Info: This is a 15-minute module to be loaded into an online-learning platform. Assessment questions can be found following the text.

Investigational PD-1 Inhibitors for the Treatment of cSCC

Introduction

Cutaneous squamous cell carcinoma (cSCC) is the second most common skin cancer type in the United States, comprising roughly half of all nonmelanoma skin cancer cases (Rogers et al, 2012). Surgical removal is curative for most cSCC tumors, but a small percentage of cases will become metastatic (Bichakjian et al, 2017). While there are few treatments available for metastatic or locally advanced cSCC, immunotherapies are emerging as promising options. For example, recently, the U.S. Food and Drug Administration (FDA) approved the use of cemiplimab, a PD-1 inhibitor, for the treatment of patients with metastatic or locally advanced cSCC who are not candidates for curative surgery or radiation (FDA, 2018). It is important for healthcare providers to be aware of emerging therapies like cemiplimab and the clinical trials associated with them so that they can recommend them to patients with advanced disease.

The role of PD-1 inhibitors in the treatment of cSCC

About 14% of cSCC cases will recur or become metastatic (Bichakjian et al, 2017). As described in module 2, there have been few options for treatment and no standard of care for managing advanced disease. Immunotherapies are promising options for the treatment of cSCC because of the high tumor mutational burden and the success of immunotherapeutic treatment of cancers with similar mutagenic profiles (Jayaraman et al 2014; Pickering et al, 2014).

T cells express programmed cell death protein 1 (PD-1) on the cell surface, which binds to PD-1 ligand 1 or PD-1 ligand 2 (PD-L1 and PD-L2, respectively) to inhibit T cell activation. This inhibitory function is called an inhibitory checkpoint, and under normal circumstances, will prevent immune system overstimulation and autoimmune reactions. In some cancers, however, this pathway can be co-opted by tumors to evade the host's immune response. The main goal of immunotherapy is to block the inhibition of T cells using checkpoint inhibitors, restoring the host immune surveillance mechanisms (Pardoll, 2012; Godwin et al, 2014).

Indeed, several emerging therapeutics inhibit either PD-1 (cemiplimab, nivolumab, and pembrolizumab) or PD-L1(atezolizumab, durvalumab). These emerging therapies and their targets are summarized in Table 1.

While only cemiplimab has been approved specifically for advanced cSCC, therapeutics that have been approved for other cancers are also being tested for antitumor activity in patients with cSCC. Because few therapeutic options exist for the treatment of recurrent or metastatic cSCC, enrollment in clinical trials is recommended (Bichakjian et al, 2018). Table 2 provides a summary of ongoing clinical trials of PD-1/PD-L1 inhibitors in cSCC.

New FDA-approved therapy for advanced cSCC

<u>Cemiplimab</u>
The checkpoint inhibitor cemiplimab is a human monoclonal antibody with a high affinity for PD-1. By binding to PD-1, cemiplimab prevents inhibitory interactions with PD-L1 and PD-L2, relieving T cell immunosuppression and restoring the patient's immune surveillance capabilities (Burova et al, 2017; Bichakjian et al, 2018).

In September of 2018, cemiplimab was approved by the FDA for the treatment of patients with metastatic or locally advanced cSCC who are not candidates for curative surgery or radiation (FDA, 2018). Cemiplimab is the first therapeutic that has been approved specifically to treat cSCC, and was granted Breakthrough Therapy and Priority Review status as it progressed through clinical trials.

Over phase I and phase II trials for cemiplimab, of the 108 patients tested, (75 metastatic and 33 locally advanced cases) 47% experienced tumor shrinkage or disappearance (FDA, 2018; Regeneron Pharmaceuticals NCT02383212; NCT02760498).

In the ongoing phase II EMPOWER-CSCC 1 study, cemiplimab (3 mg/kg body weight) is being administered via intravenous infusion over 30 minutes every 2 weeks. At the time of data analysis, the overall response rate was 48% and three of the 59 patients were experiencing disease progression (Rischin et al, 2018). This trial is recruiting participants (Regeneron Pharmaceuticals NCT02760498).

Clinical trials evaluated the expression of PD-L1 in tumor and immune cells, but patient response was only correlated with tumor cell PD-L1 expression (Park 2018). Prior exposure to radiation or other systemic therapies also does not appear to influence response to cemiplimab (Rischin et al, 2018).

Adverse events were those that are common for immune checkpoint inhibitors and include fatigue, rash, and diarrhea (Migden et al, 2018). In the case of adverse reactions, withholding or discontinuation of therapy is recommended (Libtayo prescribing information, 2018).

The recommended cemiplimab dosage is 350 mg via intravenous infusion over 30 minutes every 3 weeks. No contraindications are listed (Libtayo prescribing information, 2018).

