Dr. Linda Yin:

Hello, and welcome to another episode of ENT in a Nutshell. I will be your host. My name is Linda Yin, and I am joined today by Dr. Chinkakuntlawar, who is a medical oncologist specializing in head and neck cancer. Dr. C., thanks so much for being here.

Dr. Ashish Chinkakuntlawar:

Oh, thank you, Linda. Thank you for the invitation and thank you for the opportunity to connect with colleagues everywhere.

Dr. Linda Yin:

Great. Today we're going to be talking about principles of chemotherapy, and what that means is that we're going to talk about some general principles for chemotherapy use in head and neck cancer, specifically for squamous cell carcinomas, to understand all the different chemotherapeutic options that we have available to us would of course, take years of training. But today we're just going to focus, again, on some concepts that every ENT should really understand. When should we be referring patients for chemotherapy, what patient factors are medical oncologists considering when they're evaluating patients, and what are the sentinel chemotherapy studies in our field that we should really understand. So starting with the presentation section, Dr. C., in what settings do patients get referred to you for consideration of chemotherapy?

Dr. Ashish Chinkakuntlawar:

Typically, chemotherapy in head and neck cancer is used as a part of multimodality therapy. Care for almost all of the cancer patients is nowadays multidisciplinary, but head and neck cancer is a prime example of that. I don't think you can treat any head and neck cancer patient in isolation. You mostly see patients in head and neck cancer clinic in the context of locally advanced head and neck cancers and a therapy for recurrent metastatic head and neck squamous cell carcinomas. It also plays a major role in the therapy for nasopharyngeal carcinoma, but we won't be talking about it today. It also could be in consideration for rare tumors, such as salivary gland carcinomas, sinonasal carcinomas, and occasionally, in aggressive thyroid carcinomas as well.

Dr. Linda Yin:

Now, like you talked about, we're going to be focusing on squamous cell cancers. In terms of the epidemiology of this disease, how common is it for patients with squamous cell carcinomas of the head and neck to require some sort of chemotherapy?

Dr. Ashish Chinkakuntlawar:

The burden for the incidence and prevalence is mainly carried by locally advanced head and neck squamous cell carcinomas. Almost 60% of them fall into this category. And systemic therapy plays a large role in this patient population as a radiosensitizer, and occasionally, as an induction therapy. Locally advanced head and neck squamous cell carcinomas are more common than early stage or recurrent and metastatic disease.

Dr. Linda Yin:

Now, before we go any further into this interview, you've already kind of thrown some of these terms out there. So I think we should define it for the listener. Can you explain what you mean by these different chemotherapy strategies, specifically definitive, adjuvant neoadjuvant and...

Dr. Ashish Chinkakuntlawar:

Sure. Definitive therapy or definitive cumulative therapy is where chemotherapy used concurrently with radiotherapy as a part of multimodality therapy. Usually it is with curative intent. It is a primary therapy and surgeries only used as a salvage treatment later in the follow-up. The motivation or rationale behind simultaneous use of chemotherapy here is to synergize with radiotherapy and maximize its therapeutic effect. Compare that to adjuvant therapy where chemotherapy is primarily used in the postoperative setting. In head and neck squamous cell carcinomas, adjuvant chemotherapy is almost always given concurrently with radiotherapy. The goal here is to treat the microscopic residual disease with an aim to decrease the probability of recurrence later.

Neoadjuvant induction chemotherapy is given before a local treatment modality such as surgery or radiotherapy. If chemotherapy is given before radiotherapies, often referred to as induction chemotherapy, and if it is given prior to surgery, it is often called as neoadjuvant therapy, whereas palliative therapy or palliative systemic therapy is a term used in the context of recurrent and metastatic disease that cannot be treated with surgery or radiotherapy anymore. And usually, this is an incurable context and the goal is to improve the symptom burden and the quality of life for the patient. And additionally, the goal is also to improve the survival for these patients.

Dr. Linda Yin:

And when you're seeing a patient in clinic that you're considering for chemotherapy, what sort of history are you taking from them?

