Checkpoint Inhibitor Immunotherapy for Head and Neck Cancer: Incorporating Care Step Pathways for Effective Side-Effect Management

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Abstract

The introduction of immunotherapy to treat recurrent/metastatic head and neck squamous cell carcinoma in 2016 has provided new valuable treatment options to many cancer patients. Pembrolizumab and nivolumab, which are classified as immune checkpoint inhibitors of programmed cell death protein 1, have shown clinically significant activity in patients who progressed on or after platinum-based regimens, and these agents are now US Food and Drug Administration approved for this indication. These treatments can result in unique immune-related adverse events (irAEs) that many health-care providers have difficulty identifying and managing. This article addresses the important role advanced practice providers play in a care team. Their experience is vital to managing the irAEs that can occur in patients being treated with immunotherapy agents. Their early experience with these newer therapies allows them to help educate and support not only patients but other health-care providers as well. The Care Step Pathways (CSPs) created as part of the Immuno-Oncology Essentials initiative are excellent tools to help with the diagnosis and management of many irAEs. This article summarizes the CSPs on specific considerations when managing thyroiditis, mucositis/xerostomia, skin toxicities, and hepatotoxicity, and addresses the special concerns of the head and neck squamous cell carcinoma population.

The introduction of immune checkpoint inhibitor (ICI) therapy with pembrolizumab and nivolumab has provided a significant benefit for patients with recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC). Nevertheless, the incorporation of these agents into the treatment algorithm has also posed a challenge for the multidis-

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ciplinary oncology team charged with the identification and management of immune-related adverse events (irAEs) associated with these newer therapies.

In 2017, the Melanoma Nursing Initiative (MNI) developed a series of advanced practice provider (APP)–focused educational materials to improve the recognition and management of irAEs in the setting of melanoma (Rubin, 2017). Those materials were quickly adopted by healthcare providers (HCPs) working with other tumor types. To address the contextualization of the MNI materials for use in various tumor types, the AIM with Immunotherapy Immuno-Oncology Essentials—or IO Essentials—initiative was commissioned. This article features a review of the use of the IO Essentials materials available at aimwithimmunotherapy.org for use in HNSCC. Companion articles on specific tumor-specific carveouts are also included in this supplement, including one on lung cancer (Davies, 2019) and another across remaining tumor types (Wood, 2019). This supplement also features a global article on the principles for triaging irAEs via telephone and in the office setting (Hoffner & Rubin, 2019).

CARE STEP PATHWAYS OVERVIEW AND DEVELOPMENT

The Care Step Pathways (CSPs), which debuted in MNI, were designed to assist HCPs in identifying, grading, and managing irAEs in patients receiving ICIs. This article will reference all 12 CSPs featured on the IO Essentials site (see Table 1 and the Appendix). It includes an in-depth discussion of four CSPs: thyroiditis, mucositis/xerostomia, skin toxicities, and hepatotoxicity. Some of these have special relevance to HNSCC because of their anatomic location, baseline comorbidities associated with prior radiation therapy, or the malignancy itself.

The 11 CSPs developed by the MNI have been updated here, and a 12th CSP has been added on adrenal insufficiency. In updating these CSPs, the IO Essentials faculty reviewed them with an eye toward relevancy across tumor types. In addition, the CSPs were modified to address recently released guidance on irAE management from the Society for Immunotherapy of Cancer (Puzanov et al., 2017), American Society of Clinical Oncology (Brahmer et al., 2018), and the National Comprehensive Cancer Network (NCCN, 2018). The IO Essentials site contains other HCP and patient education tools, which will also be discussed.

RATIONALE FOR AND USE OF IMMUNOTHERAPY IN HEAD AND NECK CANCER

Head and neck squamous cell carcinoma is the sixth most common cancer globally, with a high mortality rate of 40% to 50% (Mandal et al., 2016). For recurrent or metastatic HNSCC, prognosis is generally poor, with a median survival of 6 to 12 months. Palliative chemotherapy had been the standard of care until recently. Until the advent of immunotherapy, the only new agent recently introduced for treatment was cetuximab, a monoclonal antibody (mAb) targeting epidermal growth factor receptor

Table 1. Care Step Pathways From the IO Essentials Initiative (See Appendix)

irAE category	Toxicity	Appendix location
Most common	Skin toxicities (pruritus, rash, etc.)	Appendix A
	Gastrointestinal toxicities: diarrhea and colitis	Appendix B
	Thyroiditis	Appendix C
	Hepatic toxicities	Appendix D
Less common but serious	Additional endocrinopathies	
	Hypophysitis (pituitary)	Appendix E
	Adrenal insufficiency (adrenalitis)	Appendix F
	Diabetes	Appendix G
	Pneumonitis	Appendix H
Easily overlooked	Arthralgia/arthritis	Appendix I
	Mucositis/xerostomia	Appendix J
	Neuropathy	Appendix K
	Nephritis	Appendix L

Note. irAE = immune-related adverse event.

