# ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

Section Editor: Mark J. Ratain, MD

## HPV and Its Effect on Head and Neck Cancer Prognosis

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**H&O** Can you provide some background on human papillomavirus (HPV) and how it relates to head and neck cancer?

**MG** HPV is the most commonly acquired sexually transmitted infection in the United States and worldwide. Most people who get the infection do not have any sequelae; however, there is a small minority who develop genital cancer as a consequence of the infection. Cervical cancer is the most common of the genital cancers and HPV is necessary for its development. HPV is also implicated in some vaginal, vulvar, anal, and penile carcinomas. Over the last 12–15 years, it has become clear that HPV also infects the oral cavity, and that oral HPV infection increases the risk of head and neck cancer. Approximately 60% of oropharynx cancers in the United States are attributable to the HPV infection and most result from oral HPV 16. It is estimated that individuals with an oral HPV 16 infection have between a 15- and 200-fold increase in risk of developing oropharynx cancer. It has been determined that this type of head and neck cancer is distinct from what is considered classic head and neck cancer, which is associated with long-term use of alcohol and tobacco. HPV-associated head and neck cancers occur quite frequently in individuals who do not drink or smoke, but have occurred in those who do. This subtype of head and neck cancer tends to occur in younger people, originates from the oropharynx (particularly the tonsils), has poorly differentiated histopathology (sometimes referred to as basaloid nonkeratinizing), and is related largely to sexual behavior risk factors. The strongest risk factor identified to date in terms of sexual behavior is the number of individuals on whom someone has performed oral sex, with risks increasing and plateauing after 6 partners.

Once it was discovered that HPV-associated head and neck cancer was a unique disease entity, researchers began trying to understand what implications this finding has for the disease. It was clear that the risk factors, the presentation, and population affected varied in HPV-negative and HPV-positive cancer. Thus, the question now is whether this difference has any association to how the patient should be treated.

**H&O** What is the research that suggests that HPV-positive and HPV-negative cancers are different entities?

**MG** The first evidence to suggest that HPV-positive and HPV-negative patients might require different treatment approaches was reported approximately 10 years ago, when HPV status was linked to prognosis. This evidence emerged from a retrospective analysis, which showed that patients who had HPV-positive head and neck cancer had an approximate 60% reduction in their risk of dying compared to patients with HPV-negative head and neck cancer. This retrospective analysis had some limitations in that patients were heterogeneously treated and staged, and survival was not prospectively assessed. Further, many known prognostic factors were not accounted for.

The other research of importance in suggesting that HPV status may affect prognosis was conducted by the Eastern Cooperative Oncology Group (ECOG). ECOG 2399 was a phase II study designed to primarily evaluate organ preservation; however, it was of sufficient size to also prospectively evaluate tumor HPV status and its relationship to risk of death. The results of ECOG 2399, published in the *Journal of the National Cancer Institute* in 2008, found the same approximate 60% reduction in the risk of death as seen in the retrospective analysis. This study also had limitations, one of which was that it was too small to account for the effects of

other prognostic factors (patients with HPV-positive tumors tend to be white, have better performance status, have less weight loss, do not have anemia, have smaller primary tumors, and do not smoke) that are frequently seen in patients with HPV-positive tumors. Thus, although we saw a consistent association between HPV and survival, it could have been from these confounding prognostic factors. The other limitation was that the patients were treated with a noncommonly utilized investigational therapy (taxane-based induction followed by taxane-based concurrent chemoradiation), which led to the assumption that because this was an investigational protocol, it may not apply to patients who are receiving high-dose cisplatin with concurrent chemoradiation. It is evident that HPV status should be used as a stratification factor in all clinical trials that involve head and neck cancer patients. Many researchers believe that these are different disease entities that require specifically designed clinical trials, as they appear to have different biologic behavior and response to therapy.

**H&O** What were the implications of these early trials?

**MG** After these trials, it was very important to move the field forward to actively study the independent effect of HPV on survival in a clinical trial with uniformly staged and treated patients, in which survival was prospectively evaluated, and that was of sufficient size to account for the effects of other prognostic factors.

Four years ago, I began working with the Radiation Therapy Oncology Group (RTOG) to study the effects of HPV on clinical outcomes. Protocol RTOG 0129 was a study designed to address whether or not the addition of chemotherapy to altered fractionation increased survival; we looked at whether or not HPV was an independent prognostic factor for survival and analyzed patterns of failure comparing HPV-positive and HPV-negative patients. This was a large trial, with most patients having a diagnosis of oropharynx cancer. All patients received radiation plus high-dose cisplatin. Our analysis found that HPV was the single greatest prognostic indicator for how patients will respond when treated with chemoradiation. We also determined that all other favorable prognostic factors that are seen in HPV-positive patients only accounted for approximately 10% of the relative difference in the survival of HPV-positive and HPV-negative patients, which meant that 90% was attributable to the biologic difference in response to therapy for the HPV-positive and HPV-negative patient.

In this study we also analyzed the effects of tobacco use and found that tobacco modified the survival of HPV-positive and HPV-negative patients. In our ranking of prognostic factors that were independently associated with survival, we found that the second most important factor was smoking, with an estimated reduction in survival of approximately 1% per pack year, followed by clinical staging. These findings called into question whether to incorporate biologic and behavioral factors into the algorithm for determining risk-based therapy. This was a move toward personalized therapy, as we were now able to distinguish patients who had an HPV-negative cancer and were smokers from those patients who had HPV-positive cancer and never smoked. The questions that arose from the study results related to whether to intensify therapy for the HPV-negative heavy smoker in order to improve survival, and whether it would be better to shift the focus to maximizing quality of life and minimizing morbidity of therapy in HPV-positive never smokers, since they have a 90% 5-year survival rate and have to deal with the consequences of concurrent chemoradiation therapy for 30–50 years.

