

Multimodal Therapies for Head and Neck Cancer

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Presenters' disclosures of conflicts of interest are
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While the majority of head and neck cancer is preventable and tobacco-related head and neck cancer is actually decreasing in the United States, throat cancer related to the human papillomavirus (HPV) has become increasingly widespread. At JADPRO Live 2018, Julie Bauman, MD, MPH, a professor of medicine at the University of Arizona Cancer Center, evaluated the risk factors and available prevention and treatment strategies for the throat cancer epidemic. Dr. Bauman also assessed the impact of multimodal therapy for patients with head and neck cancer, including surgery, radiation, and immunotherapy. Abby Fuoto, DNP, ANP-BC, AOCNP®, ACHPN, a nurse practitioner at the University of Arizona, discussed an interdisciplinary approach to symptom management during curative-intent treatment and palliative strategies at the end of life.

THE EMERGING EPIDEMIC

As Dr. Bauman explained, the vast majority of head and neck cancer is preventable first and foremost by tobacco cessation or tobacco and alcohol modulation, but also with the

HPV vaccine. Squamous cell carcinoma of the oral tongue, or the mobile component of the tongue, is almost always related to environmental carcinogenesis, said Dr. Bauman, who noted that the classic risk factors include tobacco use, alcohol use, and age greater than 40 (Schwetschenau & Kelley, 2002).

Human papillomavirus genotype 16, however, is responsible for the emerging epidemic. This DNA virus causes half of cervical cancer and approximately two-thirds of oropharynx cancer, said Dr. Bauman. Moreover, if oropharynx cancer is caused by HPV and not by tobacco exposure, it is almost exclusively HPV 16.

“In the mid 1980s, 17% of patients diagnosed with oropharynx cancer were infected with HPV,” said Dr. Bauman (Chaturvedi et al., 2011). “However, in the 2000s, that had increased to 72%.”

OROPHARYNX CANCER RISK FACTORS

Similar to cervical cancer, the established behavioral risk factors for oropharynx cancer include age at sexual debut (< 19 years), number of lifetime sexual partners (> 5), age at first oral sex (< 21), and infrequent use of

condoms or other barrier methods (Gillison et al., 2008; Tachezy et al., 2009).

Also similar to cervical cancer, but in a different part of the body, a critical risk factor for oropharynx cancer is persistent oral infection with high-risk HPV. Men are also at greater risk for HPV-related throat cancer. Across all races and ethnicities, said Dr. Bauman, an approximately 5-to-1 ratio of males to females affected by HPV-related throat cancer is observed.

The HPV vaccine, which is indicated in both males and females, is strictly a cancer-prevention vaccine. There are currently three US Food and Drug Administration (FDA)-indicated HPV vaccines: the 4 valent, the 2 valent, and the 9 valent. In October 2018, the FDA approved a supplemental application for the 9 valent, expanding the approved use of the vaccine to include women and men aged 27 through 45 years (FDA, 2018).

DESTIGMATIZATION

“I now make it a point during the very first visit with a patient to destigmatize HPV-related cancer,” said Dr. Bauman, “At least half of my patients have HPV-associated cancer, and they often arrive with their partner feeling scared.”

A survey of over 4,000 females conducted by the National Health and Nutrition Examination Survey between 2003 and 2006 found that 42.5% tested positive for any HPV (Hariri et al., 2011). HPV 16, the virus that causes cervical cancer and throat cancer, was identified in 4.7% of this population. A separate study looking at the natural history of HPV infection in men detected any HPV in 65% of the population, while 6.5% tested positive for HPV 16 (Giuliano et al., 2008).

“These data show you that HPV is actually quite ubiquitous in the human population,” said Dr. Bauman, who emphasized that rates of clearance of infection are high, although immunity may differ among males and females.

As Dr. Bauman reported, recent data suggest clear differences in the rate of persistent oral HPV infection between the two sexes. Men who have an incidence of HPV infection of the mouth clear it much more slowly and less often than women do. At 12 months, after first recognition of oral HPV infection, 70% of men will have cleared it vs. 90% of women, and the time to clearance is 5.3

months for men vs. 3 months for women (D’Souza et al., 2016).

By the time HPV has transformed itself into cancer, however, it is no longer an active virus, Dr. Bauman noted (D’Souza et al., 2016).

“As we confront this epidemic, the good news with HPV is that it has a superior prognosis to cancer caused by tobacco and alcohol,” said Dr. Bauman (Ang et al., 2010). “In patients with HPV-associated cancer, the chance of complete and permanent remission is somewhere on the order of 90%.”

MODERN TREATMENT STRATEGIES

Despite the high rate of complete remission, however, patients still must endure brutal and difficult treatment with toxic therapies, which is why deintensification is under investigation.