(EGFR). Unfortunately, cetuximab only added 2.7 months of additional survival time over platinum-based chemotherapy (Vermorken et al., 2008). Other agents used for R/M HNSCC include platinum compounds such as cisplatin and carboplatin, and cytotoxic chemotherapies such as docetaxel, paclitaxel, fluorouracil, and methotrexate.

There is a mechanistic rationale for consideration of immunotherapy in R/M HNSCC. Head and neck squamous cell carcinoma is characterized by a high mutational burden and an immunosuppressive environment characterized by the presence of regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs; Cancer Genome Atlas Network, 2015; Nordfors et al., 2013). Human papillomavirus–positive (HPV+) HNSCC tumors have a high CD8/Treg ratio, which has been associated with improved disease-free survival compared to HPV-negative tumors (Nordfors et al., 2013). These findings suggest that the modulation of the immune response is beneficial in HNSCC. Moreover, these Treg cell populations express immune checkpoints and thus can be effectively targeted by ICIs (Moskovitz, Moy, & Ferris, 2018).

An appreciation of immunosuppressive tumor mechanisms in HNSCC led to the design of immunotherapeutic approaches and clinical trials. Pembrolizumab and nivolumab, which are classified as ICIs of programmed cell death protein 1 (PD-1), have shown clinically significant activity in patients who progressed on or after platinum-based regimens, and these agents are approved for HNSCC (Ferris et al., 2016; Seiwert et al., 2016).

In 2016**,** pembrolizumab became the first anti–PD-1 immunotherapy approved by the US Food and Drug Administration (FDA) for use in R/M HNSCC. Pembrolizumab is indicated as monotherapy for the treatment of R/M HNSCC that has progressed on or after platinum-containing chemotherapy. Pembrolizumab was granted accelerated approval based on the positive findings of the KEYNOTE-012 study (Seiwert et al., 2016). However, continued approval was contingent on the randomized, phase III confirmatory KEYNOTE-040 study, which was recently published (Table 2; Cohen et al., 2019). The PD-1 inhibitor nivolumab is FDA approved as monotherapy for patients with R/M HNSCC with disease progression on or after a platinum-based therapy. Nivolumab's approval was based on the CheckMate 141 phase III trial, as discussed in Table 2. Recently, data from the KEYNOTE-048 study that was presented demonstrated

Table 2. Key Registration Studies for Pembrolizumab and Nivolumab in Head and Neck Squamous Cell Carcinoma

Drug	Study name	Study design	Outcomes	Reference
Pembrolizumab	KEYNOTE-040	• Phase III, randomized open-label trial • N = 247 patients were randomly assigned to pembrolizumab at 200 mg every 3 weeks intravenously for 24 months, and N = 248 were randomly assigned to IC of standard doses of methotrexate, docetaxel, or cetuximab intravenously (standard-of-care group)	• Median overall survival: 8.4 months for pembrolizumab vs. 6.9 months for IC (HR, 0.80, 0.65–0.98; nominal *p* value = .0161) • Objective response rate[a]: 14.6% for pembrolizumab vs. 10.1% for IC (nominal *p* value = .06)	Cohen et al., 2019
Nivolumab	CheckMate 141	• Phase III, randomized open-label trial • N = 361 patients with RHNSCC received either nivolumab or IC	• Overall survival: 36% with nivolumab at 1 year (95% CI = 29%–43%) and 17% with IC (95% CI = 9%–27%) • Overall response rate: 13% with nivolumab vs. 5.8% for IC	Ferris et al., 2016

Note. IC = investigator's choice; HR = hazard ratio; RHNSCC= recurrent head and neck squamous cell carcinoma; CI = confidence interval. Information from Bristol-Myers Squibb (2018); Merck Sharp and Dohme (2018).
[a]Includes both confirmed and unconfirmed complete or partial responses.

a survival benefit for pembrolizumab monotherapy or pembrolizumab combined with chemotherapy in the first-line setting for the treatment of R/M HNSCC. The treatment was recommended based on the expression of programmed cell death ligand 1 (PD-L1) in tumor and stromal cells. An expanded indication for pembrolizumab based on these results is expected in the near future (Burtness et al., 2018; ClinicalTrials.gov, 2018).

