Transcript Details
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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Exploring the Treatment Landscape for Head & Neck Cancer

Announcer:
Coming to you from the ReachMD studios in Fort Washington, Pennsylvania, this is Project Oncology on ReachMD. I'm Dr. Jacob Sands, and on this episode, we're going to hear from Dr. Nabil Saba, a professor and vice chair for Quality and Safety in the Department of Hematology and Medical Oncology at the Emory University School of Medicine. Dr. Saba spoke with me about how the COVID-19 pandemic has changed our approach to head and neck cancer care. Here's what he had to say.

Dr. Saba:
Head and neck cancer traditionally has been a disease that is focused mostly on HPV-negative disease, and then, over the last couple of decades, the major change has been the discovery of HPV-positive disease, specifically HPV-positive oropharynx cancer, which is cancer of the tonsil and base of tongue, and this is a very biologically different disease than the traditional smoking-related head and neck cancer. And we've been dealing with this major change or understanding for the past couple of decades, and we continue to deal with this because this disease behaves very differently than the traditional smoking-related head and neck cancer.

We know that biologically head and neck cancer which is HPV-positive is quite different than HPV-negative disease, and head and neck cancer as an organ site basically offers the advantage of studying 2 biologies within the same anatomic location. That is a virally mediated cancer through the human papilloma virus or the non-virally mediated cancer, which is basically leading to a situation of immune escape and immune suppression through its higher mutation rate compared to the HPV-positive disease, whereas the HPV-positive disease basically is immunogenic through the fact that it is a virally mediated cancer, and therefore, relying on an immune modality to treat this disease is important.

I have to mention our work here at Emory—which was published recently in *Nature,* which is a collaboration between the Emory Vaccine Center and the Winship Cancer Institute looking specifically at the B-cell responses—focused on HPV-related head and neck cancer where we basically got tumors from patients with HPV-positive head and neck cancer and analyzed in detail the immune microenvironment of these tumors, whether it is in the direct immune microenvironment of the tumor itself or the draining lymph nodes for these tumors, and we were not surprised really because we've known all along that the immune system recognizes HPV-related antigens and surmounts an attack to these antigens, specifically the HPV-related proteins E6 and E7, but this work basically showed us that this immune reaction is very, very specific towards these HPV-related proteins and occurs over a long period of time, similar to what happens with chronic HIV infection and unlike what happens with an acute, for example, flu infection or an acute viral infection. The reaction from the innate immune system is very specific to these HPV proteins discovering also that E2, which is another HPV-related protein, seems to be the target of this reaction specifically in oropharynx cancer unlike the case in cervix cancer where E6 and E7 are the 2 predominant proteins with an HPV-related disease.

This has also opened the door to ask the question: What is the role of immunotherapy in treating patients who have never received any treatment? In other words, patients who have not had radiation, patients who have not had chemotherapy. Can we treat these patients with early-stage disease with an immunotherapy approach?

These immune checkpoint inhibitors have been now introduced into the definitive treatment of locally advanced disease, and these trials basically have combined HPV-positive and HPV-negative groups under the umbrella of one study. Some people think it is the right way to do this. Biologically, certainly it makes sense to look at these 2 diseases as 2 separate entities because of the difference in clinical behavior and the difference in biology. Nevertheless, one of the latest trials that has been reported is called the JAVELIN trial, which was reported at ESMO 2020, and unfortunately, to the disappointment of all of us, the addition of PD-L1 inhibitor to the backbone of radiation and cisplatin chemotherapy did not seem to basically lead to any improvement from the analysis of this trial so one could ask

several questions. Why is it that these agents seem to work effectively in the recurrent metastatic disease, but when you add them to the backbone of radiation and cisplatin, we don't seem to observe a benefit? Is it really related to the drug or the agent? Is it related to the sequencing of the treatment? Would the addition of a PD-L1 inhibitor or an immune checkpoint inhibitor during the course of radiation therapy be detrimental to these immune cells that we just talked about that seem to be very specific in attacking the tumor and seem to be located in very close proximity to these tumor cells? What is the effect of radiation on these cells? And what is the effect of combining these immune checkpoint inhibitors to radiation? There are so many questions that one could ask, but I'm hoping that the future of these studies or the future studies will basically focus on trying to answer these questions and try to answer what would be the best way to use these agents in the definitive treatment setting.

So this is just a snapshot of what has happened lately.

When we look at the impact the immunotherapy has had on our day-to-day practice in head and neck cancer, we went from a situation 4 years ago where the first-line therapy for recurrent metastatic patients was cytotoxic chemotherapy. We were ecstatic when the EXTREME trial was read as positive back close to 2008 looking at the addition of cetuximab, which is an EGFR monoclonal antibody to chemotherapy and showing for the first time that we could actually improve the outcome for patients with recurrent metastatic disease, but nothing really has happened since the publication of the EXTREME trial between 2008 and 2016, close to a decade there, without major improvements in the treatment of metastatic disease.

So we went from this situation in 2016 to a situation now where every patient with recurrent metastatic head and neck cancer needs to be offered immunotherapy unless there is really a contraindication to deliver these drugs, and the immunotherapy can be delivered as single agent for patients who have never had prior therapy. Usually, it's pembrolizumab based on the results from KEYNOTE-048. And certainly, patients who have PD-L1 positive disease usually are treated with single-agent pembrolizumab unless there is a critical need to produce an immediate response because single-agent immune checkpoint inhibitor response rate remains to be lower than chemotherapy response rate, and so, because of this, I think the majority of patients still would be getting single-agent immune checkpoint inhibitors with the caveat that some patients will need the addition of cytotoxic chemotherapy to be able to produce that initial response. Those are your patients with bulky disease, patients where you need to improve functionality because the tumor is affecting their day-to-day function, or patients with very bulky disease, because there is a suggestion that these immune checkpoint inhibitors may not be as effective when the disease volume exceeds a certain volume. So we're still trying to refine this process, but the major change or the major shift is that the first consideration now is for immune checkpoint inhibitors.

For patients who fail the immune checkpoint inhibitors, we really found ourselves now to be in somewhat of a vacuum despite the fact that over many, many years we've used chemotherapy, and we could certainly revert back to systemic therapy agents, such as cytotoxic chemotherapy such as cetuximab, but the question is, Does this apply to all patients who fail immunotherapy? There is some data from the CHECKMATE-141 suggesting that not all patients who progress would basically continue not to benefit from the continuation of immune checkpoint inhibitors. There is maybe a subset of patients who may be able to still derive some benefit despite the progression.

There is now a group of trials which are actually trying to reverse this resistance to immune checkpoint inhibitors by adding other agents, whether it be a STING agonist, whether it be a VEGF agonist, whether it be a tyrosine kinase inhibitor and multityrosine kinase inhibitor, trying to see if the addition of these agents which do have some immune modulatory effects would actually change the response and change the outcome and whether you could reverse the biology of the disease by adding these agents down the line.

This is as far as the recurrent metastatic disease. I think we will see how these efforts will pan out over the next several years.

Announcer:
That was Dr. Nabil Saba from the Emory University School of Medicine sharing how head and neck cancer care has changed due to the COVID-19 pandemic. I'm Dr. Jacob Sands. To access this episode and others in our series, visit ReachMD.com/ProjectOncology, where you can Be Part of the Knowledge. Thanks for joining us.