Key Findings: HPV Cancers, Lung Cancer Diagnosis

Experts highlight key solid tumor findings over the past year

CHICAGO—A sharp rise in the incidence of human papillomavirus (HPV)—associated cancer of the oropharynx—in stark contrast to steady declines in HPV-unrelated oropharyngeal cancer due to decreases in smoking—virtually guarantees that clinicians will soon begin to see patients with this disease in their practices, according to Ezra Cohen, MD, a head and neck cancer specialist at the University of Chicago speaking about recent developments in squamous cell cancer of the head and neck (SCCHN).

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‘HPV-positive oropharynx is going to be, in the very near term, the most common virally associated cancer that we see. It is a disease that I have no doubt you will see in your clinics. We are on the cusp of this epidemic.’

—Ezra Cohen, MD

patients had significantly better overall survival (OS) rates than patients with HPV-negative tumors (82.4% and 57.1%, respectively) and a 58% reduction in the risk for death (hazard ratio [HR], 0.42; 95% confidence interval [CI], 0.27-0.66).

The data also revealed an “intermediate” group of HPV-positive patients with a history of smoking who did not fare as well as their HPV-positive non-smoking counterparts, but who did better than patients with HPV-negative tumors. Overall three-year survival rates based on risk category were 93% for those with low-risk oropharyngeal squamous cell carcinoma, 70.8% for those with intermediate risk, and 46.2% for those at high risk.

Several differences between HPV-positive and HPV-negative SCCHN—present in 50% to 60% of tumors—and provided the first evidence that as many as 50% of tumors involve mutations in the Notch signaling pathway, Dr. Cohen said.

“These are inactivating mutations, suggesting that there is a block in the differentiation of these squamous cells that allows somehow the second and perhaps the third hit to lead to the carcinogenic process. We’re still trying to find out exactly when these Notch alterations in the pathway occur,” he said.

Dr. Cohen and his colleagues at the University of Chicago have taken these findings one step further by linking genetic profiles of SCCHN tumors with outcomes. Sequencing on 130 primarily stage IV tumors homogeneously treated with chemotherapy and including a mix of HPV-positive and HPV-negative tumors revealed five subgroups: hypoxic, basal, classical, HPV-a and HPV-b.

“With the clinical annotation, what we were able to see is that the HPV-positive cancers begin to separate out into HPV-a, which is a very good performing group in terms of outcome, and HPV-b, which is a poorer performing group and is very similar to the basal type of the HPV-negative cancers,” he said.

Avoid FDG-PET as Treatment Planning Tool in Lung Cancer

Do not rely on fluorodeoxyglucose positron emission tomography (FDG-PET) as a basis for changes in lung cancer therapy. This was a key take-home message from a review of advances and controversies in lung cancer presented by Ramaswamy Govindan, MD, a professor of medicine at Washington University School of Medicine in St. Louis.

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The PET scan is a wonderful scan, but like many things in life, it’s good but not great. There are limitations,” Dr. Govindan said.

He noted findings from the ACOSOG Z403 trial of the accuracy of FDG-PET in diagnosing non-small cell lung cancer (NSCLC; J Clin Oncol 2012;suppl:abstr 7008). The study, which enrolled patients at 51 sites in 39 cities, revealed an overall accuracy rate of only 73%, an accuracy rate of less than 50% for lesions 2 cm or smaller, and sensitivity and specificity rates of only 82% and 31%, respectively.

The study counters previous meta-analyses showing high sensitivity and specificity with FDG-PET, at 94% and 83%, respectively.

Expanding on these results with his own recommendations, Dr. Govindan advised clinicians also not to use FDG-PET as a basis for treatment decisions.

“As a person practicing in a tertiary care center, I see a number of patients getting PET scans over time, and the chemotherapy decisions are made based on the PET scan results,” Dr. Govindan said. “Quite often it’s distressing to see that the chemotherapy was changed or something was altered because SUVs [standardized uptake values] went from 4 to 5. Keep in mind that so many things can affect SUV.

“Of course, if it is a new lesion ... and is really suspicious of cancer, that’s a different thing,” he said. “But please don’t change your therapy based on SUV changes.”

He also recommended against using FDG-PET to assess responses to therapy and following chemotherapy and radiation.