In KEYNOTE-012, pembrolizumab was well tolerated, with 10 (17%) of 60 patients having grade 3 to 4 drug-related adverse events, and 27 (45%) of 60 patients experiencing a serious adverse event. There were no drug-related deaths (Seiwert et al., 2016). Signals that seemed unique to HNSCC with pembrolizumab included facial edema (10% all grades; 2.1% grades 3–4) and new or worsening hypothyroidism (14.6%; Merck Sharp & Dohme, 2018). Treatment-related adverse events of grade 3 or 4 occurred in 13.1% of the patients in the nivolumab group vs. 35.1% of those in the standard-therapy group (Ferris et al., 2016). The most common adverse events experienced in the nivolumab trial included fatigue, diarrhea, nausea, vomiting, pruritus, anemia, and cough (Bristol-Myers Squibb, 2018).

DOSING AND ADMINISTRATION

For R/M HNSCC, the recommended dosage of pembrolizumab is 200 mg administered as an intravenous (IV) infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity is reached (Merck Sharp & Dohme, 2018). Nivolumab is administered as 240 mg IV over 30 minutes every 2 weeks or 480 mg IV over 30 minutes every 4 weeks until disease progression or unacceptable toxicity is reached (Bristol-Myers Squibb, 2018).

Some points to keep in mind when administering these agents include (Bristol-Myers Squibb, 2018; Merck Sharp & Dohme, 2018):

- It is important to ensure IV access before administration
- These agents should not be administered with other drugs through the same line
- Both agents require an in-line or add-on filter
- The duration of therapy has not been established; institution and providers vary in their practices when using ICIs
- Severe anaphylactic reactions are rare, but patients should be monitored. Milder reactions can be managed by slowing the infusion, whereas reactions ranging from severe to life-threatening necessitate infusion termination and discontinuation, with management via institutional protocol. In the cases of more severe reactions, premedication with an antipyretic and antihistamine may be considered for future doses

OVERVIEW OF IMMUNE-RELATED ADVERSE EVENTS

As discussed, irAEs can affect almost any body system (Brahmer et al., 2018; Puzanov et al., 2017). Management of irAEs is based on the specific AE and its severity, which, when possible, is graded by the Common Terminology Criteria for Adverse Events (CTCAE) on a scale from 1 (mild) to 5 (death; U.S. Department of Health and Human Services, 2017). Milder presentations may in some cases require only monitoring, but moderate or severe irAEs could require interruption or discontinuation of immunotherapy along with the initiation of steroid therapy (Brahmer et al., 2018; Kumar et al., 2017).

In the following sections, we provide details about the assessment and management of thyroiditis, mucositis/xerostomia, skin toxicities, and hepatotoxicity. We also provide information about nutritional counseling, since anorexia and eating difficulties can occur with these agents in patients with HNSCC.

Thyroiditis (Appendix C)

Thyroiditis is defined as an inflammation of the thyroid gland. The function of the thyroid is closely monitored in HNSCC because of its close proximity to the radiation field in patients who have received radiation therapy. The thyroid gland can also be affected by the immune checkpoint blockage, as has been discussed previously.

In patients receiving immunotherapy as a single agent, hypothyroidism or thyroiditis resulting in hypothyroidism occurred in 8.5% of pembrolizumab-treated patients and 9% of nivolumab-treated patients. Hyperthyroidism occurred in 3.4% of pembrolizumab-treated patients and 2.7% of nivolumab-treated patients (Bristol-Myers Squibb, 2018; Merck Sharp & Dohme, 2018).

As discussed in the CSP, HCPs need to monitor the thyroid function prior to and periodically during treatment. The best way to monitor is via blood tests. Thyroid-stimulating hormone (TSH) levels and free thyroxine (free T4) should generally be monitored at baseline and every 4 to 6 weeks while on immunotherapy.