Dr. Ashish Chinkakuntlawar:

As a medical student resident and even as a practicing physician, I think this aspect of patient evaluation is very important. There are many factors to consider, and I think it is worth spending a lot of time here with the patient. The things that I personally focus on is whether the patient is getting therapy in the context of curative or palliative intent, and if it is curative, whether it is adjuvant or definitive therapy, a patient's age, performance status, medical comorbidities such as heart, lung, kidney disease, whether they have a hearing loss, tinnitus, neuropathy. I also pay special attention to their profession and hobbies because the toxicities that we can expose them to can have a profound effect on their hobbies and profession in the future. Taking a good history with regards to their current medications, including supplements such as herbal supplements and medical marijuana use or other recreational drug use is also important.

It is also very important, especially in the context of head and neck cancer, to ask them about their social and family support, their symptom burden, including dysphasia, pain, weight loss, any other associated symptoms. It is also important to ask about history of smoking, alcohol use, and also very important to differentiate smoking from smokeless tobacco as often, patients will say no to smoking but won't warrant of the history for smokeless tobacco. In countries outside of the United States, there are other forms of tobacco such as betel nut or flavored and non-flavored chewing tobacco that is commonly used.

It is also very important to ask them about their past history including any previous cancer or therapy given for that cancer, including radiotherapy and chemotherapy, as there is a definite dose or a lifetime dose that can be given for certain chemotherapies and definitely for radiotherapy. It is also

important to ask about allergies that could be important to know when you are planning further treatment.

Dr. Linda Yin:

I think that's very comprehensive. And I often hear medical oncologists speak about a patient's performance status. Can you tell us how you're defining this and what that means?

Dr. Ashish Chinkakuntlawar:

There are many ways to define this, but the two most commonly used scales are ECOG performance status or the Karnofsky score. I think it is okay to remember at least one of them when you are evaluating the patient. It's an easiest way to determine how fit your patient is and how the cancer is affecting them. For example, ECOG is graded from grade zero to five, where zero is fully active with no symptoms from the cancer, to five where the person has died. And grade one, two, three, and four are varying degrees of disability from the cancer.

Dr. Linda Yin:

And you also talked about important things to ask in terms of the medical history. Are there any specific comorbidities that you focus on that may pose a risk to chemotherapy and may even be contraindications for certain types of chemotherapy?

Dr. Ashish Chinkakuntlawar:

Absolutely. I usually, in the context of head and neck cancers, ask about coronary artery disease, diabetes, neuropathy from diabetes or any other cause, hearing loss, tinnitus, autoimmune disease, chronic infections such as HIV and other hepatitis infections. Also very important to know about their psychosocial history, including a history of any major depression, anxiety, or panic attacks. And there are certain groups that also deserve special attention such as geriatric patients. And I usually ask them about falls recently, dementia, who their primary care taker is and where do they live? And in young patients, it is also very important to go over their sexual history, including use of contraception and any plans to have kids in the future as some chemotherapies could definitely affect their fertility in the future.

Dr. Linda Yin:

And moving on to the physical exam, after you've obtained all this history, what sort of physical exam do you perform in the office before you're initiating chemotherapy?

Dr. Ashish Chinkakuntlawar:

Just like the history taking, I think this is also a very important part of patient evaluation which unfortunately is not getting a deserved attention nowadays. I usually do a very comprehensive physical exam, including a skin, ear, and scalp examination in the context of head and neck cancers, palpate their lymph nodes, and carefully inspect their oral cavity and palpate the oral cavity in addition to the usual examination of heart, lung, and central nervous system. This is very important to remember considering that we are relying on scans more and more and unusual things that we are facing such as COVID-19 pandemic, where we are probably going to use more and more telemedicine. Unfortunately, in head and neck cancers, filling, palpating, looking is very important. And hence, these things will be important for us to stick to in the future even if the other parts of the medicine changes.

Dr. Linda Yin:

Yeah, I think that's a great point. Moving on to the workup, some of these scans and such as you say. So say you're evaluating a patient, again, for consideration of chemotherapy. What are some basic lab studies that you might get, or even other tests that you might get before starting?

