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Rationale for Combining Radiation and Immunotherapy in Resectable Locally Advanced HNSCC

Announcer:
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Dr. Lee:
This is CE on ReachMD, and I'm Dr. Nancy Lee. In this brief lecture, I'll review the rationale for combining radiation and immunotherapy in resectable locally advanced head and neck squamous cell carcinoma.

So what is the rationale of combining radiation and immunotherapy? Well, as the slide shows here that radiation actually has a profound effect on our body's immune response. Radiation forms rupture-prone micronuclei, which will spill the genomic DNA into the cytoplasm of the cell. It will activate a pathway called the cGAS-STING pathway, which in turn will activate a type 1 interferon signaling and then initiate a T cell immunity.

Radiation can release the cancer cell antigen as the cells die from the radiation, and the cancer antigen presents to the dendritic cells, or antigen presentation cells. It will prime the T cells, which is important to traffic the T cells to the tumor. And thus, the T cell will then be recognized by these tumor antigen. And then you can see the effect of where the T cell will then kill and recognize the antigen and thus pairing up to kill the tumor.

With that said, it really makes sense that every time we use immunotherapy, we should consider radiation therapy. Because let's say you have a tumor that is immunotherapy cold. Can we make it hotter by the addition of radiation? So it seems like the rationale is so sound, because we initiate this kind of cancer cell death where the antigen release is recognized by our body's T cell.

But the problem is the tumor microenvironment is much more complex than we think of. There are some stimulatory cells and there are some immunosuppressive cell, and this is what I call the yin-yang of immunotherapy and radiation.

So but with that background in mind, what does the preclinical data show? Multiple groups have shown that if you combine, whether it's other cancer models or head and neck cancer model, that if you combine anti–PD-L1 with radiation, you have less growth of the tumor. And it makes sense; there seems to be a synergistic effect.

However, when we come into the definitive, unresectable setting, there are now at least 10 to 12 randomized studies showing that the addition of immunotherapy did not improve the progression-free survival of patients given definitive chemoradiation.

But the good news is that there are 2 trials that were recently presented, and one trial is FDA-approved, the KEYNOTE-689, where we

gave, in resectable head and neck cancer perioperative, meaning we give 2 cycles of pembrolizumab before surgery, followed by radiation plus or minus chemotherapy, depending on pathologic features, with the addition of pembrolizumab followed by 12 additional cycles of pembrolizumab. And this is compared against chemoradiation. And this trial was a positive trial in favor of the experimental arm, improving the event-free survival.

This really gives us a lot of great excitement, because not only is KEYNOTE-689 positive, the NIVOPOSTOP study, as well, is positive.

And then lastly, really very exciting is to know that giving pembrolizumab before surgery, we actually had to use less chemoradiation postoperatively, suggestive of a downstaging of tumor with the use of immunotherapy before surgery.

So in conclusion, in the postoperative setting, given KEYNOTE-689 and NIVOPOSTOP, they're positive in favor of the addition of concurrent PD-1 with chemoradiation. So this shows that a lot of research should be done in really selecting which patients need to give immunotherapy in addition to chemoradiation to improve the overall outcome.

Well, my time is up. I hope I've given you something to think about. Thank you so much for listening.

Announcer:
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