Because the signs and symptoms of thyroiditis can be subtle, patients need to be advised that thyroiditis is a possible side effect. Patients should be instructed to let the provider know if they are having any clinical signs or symptoms, such as fatigue, cold or heat intolerance, constipation, weight loss, dry skin, brittle hair, palpitations, or a jittery feeling. Some patients with HNSCC who have received radiation will have hypothyroidism at baseline. In this case, we will continue to monitor labs and adjust medications accordingly. Many of these patients will have an endocrinologist or general practitioner who monitors this as well, and care should be coordinated with those providers.

As shown in the CSP, for patients who develop mild hypothyroidism, immunotherapy treatment should be continued. If symptomatic, the patient should be placed on a thyroid replacement hormone, such as levothyroxine. The starting dosage for immunotherapy-related hypothyroidism is the same as for the general population, approximately 1 to 1.6 μg/kg/day. The clinician should monitor thyroid function throughout treatment (every 4–6 weeks), and medication dosage should be adjusted accordingly (Puzanov et al., 2017).

As shown in the red flags section of the CSP, hypothyroidism can become severe and life-threatening if it goes undiagnosed, and patients can develop myxedema, a very rare but life-threatening condition (Khan, Rizvi, Sano, Chiu, & Hadid, 2017; Tanaka et al., 2016). Signs and symptoms include intense cold intolerance and drowsiness followed by profound lethargy and unconsciousness. A myxedema coma may be triggered by sedatives, infection, or other stresses the patient may experience. It is important to get emergent medical treatment and collaborate with endocrinology if myxedema occurs.

Patients should be informed they can become hyperthyroid before becoming hypothyroid. If the patient develops asymptomatic hyperthyroidism, it is appropriate to continue with immunotherapy treatment and monitor the labs closely. If the patient becomes symptomatic, such as experiencing palpitations or feeling jittery, treatment with a beta blocker could be initiated, and immunotherapy treatment can be held. If necessary, radioactive iodine or methimazole treatment can be initiated to treat the hyperthyroidism. Collaboration with an endocrinologist should also be considered. Since hyperthyroidism often progresses to hypothyroidism, laboratory tests can be repeated in 4 to 6 weeks for patients being treated for hyperthyroidism, although the test might be repeated earlier (at 2 weeks) if the hyperthyroidism is severe. If needed, TSH-receptor autoantibodies can be checked to determine if there is an autoimmune thyroiditis. For acute thyroiditis, a short period of 1 mg/kg of prednisone or an equivalent formulation may be helpful.

As discussed in the red flag section of the CSP, patients will need to seek emergent medical attention if there is swelling of the thyroid gland, causing a compromised airway. Hyperthyroidism also places the patient at risk of thyrotoxic crisis or "thyroid storm," a sudden intensification of symptoms leading to a fever, rapid pulse, and even delirium. Such cases will need to be managed in the inpatient setting and may require thyroid-suppressive therapy, fluid resuscitation, electrolyte replacement, and management of tachycardia. PD-1 inhibitor therapy is restarted when symptoms are mild and considered tolerable by the patient and when labs have normalized.

Mucositis/Xerostomia (Appendix J)

Oral mucositis is an inflammatory process of the mucous membranes that causes painful ulcerations in the mouth. This is often a significant problem for patients who undergo chemoradiation therapy for head and neck cancer. Oral mucositis caused by immunotherapy is uncommon (generally occurring in less than 10% of patients) but appears more frequently with anti–PD-1 inhibitors than with cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) inhibitors (Villadolid & Amin, 2015). Patients with HNSCC may have baseline inflammation of the mucosa because of prior radiation. Except under clinical trials, currently radiation therapy and immunotherapy are not often given at the exact same time in HNSCC patients, which can help differentiate the etiology.

Oral mucositis can be extremely painful and can interfere with the patient's ability to maintain adequate nutrition or even communicate. As illustrated in the CSP assessment section, it is important to assess for functional causes of anorexia such as mucositis vs. the more generalized anorexia that can occur with the disease and treatment. Management relies on symptom management and prevention of complications, which includes pain control, nutritional support, and prophylaxis/treatment of secondary infections (van der Beek et al., 2012). In the early stages, our clinic typically recommends a mixture of baking soda and water, which can help calm down the inflammation, prevent mouth sores, and heal any mouth sores that may be present. It can also help keep the mouth clean. Another oral rinse, called FIRST Mouthwash or magic mouthwash, may provide local relief. There are many different combinations of this medication, but most commonly it contains an antacid to coat the inside lining of the mouth, an antihistamine to decrease inflammation, and a local anesthetic to reduce pain. Other ingredients could include an antibiotic, antifungal, or corticosteroids.