“In my practice, I never use PET scans for follow-up of response to therapy. I only use CT [computed tomography] scans,” he said.

Research is exploring whether post-therapy PET scans can predict outcomes, but “unless we learn more from that [study], I would advise you not to use PET scans following chemotherapy and radiation treatment,” he added.

Benchmark for Anal Cancer Treatment Response Time; New Standard for Metastatic CRC

Don’t evaluate patients too soon to make a decision about whether they are failing chemotheraphy and radiation treatment for anal cancer and should be referred for salvage surgery, David H. Ilson, MD, PhD, a medical oncologist at Memorial Sloan-Kettering Cancer Center in New York City, said in a presentation on gastrointestinal cancers.

Dr. Ilson reviewed findings from ACT (Anal Cancer Trial) II, presented at the American Society of Clinical Oncology meeting (abstract 2004), which looked at the optimal timing of response assessment in patients with squamous cell carcinoma of the anus. The study was done...
in the context of a randomized trial of mitomycin versus cisplatin during radiation for anal cancer with or without maintenance chemotherapy. No differences were found between the two agents, and maintenance therapy added no benefit.

But the study provided some new guidance for clinicians on when to assess complete response to treatment. Patients were evaluated at 11, 18 and 26 weeks following chemotherapy and radiation. Complete responses were found in 65.2%, 75.4% and 84.1% of patients at the three intervals, respectively. “What this tells us is that we shouldn’t jump the gun in these patients. We shouldn’t really evaluate too soon to make a decision about whether they’re failing treatment,” Dr. Ilson said. “I think this establishes a benchmark in clinical practice for when we should make the decision about referring patients for surgery or just observing them.”

Dr. Ilson also reviewed findings from the VELOUR trial (ESMO/WCGC 2011; abstract O-0024) which establishes a new standard in second-line treatment for metastatic colorectal cancer (mCRC). Ziv-aflibercept improved tumor response in second-line treatment for mCRC, particularly in bevacizumab-naïve patients, and received FDA approval in August.

“Based on these data, we now have an improved drug for up-front resistance to FOLFOX [5-fluorouracil, leucovorin, oxaliplatin and bevacizumab] and FOLFIRI [fluorouracil, leucovorin and irinotecan] and aflibercept and FOLFIRI is now an option for patients in second-line treatment,” Dr. Ilson said.

In VELOUR, patients who had failed front-line treatment were randomized to second-line treatment with FOLFIRI with or without ziv-aflibercept. Median OS and progression-free survival (PFS) were 13.5 and 6.9 months, respectively, in the ziv-aflibercept group and 12.1 and 4.7 months for patients who received placebo (HR, 0.817; P=0.0032; and HR, 0.758; P=0.00007, respectively).

The study also found that prior bevacizumab exposure did not mitigate the potential benefit from ziv-aflibercept. Response rates were 11.7% in patients who did and 23.3% in patients who did not receive prior bevacizumab (compared with 8.4% and 12.4% in the respective placebo groups).

Overall, adverse events that led to discontinuation of treatment were about 15% higher in the aflibercept arm, but most of the toxicities were manageable, Dr. Ilson said.

Dr. Ilson also highlighted a randomized Phase II trial of ECX (epirubicin, cisplatin and capecitabine) chemotherapy with or without rilotumumab in first-line treatment for patients with unresectable, locally advanced or metastatic gastric or gastroesophageal cancer (Clinicaltrials.gov identifier: NCT00719550).

Rilotumumab is a monoclonal antibody that targets the hepatocyte growth factor ligand that activates the MET pathway. Patients were randomized to receive two different dose levels of rilotumumab plus ECX versus placebo plus ECX.

The addition of rilotumumab improved median PFS from 4.2 to 5.6 months (HR, 0.64; 80% CI, 0.48-0.85) and median OS from 8.9 to 11.1 months (HR, 0.73, 80% CI, 0.53-1.01). Response rates were 38% and 21% in the two groups, respectively. The trial favored the lower dose as superior, Dr. Ilson said.

The benefit for PFS and OS in this study was limited to the c-MET high expressers, he said, noting that about 40% of gastroesophageal cancers overexpress the c-MET pathway.

Based on this trial, Amgen plans to conduct a Phase III trial in c-MET high expressers of ECX chemotherapy with and without rilotumumab, he said.

—Susan Birk

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