Now that we recognize that HPV status is such an important prognostic factor, we need to ascertain how it should affect our clinical trial design and how we treat patients. There is an evolving consensus that it is necessary to collect more data by conducting randomized phase III trials comparing 2 standard of care options in the HPV-positive patient population, and many cooperative groups have initiated trials specifically targeting this population.

**H&O** Do we know why patients with HPV-positive tumors have better survival than those with HPV-negative tumors?

**MG** RTOG 0129 provided some insight as to the multifactorial reasons why the HPV-positive patient does better than the HPV-negative patient. One of the reasons considered was the tracking of other prognostic factors, which clearly play a role in survival differences. Another reason was the demonstration that local regional control was markedly improved in the HPV-positive versus HPV-negative patient, and whether that is due to increased radiation sensitivity or radiosensitization by cisplatin was unclear. It was evident that radiation sensitivity played a role but whether or not there was any further benefit from the addition of cisplatin to radiation is still an important unanswered question.

**H&O** Vaccination has been mentioned as a preventive measure. Do you think it will play a role in cancer reduction?

**MG** The HPV vaccines that have been approved by the US Food and Drug Administration, Cervarix and Gardasil, include coverage for HPV16—the HPV type that is overwhelmingly responsible for HPV-positive

head and neck cancers (an approximate 90–95% of head and neck cancers are HPV16-positive). In every clinical trial of Cervarix or Gardasil, the vaccines were extraordinarily effective in preventing new and persistent HPV 16 infections and lesions, or precancers, of the vulva, vagina, cervix, and anal dysplasias (for which data are not yet published). Initially, the model systems that generated the HPV vaccine program were oral cancer models in dogs; virus-like particles were created from canine oral papillomavirus similarly to how these human vaccines were produced. These models were shown to be 100% effective in protecting against oral cancers in dogs, and the passive transfer of serum from immunized dogs to unimmunized dogs conferred that protection. There has been research done at the University of Washington demonstrating the presence of oral antibodies against HPV16 in vaccinated women, thus it is known that they get into the oral cavity from the serum.

Indeed, there is every reason to be optimistic about vaccination for prevention of head and neck cancer, but at present the vaccine cannot be recommended for this indication because the studies of whether or not the vaccines protect against oral HPV16 infections have not been done.

### H&O Will treatment options vary for HPV-positive and HPV-negative patients?

**MG** Although there are no data to suggest that one treatment should be preferred over another for either patient population, investigators are considering HPV status in their clinical decision-making. Currently, there is an ECOG protocol, ECOG 1308, that is open and accruing patients. It is a study designed specifically for the HPV-positive population. It is a follow-up based on the findings of ECOG 2399, which demonstrated that the HPV-positive patient had a higher response to induction chemotherapy and also a higher overall response. The ECOG 1308 protocol is a phase II study designed to evaluate whether or not patients who have a complete response to induction chemotherapy can receive a lower dose of radiation therapy with concomitant cetuximab therapy without compromising progression-free survival. I think the community will be paying close attention to this study as it investigates whether or not we can take advantage of the increased responsiveness to induction chemotherapy in this patient population and whether we can subsequently reduce the total radiation dose and substitute concurrent radiation therapy with a biologic rather than chemotherapy to reduce morbidity, all without compromising the control of the disease.

### H&O Is HPV testing a standard procedure?

**MG** There is no commercially available, validated assay for measuring HPV status in a patient. Our laboratory uses in situ hybridization and p16 immunohistochemistry, which have become the gold standard tests and are available at an increasing number of institutions. Other centers have performed invalidated assays, which have not been evaluated in clinical trials. We are aggressively working on developing and validating a commercial assay that can be done in a standard pathology laboratory, and I am hoping that we will be in a position to present the data at next year's meeting of the American Society of Clinical Oncology (ASCO).

### H&O Can you discuss the study you presented at this year's ASCO meeting?

**MG** The study we presented at this year's ASCO meeting (RTOG 9003) was an analysis of an older clinical trial conducted in the 1990s by RTOG in which patients were treated with radiation alone. RTOG 9003 was a randomized 4-arm study looking at the effects of radiation fractionation delivery on locoregional control. What was noteworthy was the consistency of the findings in our analyses of both RTOG 9003 and RTOG 0129, which enrolled patients in the mid 2000s. The effects of HPV status on survival were essentially similar. An absolute difference in overall survival of 30% was seen in both trials. HPV status, smoking, and clinical stage were the most important factors for survival.

There were also some interesting differences in the studies. One difference was that HPV-positive tumors were less frequent in the 1990s; they only accounted for 39% of oropharynx tumors. The other noteworthy difference was the proportion of the patient population that smoked and the average amount of tobacco smoked in the HPV-positive and HPV-negative patients. The HPV-positive patients had, on average, 29 pack years of tobacco exposure in the earlier trial (RTOG 9003). This exposure had decreased to 12 pack years in RTOG 0129. This calls into question how much of the improvements in absolute survival observed in clinical trials over time is due to changes in therapy over time. These trends—reduction in tobacco use and changes in sexual behavior—that are largely driven by social factors may explain the improvement in absolute survival in this patient population.