HPV Confers Survival Advantage in Skin Cancer

Positivity linked with a 79% lower risk of death for head and neck SCC patients.

BY FRAN LOWRY
Orlando Bureau

CHICAGO — A prospective analysis of a phase II Eastern Cooperative Oncology Group study confirms what has up to now been reported only in retrospective, single-institution studies: head and neck squamous cell cancer patients infected with the human papilloma virus have significantly better survival than do their counterparts without the virus.

Human papilloma virus (HPV) positivity conferred a 79% lower risk of death in the multicenter ECOG 2399 study, Dr. Carole Fakhry reported at the annual meeting of the American Society of Clinical Oncology. She said HPV status should now be considered a biomarker for prognosis in head and neck squamous cell cancer (HNSCC). Moreover, these results may necessitate a reinterpretation of survival rates in previous trials to determine whether survival differences were in fact due to HPV status, rather than to the actual therapy that was used, according to Dr. Fakhry of the Johns Hopkins Medical Institutions in Baltimore.

The primary objective of ECOG 2399 was to assess organ preservation with taxane-based induction chemotherapy followed by taxane-based concurrent chemoradiation in resectable stage III and IV larynx and oropharyngeal cancer patients. The trial also sought to estimate disease-free survival and patterns of failure.

Dr. Fakhry and associates evaluated pathologic tissue samples from 96 study participants for the presence of HPV infection, then determined prognostic factors, treatment response, and survival outcomes in terms of HPV status.

HPV status—in particular HPV-16, the dominant viral isolate known to be responsible for a subset of HNSCC—was assessed with in situ hybridization, polymerase chain reaction, and line blot tests. These tests also screened for HPV-31, 33, and 35, which are the other isolates that have been linked to HNSCC.

A total of 40% of patients (38) were found to be HPV positive, and all had oropharyngeal tumors. They were more likely to have a better ECOG performance status and lower cumulative lifetime exposure to smoking than were HPV-negative patients. They were also more likely to be male, have less weight loss on presentation, and present with a stage T2 tumor, Dr. Fakhry reported.

HPV-positive patients had a higher response to induction and chemoradiation therapy. Response rates after induction chemotherapy were 81.6% for HPV-positive patients vs. 55.2% for HPV-negative patients ($p=0.01$). After chemoradiotherapy, they were 84.2% vs. 56.9%, respectively ($p=0.07$).

At a median follow-up of 39 months, progression risk was 72% lower and risk of death was 79% lower in HPV-positive patients, compared with HPV-negative patients. These figures were derived from a Cox proportional hazards model, Dr. Fakhry said.

Discussant Thomas F. Pajak, Ph.D., of the Radiation Therapy Oncology Group in Philadelphia said these results are impressive at first glance, but that he was troubled by the Cox analysis in the trial. He proposed that the investigators generate a new Cox model, restrict it only to oropharyngeal patients, and compare HPV status to no more than three other factors in order to obtain a new, and more reliable, estimate of the risk of death. "A Cox model with too many variables in it is unreliable," he said.

In another presentation that looked at HPV-associated HNSCC, Dr. Anil K. Chaturvedi of the National Cancer Institute reported that HPV-related HNSCC has increased in the United States during the last three decades, particularly among white men aged 40-59 years.

Using data from the Surveillance, Epidemiology, and End Results (SEER) registry for the period 1973-2003, Dr. Chaturvedi and co-investigators also found that HPV-related HNSCCs were being diagnosed at more advanced stages and at significantly younger ages. These trends became apparent in the early 1990s. Meanwhile, the incidence of cancers not related to HPV decreased in both men and women, especially in those over the age of 40.

He said the increasing incidence of HPV-linked HNSCC could be due to changes in sexual behavior, and that the decreasing incidence of cancers not related to HPV could be due to the decreased prevalence of smoking. ■

Largest Study Yet Supports Gardasil's Safety, CDC Reports

BY HEIDI SPLETE
Senior Writer

ATLANTA — Clinicians can be more confident about the safety of Gardasil, the quadrivalent human papillomavirus vaccine, because postlicensure safety data from the first year of widespread use confirm that serious adverse events associated with the vaccine are rare.

"Postlicensure safety reporting for HPV4 has occurred at relatively high levels, as is expected for a newly licensed product that has garnered significant public attention," said Dr. John Iskander, who presented the postlicensure data at a meeting of the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices.