Dr. Ashish Chinkakuntlawar:

Usually we start with a complete blood count and a comprehensive metabolic panel. Both of these studies will allow us to evaluate their bone marrow function and kidney and liver function to plan appropriate chemotherapies. I also pay special attention to blood glucose as you can certainly miss a mild or a prediabetes or untreated diabetes, which could be worsened by use of dexamethasone as well as dehydration that most patients experience during chemoradiotherapy. We also usually do a baseline audiogram if you are planning to use cisplatin in any form, and especially with high dose cisplatin.

Dr. Linda Yin:

Now, shifting to chemotherapy in the postoperative adjuvant setting, here, what are you using and what tests are you using to guide your decision making?

Dr. Ashish Chinkakuntlawar:

There are many things to consider. And like I said previously, head and neck cancer is a prime example of a multidisciplinary effort. So usually, it's not a test, but a discussion with a surgeon, a thorough evaluation of a operative report is very important to determine if a patient's resection was optimal or not. And then other things such as pathology report, including margin status, nodal involvement, external extension in those lymph nodes, or perineural invasion and lymphovascular invasion in the primary tumor are things that are important to determine when you plan the adjuvant treatment.

Dr. Linda Yin:

And now, in talking about chemotherapy now for the recurrent or metastatic setting, what sort of imaging workup do you need to evaluate metastatic disease before you start chemotherapy?

Dr. Ashish Chinkakuntlawar:

Most of the time we rely on a PET scan to evaluate the distant metastasis, as well as look at the local regional spread. In head and neck squamous cell carcinomas, metastases usually are in lymph nodes, lungs, livers, and bones, and PET scan allows you to evaluate for all of those. If that is not available, you could certainly get a CT scan of the neck, chest, abdomen, and pelvis. It should be a reasonable test as well. Brain is not a very common site of metastasis for head and neck squamous cell carcinomas. It can sometimes happen in HPV positive disease, but if patient doesn't have any symptoms, there is no need to obtain any brain imaging on a routine basis.

Dr. Linda Yin:

And how about, we talked a little bit about the surgical pathology, how about immunohistochemistry or histologic studies? Are there any that could be helpful in deciding which therapy that we should start?

Dr. Ashish Chinkakuntlawar:

As a part of evaluation, there are certain immunohistochemical markers or testing that we perform on surgical pathology specimen that guide our decisions. They don't necessarily change the treatment

paradigms today, but this certainly will help us prognosticate in case of head and neck squamous cell carcinomas. In case of oropharyngeal carcinomas, HPV status is very important. This can be accomplished by staining for p16 more specific tests such as HPV in situ hybridization or PCR studies. In case of nasopharyngeal cancer, EBV positivity could also be looked at. And then in the context of recurrent and metastatic head and neck squamous cell carcinomas, assessment for PD-L1 status will help you determine the treatment with regards to immunotherapy or immunotherapy with chemotherapy.

Dr. Linda Yin:

Yeah, let's talk a little bit about PD-L1. So I think this is a confusing subject for a lot of people. So what is PD-L1? And then what is the CPS score that can sometimes be calculated from this? And how are you using that to guide your decision making?

Dr. Ashish Chinkakuntlawar:

You are not alone. This is a confusing thing for all of us, because all of these assays have been designed by different companies with different antibodies, different cutoffs, and given different names such as combined positive score or tumor proportion score. And so it is not uncommon to get lost in this world. The combined positive score used in head and neck squamous cell carcinomas is a percentage of PD-L1 positive cells within a tumor as a percentage. Usually this is only used for pembrolizumab, which is one of the anti-PD-L1 antibodies. There are other scores with different names for other immunotherapies.

Here I will use this opportunity to explain how the PD-L1 therapy, anti-PD-L1 therapies or PD-L1 therapies work. Normally beyond innate immune response, our bodies utilize acquired immune response to respond to pathogens and amplify the initial immune response and generate memory and preserve that memory. This is accomplished by presentation of antigen-presenting cells, such as dendritic cells and interacting with the T cells through T cell receptors.

