical. Professor Wilkinson presented her HPV Core Messages study, which aimed to develop and evaluate a set of evidence-based, core HPV messages to improve informed patient choice, reduce patient anxiety and promote disease control. Study methods were described and a number of direct quotations from study participants were shared. The results illustrated a poor knowledge of HPV, supporting conclusions from previous research. Ten core HPV messages, using pictures and numbers to represent HPV risk and consequences, are being field-tested, with the aim of developing scripts for consultations. Professor Wilkinson concluded by

suggesting a number of implications for clinical trials, including the importance of providing accurate, honest and evidence-based information on HPV, the potential to include secondary outcome measures like HPV-related emotional distress, information uptake and HPV knowledge and the value of a multidisciplinary team.

Breakout Sessions

Breakout session 1: Trials of novel therapies and vaccines

The first breakout session, chaired by Professor Peter Stern, focussed on two main questions: impact of HPV vaccination of girls on burden of disease and trial development opportunities for the use of novel therapies or vaccines in HPV-driven cancers.

The session began with a discussion on the importance of measuring the impact of HPV vaccination on infection in the UK both in vaccinated and non-vaccinated populations. The group agreed that the UK is in a unique position due to the high uptake of vaccination and that two different HPV vaccines will have been used over defined periods of time. Furthermore, as the cervical screening programme is likely to change, it would be helpful to have a clear sense of the impact before and after any major programme modifications. Universal vaccination of boys was briefly discussed, where it was noted that due to the high vaccination coverage of girls, this is unlikely to be cost-effective.

A number of issues were raised by the group during the discussion surrounding trial development opportunities for the use of novel therapies or vaccines in HPV-driven cancers. These included the importance of accurate patient selection, the need to design a trial that has practice-changing implications, the likelihood of funding difficulties and whether to include only one cancer type or stratify across different tumour types. Through discussion, the group developed a trial design for a non-randomised, phase II 'proof of principle' study to test a therapeutic vaccine in HPV-positive, relapsed head and neck cancer, with an analysis of immune responses in blood and tumour tissue linked with clinical outcomes. Group members considered a number of potential modifications including the feasibility of a randomised trial with a control arm and the addition of cervical cancer patients, concluding further discussions were necessary to ensure the trial design is appropriate.

Breakout Session 2: Trials of HPV biomarkers for diagnosis or treatment stratification

The second breakout session, chaired by Professor Hisham Mehanna, aimed to address four points related to the use of HPV as a biomarker: validity of HPV as a biomarker for treatment response or as a prognosis classifier, evidence to support HPV as a biomarker in this setting, requirements to use HPV as a biomarker in each relevant cancer type and what studies would be considered top priority. Each point was considered in the context of cervical, oropharyngeal, penile and vulval cancer.

The use of HPV status in cervical cancer is well established. Stratifying patients into risk-associated subgroups using other markers such as HPV type, in addition to HPV positivity, before looking at

treatment response was addressed. The group also discussed stratifying patients by CIN status along with level of genetic abnormality and investigating potential for a correlation with progression to cancer.

It was noted that molecular biomarkers of HPV deregulation (such as p16, Ki67, MCM, K17, K7, K2, and HPV E4) may be used to better understand the molecular significance of a HPV positive result, but that some of these have not yet been validated sufficiently for routine use. It was also noted that current research suggests that distinctive epigenetic changes in the HPV genome may be related to disease severity. Pilot studies are likely to be required to evaluate such discriminatory 'disease-status' tests as a follow up to HPV typing alone.

A strong evidence base for HPV as a prognostic marker in oropharyngeal cancer exists. Studies suggest patients may be stratified into risk-associated groups based on HPV status along with secondary factors, such as smoking and nodal status. The results of these studies have now been replicated in several cohorts. Treatment-specific, biomarker-led studies of each risk-associated group should now validate this evidence for the use of HPV, in combination with additional factors, as a prognostic classifier.