In the mild or grade 1 setting of mucositis, the CSPs anticipate immunotherapy treatment to continue. We emphasize the importance of basic oral hygiene. Avoidance of hot, spicy, and acidic foods may be beneficial for the patient. Alternative treatments can include zinc supplementation or a 0.2% zinc sulfate mouthwash, probiotics, or benzydamine hydrochloride.

As shown in the grade 2 management section of the CSP, analgesics and corticosteroid rinses are most beneficial in managing the pain associated with oral mucositis. If mucositis persists for longer than 12 weeks, treatment is typically held until the mouth sores resolve. Of note, it is important to monitor mucositis closely to make sure it is not a disease recurrence. Some of the more severe cases may require supplemental nutrition and the potential use of systemic opioids for management.

When mucositis presents at grade 3 or 4, it is considered severe or life threatening. Nivolumab is to be withheld for the first occurrence of a grade 3 event. Immunotherapy should be discontinued for any grade 4 event or grade 3 event persisting for longer than or equal to 12 weeks or for any recurrent grade 3 event. Hospitalization may be necessary if no oral solids or liquids can be tolerated. Supplementation is often needed, and the use of analgesics or systemic opioids may be indicated. It is important to note that the role for systemic corticosteroids is unclear for this irAE.

Xerostomia, or dry mouth, is very common in patients with HNSCC. In a recent study that evaluated outcomes for patients with HNSCC from 2011 to 2016, one third reported experiencing xerostomia (Peach et al., 2018). In that study, patients had been receiving radiotherapy and conventional HNSCC treatments, not ICIs, so it is reasonable to expect that a substantial proportion of patients will be affected at baseline. Generally, xerostomia has been reported in 6% of nivolumab-treated patients and 4% to 7.2% of pembrolizumab-treated patients (Rizvi et al., 2015; Robert et al., 2015; Topalian et al., 2014). The specific incidence rate in patients with HNSCC is unknown. However, in our hands, the rates are higher than those reported generally with PD-L1 inhibitors, given the baseline risk factors.

As shown in the CSP, patients should be queried about the sensation of dryness in their mouth, how that affects their ability to eat and/or sleep, and any measures they have taken to alleviate it. The grading of xerostomia is from grade 1 to grade 3 according to the CTCAE version 5 criteria. It is based on symptomatology, dietary alterations, and unstimulated saliva flow (U.S. Department of Health and Human Services, 2017). The overall strategy for management includes assessing for other potential etiologies, including conditions such as sicca/Sjögren syndrome, or concomitant medications or alternative/complementary therapies. For mild cases, it can be anticipated that immunotherapy can continue, and patients should be advised to modify their diet. For moderate xerostomia, patients should be advised to add moisturizing agents such as synthetic saliva, oral lubricants, or saliva stimulants. Secretagogues can be used, including sugarless gum and natural lemon. Pharmacologic interventions such as pilocarpine or cevimeline hydrochloride can be considered. For grade 3 events persisting more than 12 weeks, immunotherapy may be held and permanently discontinued.

Oral mucositis and xerostomia can easily decrease the patient's willingness to continue with treatment. Even with all the advances in medi-

cine, there is currently no prophylactic therapy with proven efficacy. Monitoring weight, hydration status, and nutritional intake is important for this population. A nutrition referral may be made, and patients may require tube feeding or total parenteral nutrition until symptoms abate. Many patients continue to have xerostomia even after treatment is completed. This is very frustrating to many patients as it continues to affect their quality of life.