On the surface of the T cells, we also have costimulatory molecules such as CD28, that augment the T cell activation. Think of T cells as cars and CD28 would be an accelerator. However, you don't want your car to accelerate forever. So we also have brakes on the T cells, and these brakes are called checkpoints, and there are many of them. One of them is called the programmed cell death protein 1 or PD-1. PD-1 interacts with this ligand, PD-L1 or L2, and some tumors, including head and neck squamous cell carcinomas, express PDL-1 on their surface and use this interaction to put brakes on the T cells and dampen the immune response. Checkpoint inhibitors or what we commonly call immunotherapy, such as PD-1 inhibitors, break this interaction, which is analogous to taking the brakes off of your car, and thus turning the T cell on again.

Dr. Linda Yin:

Thank you for that explanation. I think that's one of the best ones I've heard to help understand these immune checkpoint inhibitors. I do want to get into more about the meat of these medicines and their mechanisms of action, but before we do that, one last question about workup. I understand that genetic testing of tumors is becoming a more popular thing in other pathologies, including those in the head and neck, for example, for thyroid cancers. Is there any role of this in the squamous cell world? And are you using this in your practice?

Dr. Ashish Chinkakuntlawar:

Definitely. Currently, I mainly use somatic or tumor mutational profile, mostly in the context of recurrent and metastatic disease. Most of the patients who have a metastatic disease have very limited

therapeutic options and somatic mutational profile helps them chart out next line of therapies in the context of clinical trials or targeted therapy. Having said that, in the primary setting, there is not much use for somatic testing yet, but we know that HPV negative disease has increased incidents of p53 mutation. In comparison, the HPV positive disease rarely has p53 mutation, but has mostly mutations in the PI 3-kinase and downstream pathways.

Dr. Linda Yin:

All right, let's talk a little bit about pharmacology now. So we've used the term chemotherapy so far, but really what this means now, it's a broad term that not only includes our traditional cytotoxic chemotherapies, but also new targeted therapies and like we already talked about, immunotherapies. So really maybe a better word for these therapies is really systemic therapy. So can you talk a little bit about these general classes of systemic therapies that we have available to us in head and neck cancer?

Dr. Ashish Chinkakuntlawar:

Absolutely. We just talked about immunotherapy and its mechanism of action. These are usually monoclonal antibodies that activate our own immune system to destroy the tumor cells. In comparison, the targeted therapy are newer drugs that act on specific molecular targets. These include drugs such as cetuximab or tyrosine kinase inhibitors such as afatinib, that target the epidermal growth factor receptor pathways. The standard cytotoxic chemotherapies or the traditional chemotherapy that we call chemotherapy are the drugs that affect rapidly dividing cells via inhibition of cell division through a variety of mechanisms such as inducing DNA damage or inhibiting DNA synthesis or interfering with the process of cell division.

Dr. Linda Yin:

Yeah, let's talk a little bit about that. So cisplatin is one of the commonly used drugs and heavily featured in this talk. Can you talk a little bit about its mechanism of action and some of the side effects and toxicity profile to watch out for?

Dr. Ashish Chinkakuntlawar:

Cisplatin basically inhibits DNA replication. When you give this drug, it enters the cells and it binds to the DNAs chains and cross-links them, and it prevents the unwinding replication and eventually leads to the inability of the cancer cell to repair its DNA damage and cell death. This effect is obvious in rapidly dividing cells, such as tumor cells, or also in other normal cells, such as bone marrow, which leads to the toxicity of the drug. It usually causes cytopenias, but it also can be directly toxic to organs such as kidneys or inner ear leading to hearing loss and tinnitus. It also can cause peripheral neuropathy and in acute context, it can also lead to dehydration, electrolyte disturbances, such as hypomagnesemia and nausea and vomiting. Out of these side effects, ototoxicity and peripheral neuropathy sometimes can be permanent.

Dr. Linda Yin:

And regarding cisplatin, now we talked about using it to an uncommon fashion with radiotherapy and often hear the term cisplatin being used as a radiosensitizer. Can you tell us what that means?

Dr. Ashish Chinkakuntlawar:

Cisplatin is often given with radiotherapy in the context of head and neck squamous cell carcinomas, and referred to as a radiosensitizer because when you give cisplatin along with radiotherapy, it sensitizes the cancer cell to radiotherapy-induced damage, leading to more effect to therapy.