Very little evidence currently exists to support the use of HPV as a biomarker in penile and vulval cancer. The development of a national registry to collect data on penile and vulval cancer patients to record the association of HPV prevalence and survival would be beneficial and further investigations to establish useful biomarkers in this setting should be considered.

Breakout session 3: Trials of HPV screening

The third breakout session, chaired by Professor Henry Kitchener, looked at how HPV could be used as a biomarker or risk stratification in trials, focussing on refining current pilot ideas, exploring how best to influence the Health Protection Authority (HPA) and considering relevant psychosocial measures and economic factors.

Within the gynaecological setting, discussion focussed around the potential for a self-screening programme using an at-home swab test for HPV rather than the traditional cytology test. Preparatory work was recommended by the group to ascertain whether self-screening would be accepted by women. The discussion raised many psychosocial issues for consideration, and whilst the primary endpoint of this programme would be diagnosis of HPV, increase in uptake and social acceptability would feature heavily.

The first group of HPV-vaccinated women will be due for cervical screening in 2015. Consideration needs to be given to how screening of this cohort will be handled and the current lack of planning for the screening of vaccinated versus unvaccinated patients was noted with concern.

The potential for head and neck cancer screening was discussed, with a general feeling that whilst the rise in cases could be considered an epidemic, screening may not be a worthwhile venture. In the 15

years it may take to implement a programme, it is likely numbers will have already plateaued, possibly due to epidemiological changes.

Anal cancer was considered a more feasible area for screening. Professor Kitchener advised that testing will soon begin in a high risk group of patients in Manchester using a variety of methods. It was agreed that consenting those people involved in testing to be contacted regarding future trials would be a positive step forward.

General discussion

Following the breakout sessions, the breakout session chairs gave brief summaries of the discussions that took place in their respective sessions and the floor was then opened to general discussion, chaired by Professor Henry Kitchener.

The session began with a question as to whether there were high-risk groups related to HPV-driven cancers (other than cervical) where screening might be of value. There was debate as to whether this was possible in head and neck cancers, mostly due to a lack of a precancerous lesion, but also based on data from a retrospective analysis of tissue from tonsils that did not find any evidence of HPV. The group suggested this could be due to methodological issues or test sensitivity.

Professor Kitchener queried the group on the feasibility of introducing HPV self-testing nationally and there was general agreement that this was a natural 'next step' for the screening programme.

The trial idea that arose from breakout session 1 was readdressed and group members suggested that obtaining a vaccine from a company was a genuine possibility. There was a discussion around the intricacies of completing the study in a 'window' setting pre-surgery, including timing of the biopsies, timing of the measurement of immune response and specifically, what to analyse from the samples.

A number of issues were raised at the end of the session around the use of prophylactic HPV vaccines including reiterating the importance of evaluating the benefits of vaccination, assessing possible reduced dosage schedules and evaluating potential vaccination strategies for men-who-have-sex-with-men although key data to support such an evaluation are absent currently.

The meeting was brought to a close and delegates thanked for their attendance and valuable input.

Recommendations for clinical trials

The HPV workshop successfully provided an update of current HPV knowledge and resulted in new trial ideas that have the potential to significantly improve patient outcomes:

- A trial evaluating the efficacy and acceptability of HPV self-testing in cervical screening
- A non-randomised, phase II 'proof of principle' study testing a therapeutic vaccine in HPV-positive, relapsed head and neck and cervical cancer

- A retrospective HPV biomarker study of archived oropharyngeal cancer tissue from clinical trials
- An interventional study for improving outcomes of intermediate and high-risk oropharyngeal cancer
- A retrospective pilot study to examine the utility of disease-stratification markers or marker combinations, as an adjunct/alternative to pathology in the follow-up of HPV-positive women
- The formation of a multidisciplinary consortium of investigators interested in HPV-related trials

Mrs Jenny Lewandowski, Dr Katy Coxon, Miss Laura Chambers, Professor Henry Kitchener - January 2013