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The Growing Burden of HPV-Associated Cancers

Dr. Hamid:
Human papilloma virus, or HPV-associated cancers, are quickly becoming a global health problem. In fact, HPV is believed to be responsible for more than 90% of anal and cervical cancers, about 70% of vaginal and vulvar cancers, 60% of penile cancers, and up to 70% of cancers of the head and neck, and when it comes to tackling a global health problem like this, the topic of improved therapeutic management cannot be ignored. This is CME on ReachMD, and I'm Dr. Omid Hamid. Joining me to discuss clinical approaches to managing the burden of HPV-associated cancers are Dr. Susana Campos and Dr. Robert Ferris. Dr. Campos, Dr. Ferris, welcome to you both.

Dr. Ferris:
Thank you.

Dr. Campos:
Thank you.

Dr. Hamid:
Since you both bring such a different perspective to this discussion, I'd first like to hear about some of the major types of HPV-associated cancers each of you see in your practice. So, Dr. Campos, let's start with you.

Dr. Campos:
So, the majority of our practice in terms of HPV-infected cancers is cervical cancer, and to a lesser extent, we will see vulvar cancer as well as vaginal cancer in our clinical practice.

Dr. Hamid:
And how about you, Dr. Ferris? What are the major types of HPV-associated cancers you see?

Dr. Ferris:
Well, in head and neck and that anatomic subsite, human papilloma virus has been responsible for an increasing rate of cancers in a particular area, the tonsil and the base of the tongue. We call that the oropharynx. To a much lower degree, there is perhaps four or five percent in the oral cavity, the front part of the mouth, and a similar, you know, five or so percent, way back in the voice box, in the larynx. So, primarily, the HPV-positive head and neck cancers occur in the middle portion, the tonsil and the base of the tongue, which has been increasing at a rate of about five percent per year for about three decades.

Dr. Hamid:
For those just joining us, this is CME on ReachMD. I'm Dr. Omid Hamid, and here with me to discuss clinical decisions on HPV-positive cancers are Dr. Susana Campos and Dr. Robert Ferris. Now that we talked about the burden of HPV-associated cancers, I'd like to focus the discussion at this point on emerging treatments that may help us relieve some of that burden. So, Dr. Campos, what are some of the novel approaches to managing HPV-associated cancers?

Dr. Campos:

You know, there's been several landmarks in cervical cancer. The first landmark is when we realized the Pap smear could actually decrease mortality, and I think the second landmark dates back actually to 1999 when the NCI made an announcement that if you combined chemotherapy with radiation therapy that you actually could improve survival. Actually, analysis showed about a six percent overall survival. In addition, we've studied different compounds of chemotherapy, usually platinum-based, but those combinations, despite the fact that the combinations did improve progression-free survival in patients with cervical cancer, we did not see an overall survival benefit with those combinations of chemotherapy. In essence, some of the new novel therapies have date back several years ago to a study called GOG 227 where the use of bevacizumab was found to have about an 11 percent benefit in terms of progression-free survival, excuse me, in terms of overall survival, in terms of overall response rate. There was a clinical study called GOG 240, which looked at the combination of bevacizumab plus chemotherapy, and in that particular study, GOG 240, there was an overall survival benefit with the use of bevacizumab and also with the use of chemotherapy. So, that's actually kind of important to note, but the last several years, we kind of changed our avenue and asked the question, Can we do better than simply cytotoxic chemotherapy plus or minus a bevacizumab, an anti-angiogenesis derivative? We're looking at checkpoint inhibitors in cervical cancer, and there have been actually numerous studies actually that have shown that there's a benefit of these checkpoint inhibitors in the management of patients with metastatic cervical cancer. There was a study utilizing, looking at an objective response rate of about eight percent. There's KEYNOTE-026 that used pembrolizumab, looking at a response rate of about 12.5 percent. There was another KEYNOTE-158 study again utilizing the drug pembrolizumab, looking at an overall response rate of about 14 percent, and CheckMate 358 looked at Nivo, once again showing the objective response rate in the teens. So, as we are aware of at this point in time, there is actually an approval, an FDA approval, for pembrolizumab in patients that have received one prior line. The response rate is about 13 to 17 percent depending on which study you read, but the approval was actually restricted to PD-L1 patients that had had combined positive score of greater than or equal to 1, and that's just the checkpoint inhibitors. There've been some very good interest in a molecule called ADXS11-001, which is a live-attenuated molecule of listeria that actually secretes an HPV 16 E7 fusion protein, and in a particular cohort of individuals, about 110 individuals, there was a response rate of about 43 percent, and there's a phase 3 study that is on its way. So, it's quite exciting, but I think, you know, some very exciting work has been done by some members of the NCI looking at adoptive T cell therapy, and that's actually shown some promise in metastatic cervical cancer. The tumor-infiltrating T cells are selected for HPV E5 and E7, and they've shown some really longterm responses. One other trial that is coming to light which I'm incredibly interested in is looking at the specific antibody that targets tissue factor, which is a protein that's involved in tumor signaling and angiogenesis. So, clearly, over the last decade there has been tremendous advances in the upfront treatment of cervical cancer but also in the metastatic recurrent setting.