Dr. Linda Yin:

Great. Moving on now to some of the other cytotoxic drugs, can you talk a little bit about some other commonly used ones in head and neck cancer and a brief description of their mechanism of action?

Dr. Ashish Chinkakuntlawar:

Another commonly used platinum agent is carboplatin. It works in a similar fashion to cisplatin, but it is better tolerated. However, there is increased risk of myelosuppression and also allergic reactions with this agent. There is another class of agents called taxanes, which includes paclitaxel and docetaxel. These agents are called microtubule inhibitors and they work via prevention of a microtubule reorganization during mitosis. Their side effects include cytopenias, including neutropenia, hair loss, alopecia, mucositis, neuropathy, and again, allergic reactions.

5-fluoropyrimidine or 5-FU is an antimetabolite which is also commonly used in head and neck squamous cell carcinomas. This drug binds to thymidylate synthase, an enzyme that is involved in DNA synthesis. So this drug prevents synthesis of DNA. This drug leads to mucositis or GI side effects such as diarrhea, nausea, vomiting, and skin rash. In rare cases, it can also lead to cardiac toxicity as well. There is a special group of patients who may also have a deficiency in an enzyme called DPD, and patients who have this deficiency can have life threatening side effects from this drug due to reduced metabolism of 5-FU.

Dr. Linda Yin:

And moving on to our targeted therapies, cetuximab is often used as well. How does cetuximab work?

Dr. Ashish Chinkakuntlawar:

Cetuximab is a monoclonal antibody against wild-type EGFR. I might have said it previously or not, but head and neck squamous cell carcinomas often overexpress wild-type EGFR on their surface and this drug binds to those receptors and prevents its downstream signaling. The side effects include allergic reactions such as infusion reaction, acne from skin rash, diarrhea, and electrolyte disturbances such as low magnesium or hypomagnesemia. It also has a black box warning for a sudden cardiac death or cardiopulmonary arrest in about 3% of patients. So it's not very common, but you should be aware of that.

This drug also has some other interesting things that just patients who have rash are more likely to respond to the agent, as well as the hypersensitivity that is seen with this drug is associated with alpha-gal antibodies and more common in Southeastern United States where tick infections are common. This is the same antibody that causes red meat associated hypersensitivity as well.

Dr. Linda Yin:

That's really interesting. And now finally, the immunotherapies. We've already kind of gone into depth about their mechanism of action, but can you just introduce us to the two common ones that are used?

Dr. Ashish Chinkakuntlawar:

The two FDA approved immunotherapies used in the context of head and neck squamous cell carcinomas are nivolumab or Opdivo, and pembrolizumab or Keytruda. Both of these are anti-PD-1 antibodies manufactured by two different pharmaceutical companies. There are other immunotherapies that are on the market, but they are not yet approved for head and neck squamous cell carcinomas. And then there are many others that are in the pipeline. So this is an exciting field and will probably change significantly in the coming years.

Dr. Linda Yin:

Okay, now that we've gained some basic knowledge and basic background of some of these systemic therapies, let's talk specifics about regimens that are actually used in practice. So I understand one of the first major indications for concurrent chemoradiation therapy in head and neck cancer was in the larynx cancer world. And people often talk about the laryngeal organ preservation trials from the VA. Can you tell us a little bit about this?

Dr. Ashish Chinkakuntlawar:

The VA trial published in 1991 in New England Journal of Medicine was the seminal trial. This study used organ preservation for the first time and showed the feasibility of this approach in laryngeal squamous cell carcinomas. This trial enrolled a stage three and four laryngeal squamous cell carcinoma patients and randomized them to primary laryngectomy followed by radiotherapy, which was the standard of care at that time, versus an experimental arm where cisplatin and infusional 5-FU was given as an induction chemotherapy. And if the patient responded to this chemotherapy, then they went on to have radiotherapy as their primary treatment, thus saving the larynx. If patients did not respond to the chemotherapy, then they went on to have laryngectomy followed by radiotherapy as standard of care. But this approach, it was shown that 64% of the patients were able to save their larynx without compromising their overall survival, thus showing us that this approach is indeed feasible in majority of the patients.