“The multimodality treatment paradigms can leave a devastating symptom burden,” said Dr. Bauman. “What if that constitutes overtreatment for our patients with HPV-related cancer? What if we can deliver the same excellent rate of cure but with less toxicity?”

Although not yet standard of care, minimally invasive transoral robotic surgery that can access the oropharynx is now available at many centers.

“This is a surgery that surgeons actually love to do because the postoperative morbidity is much lower than open mandibulotomy, and patients have a much more rapid recovery, with fewer days in the hospital,” said Dr. Bauman.

Intensity-modulated radiation therapy is another technique that has improved long-term survivorship for patients who are cured. As Dr. Bauman explained, intensity-modulated radiation therapy is essentially “painted-on” doses of radiation to avoid vital structures, such as the carotid artery, the spinal cord, and the salivary gland (Tejpal et al., 2010).

BIOLOGICS AND IMMUNOTHERAPY

The use of biologics such as cetuximab (Erbix) rather than cytotoxic chemotherapies like cisplatin has also been explored. However, recently reported data from a randomized, multicenter trial demonstrated inferior overall survival and progression-free survival for cetuximab plus radiation vs. cisplatin plus radiation in HPV-positive oropharyngeal carcinoma (Gillison et al., 2018).

“This trial is truly practice changing,” said Dr. Bauman. “We are now still stuck with cisplatin plus radiation in terms of its symptom burden in our patients because there really is a substantial sacrifice in cure rate if one turns to cetuximab plus radiation.”

Finally, pembrolizumab (Keytruda) and nivolumab (Opdivo), two anti-PD-1 receptor monoclonal antibodies, have been FDA approved in head and neck cancer in platinum refractory recurrent metastatic head and neck cancer (Cohen et al., 2018; Ferris et al., 2016). As Dr. Bauman reported, investigators are also now bringing these antibodies forward into the curative intent setting, layering them onto cisplatin/radiation in the setting of high-risk HPV-negative disease or potentially substituting them for platinum in the setting of low-risk HPV-positive disease. However, these remain research hypotheses at this time, said Dr. Bauman, and do not represent the standard of care.

INTERDISCIPLINARY SYMPTOM MANAGEMENT

As Dr. Fuoto explained, symptom management during curative intent treatment, defined as either adjuvant chemoradiation or definitive treatment-for-cure chemoradiation, can be quite intense and significant (Rogers, Thomson, & Lowe, 2017). “The head and neck region is responsible for some pretty vital human functions—those predominantly of communication as well as nutrition,” said Dr. Fuoto. “Because of how many vital structures are housed in the head and neck region, it is important to involve an interdisciplinary team of specialists when taking care of these patients.”

According to Dr. Fuoto, the other thing to consider when engaging in definitive treatment is to establish expectations for patients, families, and caregivers about how intense the process is going to be. There are normal but expected side effects that are going to occur such as mucositis and dermatitis, and patients must be prepared for that.

Dr. Fuoto also recommended having patients meet with many of these interdisciplinary specialists prior to starting treatment.

“We are about to put them through some of the hardest treatment of their lives,” said Dr. Fuoto. “Meeting their providers ahead of time helps set them up for the best success.”

In terms of interdisciplinary team members, rehabilitation specialists, speech therapists, and physical therapists are important to involve both before and after treatment. These specialists teach speech and swallow exercises that patients will practice throughout treatment and recovery and, for some patients, for the rest of their lives to try and maintain function, said Dr. Fuoto. Lymphedema specialists also play an important role on the interdisciplinary team.

“In general, we think about lymphedema in terms of women who have had a mastectomy, but in head and neck cancer it can be quite disabling,” said Dr. Fuoto. “Head and neck cancer patients will typically have a little bit of a turkey waddle, but they can also have significant edema into their face and tongue, which impacts their ability to communicate, swallow, and eat.”

Additionally, if there is one available, a registered dietician can be a vital part of the team. During head and neck cancer treatment, patients lose a lot of weight, particularly lean body mass, and they are at significant risk for malnutrition. Having a nutritionist counsel them is also important in terms of tube feeding supplementation if they have a PEG (percutaneous endoscopic gastrostomy) tube, Dr. Fuoto added.

Dr. Fuoto also emphasized the importance of behavioral health, as patients with head and neck cancer have one of the highest rates of suicide amongst all cancer diagnoses.

“These patients have significant body image issues,” she explained. “Their cancer diagnosis is right here on display for the world to see, and it can be very isolating because their image has changed and communication can be very difficult as well. Many people get tired of having to repeat themselves because others don’t understand them, so they begin to withdraw.”

According to Dr. Fuoto, it’s important for behavioral health specialists to reach out and make sure that any comorbid mental health issues such as anxiety or depression are being managed during treatment.

Finally, said Dr. Fuoto, pharmacists play an important role by educating patients and providers about medication safety. Having a compounding pharmacist during treatment can be very helpful as well. ●

Disclosure

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