Dr. Hamid:
And turning to you, Dr. Ferris, are there any emerging treatments specific to head and neck-related cancers?

Dr. Ferris:
Well, in some degree, we would parallel many of things Dr. Campos mentioned. The standard of care for head and neck cancer has been cisplatin-based chemoradiation, or in the recurrent setting, cisplatin with other chemo, such as 5FU and cetuximab. A phase 3 trial recently reported in locally advanced HPV-positive patients, indicated that cisplatin was superior to cetuximab in the locally advanced setting, although a large subset, about 600 of those patients with good performance status, had equivalent outcome, and so in the locally advanced setting, we use either the EGFR-targeted antibodies, cetuximab, or the traditional chemotherapy cisplatin, as they often use in cervical and other HPV-related diseases. Now, another positive trial showed that the immune checkpoint inhibitor pembrolizumab was also effective in recurrent metastatic head and neck cancers. We have FDA approval since 2016 for two PD-1 targeted antibodies, both nivolumab and pembrolizumab, and those were used in platinum-refractory patients who had progressed within six months of platinum exposure, and just at ASCO in the past few months, a publication emerged in a presentation indicating that a KEYNOTE-048 trial showed that pembrolizumab monotherapy for PD-L1 positive tumors or pembrolizumab with chemotherapy was better than chemotherapy in first line, so an earlier stage of disease. So, the PD-1 inhibitors are now FDA approved as of June 10th, both in first line and in second line head and neck cancer. There appears to be a better response rate, an earlier response, and a more frequent response in HPV-positive head and neck cancer patients, but the longest data we have is two-year follow-up data from the CheckMate 141 trial, and that showed that overall survival was equivalent between HPV-positive and HPV-negative patients.

Dr. Hamid:
Well, it's about that time to bring this program to a close, but before we do, is there anything you'd like to revisit or discuss regarding HPV-associated cancers that was not touched upon today? Dr. Campos, let's start with you.

Dr. Campos:
Certainly. I think the most important thing to remember is that the prevention is always better than the cure, and, you know, cervical cancer is largely preventable through public health interventions, and at the present time, we have two HPV vaccines. One is the

bivalent Cervarix, which covers HPV 16 and 18, but there's also Gardasil 9, which has recently become available and actually protects against seven HPV types, including type 16, 18, 31, 33, 45, 52, and 58, but it also targets nonmalignant genital warts. So, it's important that this vaccine is talked about with young women and also young men at the same time because this is truly a preventable disease, and when we talk about burden of disease, we talk about not only morbidity with young women in terms of multiple biopsies and actually some obstetric complications but also mortality, which, you know, in the United States is high, but in developing countries almost accounts for 90 percent of women's deaths.

Dr. Hamid:
And how about you, Dr. Ferris? Would you like to add anything to that?

Dr. Ferris:
Sure, two points. One is to follow up on Dr. Campos' advocacy of the vaccines, the prevention vaccines. Although we don't yet have data as they have in cervical cancer with an actual histologic cancer endpoint, we do have a surrogate endpoint that those vaccines may be effective at decreasing persistent HPV infection in the oral cavity. There was a study from a Costa Rican cohort and then another from the NHANES trial looking at salivary HPV infection that appeared to be substantially, if not completely, eliminated by the HPV vaccine, and so it may be systemic HPV infection, including protection in the oral cavity, that these prevention vaccines help with, and this should translate into reduction in oropharyngeal carcinomas. In addition, I wanted to point out that a study using a targeted bispecific antibody, which is the M7824 in head and neck cancer patients, and this uses PD-L1 targeting with a bispecific TGF-beta receptor to trap so that it depletes TGF-beta, which is very deleterious and can often trigger regulatory suppressor T cells, and this agent M7824 was used in an expanded phase 1 trial, which was quite promising in a series of head and neck cancer patients. Where nivolumab is FDA approved and the response rate is 13 percent, in this study the overall response rate was around 22 percent and, in fact, in the HPV-positive group was even better, was 50 percent, suggesting that targeting PD-L1 as well as TGF-beta may be beneficial and points the way to combination therapies that may be more effective for the virus-induced head and neck cancers.

Dr. Hamid:
Well, with the prevalence of HPV-associated cancers growing worldwide, it's great to know that there are developing treatment options that may help us alleviate the heavy burden these cancers cause, and I want to thank my guests, Dr. Susana Campos and Dr. Robert Ferris, for helping us better understand HPV-positive cancers and what we may see in future treatment options across the varying cancer types. Dr. Campos, Dr. Ferris, it was great speaking with you today.

Dr. Campos:
Thank you.

Dr. Ferris:
Thank you.