Dr. Iskander presented safety data from the United States Vaccine Adverse Event Reporting System (VAERS) and the Vaccine Safety Datalink (VSD), two surveillance mechanisms supported by the CDC.

"The data encompass the first 11 months of the U.S. experience with Gardasil," said Dr. Iskander, an officer at the CDC's Immunization Safety Office.

The postlicensure data are likely to increase comfort levels for doctors when they talk to patients about the HPV4 vaccine.

"Now [that] the vaccine has been out for about a year, it is beginning to develop a safety record, so it should make the practitioner feel more confident in the safety of the vaccine," Dr. Joseph Bocchini Jr., the American Academy of Pediatrics' liaison to ACIP and chairman of the department of pediatrics at Louisiana State University, Shreveport, said in an interview.

More than 5 million doses of Gardasil have been distributed as of the end of March, according to the vaccine's manufacturer (Merck), although the exact number of doses that have been administered is uncertain at this time, Dr. Bocchini added.

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"The [VAERS] data encompass the first 11 months of the U.S. experience with Gardasil," said Dr. John Iskander.

So far, the HPV4 overall vaccine adverse event reporting rate is 33 per 100,000 doses, and the serious adverse event rate is 1.8 per 100,000 doses, based on VAERS data.

A total of 1,763 adverse events related to use of the HPV4 vaccine had been reported to the VAERS as of May 8. Of these, 87% involved the use of HPV4 alone. Nearly 70% of the reports involved girls and women aged 9-26 years (the age range used in prelicensure clinical trials).

"A substantial proportion of vaccine events began on the day of vaccination (39%), or in the days [immediately] following vaccination," Dr. Iskander noted. Similarly, 42% of serious adverse events occurred on the day of vaccination, with an average onset time of 1 day afterward. A total of 857 vaccine events (49%) were reported after a single dose of HPV4.

The most common symptoms in reports of serious adverse events were vomiting (14%), syncope (12%), and fever, nausea, and headache (all 11%). The most common symptoms reported with vaccine use were dizziness (13%), injection site pain (10%), syncope (10%), and nausea (9%).

Although data on associations between HPV4 use and reports of Guillain-Barré syndrome are limited, the VAERS data included 13 reports of GBS in patients who received HPV4. Of these, 11 cases occurred in girls aged 13-16 years; one case occurred in a 50-year-old woman, and the age of the other patient is unknown. More than half of these cases involved coadministration of Menactra and Gardasil.

The VAERS data also included two nonfatal cases of thromboembolism in patients who received the HPV4 vaccine.

In addition, 11 serious event reports from VAERS involved syncope, all of which occurred within 10 minutes of vaccination. "Current recommendations suggest a 15-minute waiting period after vaccination … to avoid syncope," Dr. Iskander noted. Many of the frequently reported adverse events, such as syncope, are common in the general population and do not have a specific relationship to this vaccine or to vaccinations in general, he said.

Dr. Iskander also presented details on four cases of death in patients who had been vaccinated with HPV4. The cases included a 12-year-old girl who died of myocarditis after developing ventricular tachycardia, a 19-year-old girl who died from sudden cardiac death and pulmonary embolism (her autopsy showed multiple blood clots), a 14-year-old who died from multiorgan system failure due to influenza B viral sepsis, and a fourth case for whom few data were available except her use of oral contraceptives; her death was associated with blood clots.

Gardasil has been covered under the national Vaccine Injury Compensation Program since Feb. 1, and no claims alleging injuries as a result of HPV4 had been filed as of June 7, Dr. Iskander said. Complete vaccination coverage data are not yet available, but vaccine uptake is being followed using the VSD. The VSD sites are monitoring 68,266 doses of Gardasil given between Aug. 6, 2006, and May 13, 2007, for a variety of safety outcomes including Guillain-Barré syndrome, seizure, syncope, stroke, thrombosis, and pulmonary embolism.

Serious adverse events involving HPV4 have rarely been reported; the reported deaths in vaccine recipients don't appear to be causally related to vaccination, Dr. Iskander said. But the CDC will continue to collaborate with the Food and Drug Administration, the World Health Organization, and other organizations to monitor postlicensure surveillance and other communication related to HPV4.

At future ACIP meetings, the postlicensure safety data for Gardasil may be considered in conjunction with safety data on the bivalent HPV vaccine recently submitted to the FDA by GlaxoSmithKline. ■