Skin Toxicities (Appendix A)

Skin toxicities are typically the most common adverse reactions to develop in patients undergoing treatment with immunotherapy. They occur in approximately 30% and 45% of patients treated with anti–PD-1 and anti–CTLA-4 agents, respectively (Dadu, Zobniw, & Siab, 2016). A rash or itching can develop at any time during treatment. Rashes appear faintly erythematous, reticular, and maculopapular, and are typically located across the limbs and trunk. Onset is typically rapid, occurring within the first 2 weeks of therapy (Friedman, Proverbs-Singh, & Postow, 2016). For HNSCC patients who have had prior chemotherapy and/or radiation therapy, some baseline skin toxicities may already be present. For example, if a patient underwent treatment with cetuximab, he/she may have an acneiform rash at baseline that is still lingering from this treatment. Patients who have received surgery and/or radiation therapy often have an increased sensitivity of the skin around the head and neck region. It is important to visualize the area before treatment begins in order to establish a baseline of any type of irritation they may have.

As shown in the CSP, the first step in managing skin toxicities is supportive care and preventive measures for at-risk patients. It is important to remind patients to use cleansers and moisturizers that are gentle on the skin and to avoid fragrances and dyes, as these can further irritate the skin. Avoiding direct sunlight and wearing sunscreen is also recommended.

According to the CSP, immunotherapy treatment should continue with any grade 1, or mild, skin toxicity. Oral antihistamines and corticosteroids may be used in some patients at a dose of 0.5 mg/kg/day to 1.0 mg/kg/day. It is important to continue with vigilant skin care, such as moisturizing and soothing methods.

In the setting of grade 2 toxicity, there should be consideration for holding treatment. If there is no improvement, we recommend beginning treatment with prednisone at 1 mg/kg/day, tapering over a period of 4 weeks. High-potency topical steroids and oral antihistamines can also be used in this setting. A dermatology consult can be considered for proper diagnosis, consideration of biopsy, and further treatment interventions.

Nivolumab or pembrolizumab should be withheld for any grade 3 (severe) and discontinued for grade 4 (life-threatening) skin conditions or confirmed Stevens-Johnson syndrome or toxic epidermal necrolysis. High-potency topical corticosteroids can be used, and the team should anticipate hospitalization for supportive care and initiation of intravenous corticosteroids. For grade 3 or 4 pruritus, corticosteroids at a dosage of 0.5 mg/kg/day to 1.0 mg/kg/day can be used. An urgent dermatology consult along with a biopsy would be preferred for an expedited diagnosis.

There are many red flags to keep in mind when caring for patients with skin toxicities. An extensive rash covering over 50% of the total body surface area or a rash that is rapidly progressing should be managed immediately to prevent further spread. Any anal, genitourinary, vaginal, or mucous membrane involvement should be evaluated and referred to dermatology for specialized treatment. If there is a concern for superinfection, an infectious disease and dermatology consult could be warranted.

Special attention should be given to patients who have baseline skin problems, such as eczema, allergies, or radiation skin changes. These patients can be more sensitive and may require oral corticosteroids or oral antihistamines sooner. In the HNSCC population, most patients have had surgery and/or radiation therapy, and the skin around the treatment area tends to be more sensitive.

Hepatotoxicity (Appendix D)

The liver is a targeted organ while undergoing treatment with immunotherapy agents. Although less common, hepatotoxicity occurs in approximately 1% to 2% of patients receiving PD-1 inhibitors during therapy (Dadu et al., 2016). Autoimmune hepatic injury can be referred to as immune-related hepatic toxicity or as immune-

related hepatitis (Suzman, Pelosof, Rosenberg, & Avigan, 2018).

As discussed in the CSP, while usually asymptomatic, hepatotoxicity can be detected with routine blood monitoring. All patients undergoing therapy with an immunotherapy agent should have a liver function test (LFT) checked and results reviewed prior to each dose. This includes aspartate aminotransferase, alanine aminotransferase, and bilirubin. Infections and malignancy should be ruled out. If hepatitis develops, it is important to distinguish between infectious, noninfectious, and malignant causes. Viral hepatitis should be evaluated for. Reviewing medications or use of recreational substances is also a key portion of the history. Red flags include severe abdominal pain, ascites, jaundice, somnolence, and mental status change.

When reviewing the CSP, for grade 1 toxicity, treatment can be withheld if LFTs are trending upward. A recheck of the LFTs within 1 week would be appropriate. For grade 2 toxicity, immunotherapy should be withheld and LFTs should be rechecked daily for 3 days or every 3 days. Treatment can be resumed when there is a complete or partial resolution of the adverse reaction. Oral steroids can be started at 0.5 mg/kg/day to 1 mg/kg/day of prednisone or an equivalent formulation. Intravenous steroids and hospitalization could also be considered. If LFTs normalize and symptoms resolve, steroids should be tapered over 4 weeks. Once the patient returns to baseline or grade 0 to 1, resuming treatment should be considered. If grade 2 toxicity lasts longer than 12 weeks, treatment should be discontinued.