Later on in 2003, RTOG 91-11 established concurrent chemoradiotherapy as the standard of care for organ preservation. In this trial, there were three arms, radiotherapy alone or sequential such as VA trial, where chemotherapy was followed by radiotherapy, or a third arm where chemotherapy was given concurrently with radiotherapy. And the chemotherapy here was 100 milligram per meter squared of cisplatin. And this trial showed that the concurrent chemotherapy arm was superior compared to the other two arms in organ preservation and thus establishing concurrent cumulative therapy as the standard of care approach.

Dr. Linda Yin:

And how about, moving outside of the larynx for the other subsites in the head and neck, how has concurrent chemotherapy and radiation therapy evolved at these other subsites and what are some of the sentinel trials that we should know about?

Dr. Ashish Chinkakuntlawar:

The initial two trials that established concurrent chemoradiotherapy as standard of care at other subsites included the GORTEC trial, as well as the Intergroup trials here in the United States. The GORTEC trial used a different backbone for chemoradiotherapy. They used carboplatin and 5-FU along with radiotherapy as their concurrent chemoradiotherapy strategy, whereas the Intergroup trials used 100 milligram per meter squared of cisplatin as their concurrent chemoradiotherapy approach. All of

these trials established that concurrent chemoradiotherapy was superior approach for organ preservation at other subsites, including oropharynx.

Dr. Linda Yin:

And to clarify that, superior compared to radiotherapy alone?

Dr. Ashish Chinkakuntlawar:

Correct. Compared to a radiotherapy alone or in the Intergroup trials, there were some other approaches tried as well, including a split-course RT, which was found to be inferior to concurrent chemoradiotherapy.

Dr. Linda Yin:

And what about cetuximab? Is this first-line or is this second-line? Does it work as well as cisplatin when we're using it, again, in the context of definitive concurrent chemoradiation treatment?

Dr. Ashish Chinkakuntlawar:

This is a interesting question because if you asked me this question a few years ago, cetuximab would have been a fairly good option for patients who are chemotherapy ineligible or were not eligible for cisplatin due to some preexisting comorbidities such as neuropathy or a severe hearing loss. The use of cetuximab was first demonstrated in the Bonner trial in 2006, and this trial states three or four head and neck squamous cell carcinomas at all subsite including larynx, oropharynx, and hypopharynx were included and comparison arms where radiotherapy alone or radiotherapy concurrently with cetuximab, and the cetuximab plus radiotherapy arm showed better progression through survival, as well as overall survival, thus establishing cetuximab as another approach in chemotherapy ineligible patients. And somehow, this creeped up into the treatment as an alternate approach rather than using only for chemotherapy ineligible patients.

However, two recent trials, RTOG 1016 and De-ESCALaTE HPV, which were studying cetuximab plus radiotherapy as a deescalation approach compared to cisplatin plus radiotherapy, showed that cetuximab was inferior in terms of not only a local regional control, but also overall survival in the context of HPV positive disease. Interestingly, both low risk as well as intermediate risk HPV positive cancer showed inferior survival with cetuximab. And so you should use it very carefully and only in chemotherapy ineligible patients.

Dr. Linda Yin:

Now, I'm shifting gears now talking a little bit about the toxicities of treatment. We talked about theoretical toxicities as part of a side effect profiles of many of these drugs, but how do you quantify this in the clinical setting? What does toxicity mean for the patient?

Dr. Ashish Chinkakuntlawar:

In the medical oncology world, we usually quantify toxicities using common toxicity criteria published by the National Cancer Institute, and the toxicities could be lab abnormalities or symptoms that the patient is experiencing. And you technically should record all of them at every visit. From the CTCAE, the grading for the adverse event goes from zero to five, where five is fatal toxicity. Although this is mostly done by the providers nowadays, there are pushes to include patient-reported outcomes rather than the

provider-reported outcomes. And hence, there are some new methodologies coming, including app-based coding that a patient can do using a smartphone.