For a severe grade 3 reaction, the CSP recommends permanently discontinuing nivolumab. Pembrolizumab should be discontinued for any recurrent grade 3 event or a grade 3 event lasting longer than 12 weeks. Steroids should be initiated at 1 mg/kg/day to 2 mg/kg/day prednisone or an equivalent formulation. Liver function tests should be checked every 1 to 2 days with a hepatology consult with possibly biopsy. If LFTs normalize and symptoms resolve, steroids can be tapered over the course of 4 weeks.

Life-threatening hepatotoxicity, or grade 4 hepatotoxicity, should involve permanently discontinuing treatment. Hospital admission is recommended, and steroids should be initiated at 2 mg/kg/day of prednisone or an equivalent formulation. Daily LFTs should be checked and infectious causes ruled out. Mycophenolate mofetil can be added if there is a sustained elevation and hepatitis is refractory to steroids. A hepatology consult along with a biopsy should be strongly considered.

NUTRITION

Nutrition is very important for anyone who is undergoing treatment or has completed cancer treatment. Patients with HNSCC tend to have a harder time secondary to the long-lasting toxicities such as dysphagia, xerostomia, dysgeusia, and thickened secretions. A conversation usually starts by reminding patients the importance of nutrition and how it will help them not only get through treatment but also recover faster.

In my experience, it is very helpful to have patients keep a daily journal of what they eat so they are able to track the number of calories they consume. In our clinic, we emphasize the importance of the recommended daily caloric intake to anyone going through treatment, as their metabolism is often increased and calories are burned faster, which can result in rapid weight loss. If they are unable to eat solid foods, we recommend that they replace solid foods with nutritional supplements, such as high-calorie protein shakes.

Eating becomes more difficult when patients lose their taste, have mouth sores, dry mouth, or diarrhea. Pain management is key to helping these patients get adequate intake. It is also important that they stay hydrated if they have diarrhea. Sometimes a feeding tube may be recommended for the patient's safety. Some institutions require a feeding tube prior to treatment, whereas other institutions wait to place a feeding tube until necessary.

ROLE OF THE ADVANCED PRACTICE PROVIDER

As oncology treatment options continue to advance, we will see an increase in the indications for use of immunotherapy agents related to HNSCC. Advanced practice providers have the experience, knowledge, and passion to grow with these advancements to provide patients with the care and information they need and deserve. The key

role of the APP on the care team is to prepare the patient for their immunotherapy experience and discuss baseline comorbidities and how care will be coordinated.

Providing proper patient education is important not only for the patient but for family members and caretakers. Reviewing the need for treatment and the treatment process is often a good reminder for patients, as they have likely gone through some form of treatment before. Highlighting the differences between chemotherapy and immunotherapy may be helpful, as well as reviewing additional testing that will be needed throughout treatment. More importantly, reviewing the possible irAEs to watch for should be the mainstay of the educational visit. Emphasizing the importance of reporting any unusual events, even if patients are unsure about them, can help with the overall management of irAEs if they arise. Taking immediate action can prevent further toxicity and help the patient continue on treatment for a longer period of time. The immunotherapy wallet card, provided by the specific pharmaceutical company, can be helpful, especially when presenting to a local emergency department, urgent care, or family practice that is unfamiliar with immunotherapy side effects.

Nutritional counseling throughout treatment remains relevant, as patients can lose sight of the importance of proper nutrition. When the APP sees a patient during the treatment process, it is a good time to discuss current weight and nutritional goals. Recommending other forms of nutritional support, such as a feeding tube, can be scary for patients; the role of the APP is to ensure the patient understands the necessity of these recommendations and how they can help during the treatment process.

Since immunotherapy is approved for R/M HNSCC, the APP can and should discuss goals of care with patients as they go through treatment to ensure they are living the quality of life that they wish for. If irAEs develop, communicating with the patient about their goals becomes even more important, as their quality of life can change as a result of certain irAEs. Having a close relationship with patients through this time is beneficial, as APPs can help make decisions to provide them with the quality of life they strive for.

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