Dr. Linda Yin:

Now, talking a little bit, again, about toxicities, we mentioned cisplatin and we mentioned specifically the 100 milligrams per meter squared dosing of cisplatin. Is this what's referred to as high dose cisplatin? And are there any other ways to dose cisplatin? I've seen certainly other doses in patient charts that I've read. What are the alternatives and what are the pros and cons in terms of toxicity?

Dr. Ashish Chinkakuntlawar:

The high dose cisplatin usually means 100 milligram per meter square. And in fact, that is the only dose that has level one evidence for it's used in head and neck squamous cell carcinomas. The other way cisplatin is used often is 40 milligram per meter squared weekly dose, and that doesn't usually have much evidence behind it, but most head and neck cancer experts agree that it is reasonable to use the dose in some contexts. The toxicities are more or less same that we have previously discussed, but there are some notable differences. For example, nausea, vomiting, electrolyte disturbances, cytopenias, nephrotoxicity are definitely more with high dose cisplatin compared to the weekly cisplatin. There is unfortunately no direct comparison between 100 milligram per meter square and 40 milligram per meter square in a phase three trial.

Dr. Linda Yin:

All right, now we've now mostly talked about using cisplatin in the concurrent curative definitive treatment setting. Switching to recurrent or metastatic cases now, what kind of systemic therapies have been shown to be effective for these patients?

Dr. Ashish Chinkakuntlawar:

Before 2019, the standard of care used to be the extreme regimen. This was published in 2008 where cetuximab was added to a platinum doublet and was shown to be superior in comparison to a platinum doublet. However, just recently, in 2019, KEYNOTE-048 trials studied this extreme regimen in comparison to immunotherapy alone or immunotherapy plus a platinum doublet. And the immunotherapy used in this trial was pembrolizumab, which is an anti-PD-1 inhibitor antibody that we previously discussed. In these trials, recurrent metastatic head and neck squamous cell carcinoma patients were randomized to three arms, pembrolizumab alone, pembrolizumab plus chemotherapy, or the traditional extreme regimen with cetuximab. Pembrolizumab alone performed better than extreme in patients with combined positive score of one or more, and especially well in patients with combined positive score of 20 or more, whereas pembrolizumab plus chemotherapy performed better than extreme in the total population or where combined positive score was not known or available. Now, because of this trial, pembrolizumab plus platinum-based chemotherapy is standard of care for all patients, or you can select your patients using CPS or combined positive score for pembrolizumab alone as the standard of care first-line treatment.

Dr. Linda Yin:

And finally, wrapping up now, after you've given patients some of these systemic therapies, how are you following up with them and what are some late toxicities that you might look for in follow up?

Dr. Ashish Chinkakuntlawar:

We usually follow our head and neck squamous cell carcinomas patients every three to four months for the first two years, and then every six months or annually for five years. With regards to systemic therapies, you need to watch for persistent nephrotoxicity, ototoxicity, peripheral neuropathy, and thyroid dysfunction. You should also encourage patients for smoking cessation or limiting their alcohol and encourage lifestyle modifications such as a healthy diet and regular exercise. Especially in the context of head and neck cancers, monitoring patient's psychiatric health is also very important. Major depression and suicide is far more common in head and neck cancer patients compared to the other cancer patients.

Dr. Linda Yin:

Okay, well, those are some general principles of chemotherapy in a nutshell for the ENT surgeon. Let's move on to the summary section now. So I'll be providing some key points from the talk. Chemotherapy is usually given in three major contexts as a treatment for head and neck cancer. The first is concurrently with radiotherapy as a part of definitive intent to cure therapy. The second is in the adjuvant setting, and this can be either given as adjuvant treatment after surgical resection of local regional disease, or as neoadjuvant therapy, sometimes called induction chemotherapy, prior to surgical treatment. Chemotherapy can also be used in the third way, which is a first-line therapy for recurrent or metastatic cancers.

When a patient comes into the office for consideration of chemotherapy, it's important first of all to establish with them their goals of care. Then we want to take a careful history and a comprehensive history, as well as perform a careful physical exam. The patient's performance status, that is their function in their daily lives, should be assessed before the treatment is offered. Workup prior to starting chemotherapy includes basic labs, such as a CBC and a BMP, to look for the kidney and liver functions. If cisplatin is being considered, it's also a good idea to get a baseline audiogram. And that's because of the ototoxicity side effect profile of this drug.

In terms of histopathologic studies, there are some important tests that are important to obtain before starting chemotherapy. And this includes HPV status or p16 staining of the tumor specimen. And in some cases of recurrent or metastatic disease, also staining for PD-L1, the programmed death ligand-1, to calculate the combined positive score, which may determine a patient's response likelihood to immunotherapy.

There are three types of systemic therapies that are widely used in head and neck cancer. The first is standard traditional cytotoxic chemotherapy agents, the second is targeted therapies namely, a drug called cetuximab, which is a monoclonal antibody against the EGFR receptor, as well as immunotherapies that serve to boost the body's own immune system against these tumors. Cisplatin is of course, a workhorse of head and neck chemotherapy. It is a DNA alkylating agent that cross-links DNA strands. And the main toxicities that we need to be aware of are nephrotoxicity, some peripheral neuropathy, as well as ototoxicity, the latter two of which may be permanent. Cisplatin is often referred to as a radiosensitizer because it can work synergistically with radiation therapy and compound the effect and killing tumor cells.

The feasibility and rationale behind concurrent chemoradiation therapy was first established in the subsite of the larynx. The VA larynx preservation trial showed that organ preservation therapy was indeed possible in head and neck cancers, and later trials showed that concurrent chemoradiation therapy was better than the sequential combination of chemotherapy followed by radiation therapy. Even later trials in the oropharynx and other subsites as well established concurrent chemoradiation therapy to be the standard of care across all subsites in the head and neck.

In the adjuvant setting, the determination of whether or not chemotherapy is warranted depends on two main risk factors from surgery and the surgical pathology. The first is a positive surgical margin, and the second is positive ENE or otherwise known as extra-nodal extension. That means extension of the tumor outside of the confines of the lymph node. In cases of recurrent or metastatic disease, immunotherapy is now... Immunotherapy-based regimens, I should say, is now the standard of care. For all comers, immunotherapy plus platinum-based chemotherapy has been shown to be superior to traditional chemotherapy regimens. And in those with high CPS scores, that is a high staining percentage of those PD-L1 receptors, those patients can even receive immunotherapy single agent as the first-line for recurrent to metastatic disease.

Okay, let's move on to the question section now. What is neoadjuvant chemotherapy? Neoadjuvant therapy is defined as chemotherapy that's given before the local treatment modality, which can be surgery or radiation therapy. Oftentimes, it's called neoadjuvant when given before surgery, and called induction chemotherapy when given before radiotherapy. Next question, what are some common grading systems we can use to assess a patient's performance status? The ECOG Performance Status Scale and the Karnofsky Performance Status Score are two main ways that we can assess a patient's performance status.

Next question, what is the first-line cytotoxic agent used in concurrent chemoradiation therapy for head and neck cancer? The primary cytotoxic therapy used for concurrent chemoradiation therapy is cisplatin. Cisplatin is a platinum alkylating engagement that can bind to DNA. Next question, what are the two FDA-approved immunotherapy agents that are often used as immunotherapy in head and neck cancer? The two primary immunotherapy agents used are nivolumab, otherwise known by its brand name, Opdivo, and pembrolizumab, otherwise known as Keytruda.

Next question, what are the most important pathology factors to consider when considering using chemotherapy in an adjuvant setting? NCCN guidelines dictate that the two most important risk factors that warrant consideration for chemotherapy are positive surgical margins and positive extranodal extension. Final question, what is the first-line therapy that is used for recurrent or metastatic head and neck cancer? Immunotherapy-based regimens are now the first-line standard of care for recurrent or metastatic disease. This can be pembrolizumab with the addition of a platinum agent, which can be used in all comers, or pembrolizumab alone as a single agent therapy, which should be used in patients with high PD-L1 staining and high CPS scores that respond best to this type of therapy. That's our show. Thank you for listening, and we'll see you back soon.