PD-1/PD-L1 Inhibitors currently in development

Several other therapies are being evaluated in cSCC and may eventually be incorporated into treatment plans. Table 3 shows the recommended dosages and adverse effects associated with PD-1/PD-L1 inhibitors being tested in cSCC.

Nivolumab

Nivolumab is a PD-1 –blocking antibody. The FDA has approved the use of Nivolumab to treat 8 different cancer types including metastatic melanoma, metastatic non–small cell lung cancer, recurrent or metastatic squamous cell carcinoma of the head and neck, and hepatocellular carcinoma (Opdivo prescribing information, 2017).

Currently, nivolumab is being evaluated in a phase 2 clinical trial for activity against rare skin tumors including cSCC. The primary objective of this trial is to determine the overall response to treatment with the modified herpes virus agent talimogene laherparepvec, and a secondary objective is to evaluate the impact of talimogene laherparepvec + nivolumab. This study is currently recruiting with 68 participants currently enrolled (National Cancer Institute, NCT02978625).

A retrospective study evaluating five patients that were treated with nivolumab and eight that were treated with pembrolizumab (described below) determined a response rate of 62% with

two complete responses. A single treatment-related death occurred, and 23% of patients experienced grade 3 or higher adverse events (Park et al, 2018).

Typical adverse events associated with nivolumab treatment include fatigue, rash, musculoskeletal pain, pruritus, diarrhea, nausea, asthenia, cough, dyspnea, constipation, decreased appetite, back pain, arthralgia, upper respiratory tract infection, pyrexia, headache, and abdominal pain (Opdivo prescribing information, 2017).

Nivolumab is administered as an intravenous infusion over 30 minutes, and in most cases is given at a dose of 240 mg every two weeks or 480 mg every four weeks (Opdivo prescribing information, 2017).

Pembrolizumab

Pembrolizumab is a humanized monoclonal PD-1-binding antibody. Binding of pembrolizumab to PD-1 prevents binding to both PD-L1 and PD-L2. While not FDA approved to treat cSCC, pembrolizumab is approved to treat nine other cancers including metastatic melanoma, recurrent or metastatic head and neck squamous cell cancer, recurrent locally advanced or metastatic gastric cancer, and recurrent or metastatic cervical cancer (Keytruda prescribing information, 2018). There are currently eight clinical trials evaluating the use of pembrolizumab against cSCC (U.S. National Library of Medicine, 2018).

One phase II trial is actively testing the use of pembrolizumab in patients with metastatic cSCC. As of February 2018, in a total of 10 patients, the response rate for pembrolizumab was reported to be 40%, while one patient had a complete response and 20% showed disease progression. Adverse events were hepatitis and pneumonitis (Emory University, NCT02964559).

The MK-3475-629/KEYNOTE-629 phase 2 trial is measuring the safety and efficacy of pembrolizumab in patients with recurrent or metastatic cSCC. There are 100 patients enrolled in this actively recruiting study (Merck Sharp & Dohme Corp, NCT03284424).

The CARSKIN phase 2 trial seeks to determine the efficacy of pembrolizumab against unresectable squamous cell carcinomas of the skin in patients that have not been treated with chemotherapy or epidermal growth factor receptor (EGFR) inhibitors. Out of 19 total patients, results from the first stage of the study indicate a response rate of 42%. Adverse events were rash, pruritus, fatigue, dysthyroidism, and diarrhea (Maubec et al, 2018; Assistance Publique - Hôpitaux de Paris, NCT02883556).

Other recruiting phase 2 studies include NCT02721732, which aims to determine the efficacy of pembrolizumab against rare tumors including unresectable and metastatic cSCC. NCT03057613, NCT03082534, and NCT03684785 are testing the combination of pembrolizumab with radiation, cetuximab, and AST-008, respectively. NCT03057613 and NCT03082534 are testing their respective combination therapies in head and neck SCCs, while NCT03684785 focuses on solid tumors including advanced or metastatic cSCC. These studies have not released data (M.D. Anderson Cancer Center, NCT02721732; Case Comprehensive Cancer Center, NCT03057613; Assuntina G. Sacco, NCT03082534; Exicure, Inc., NCT03684785).

The most common adverse effects associated with pembrolizumab treatment are fatigue, musculoskeletal pain, decreased appetite, pruritus, diarrhea, nausea, rash, pyrexia, cough,

dyspnea, constipation, pain, and abdominal pain. If adverse events are severe, pembrolizumab treatment should be withheld or discontinued (Keytruda prescribing information, 2018).

The recommended adult dosage of pembrolizumab is 200 mg every three weeks, and it is administered via intravenous infusion over 30 minutes. There are no contraindications listed (Keytruda prescribing information, 2018).

Atezolizumab

Atezolizumab is a monoclonal antibody that binds to the ligand PD-L1, blocking its interaction with the PD-1 receptor. The use of atezolizumab is approved for treating some cases of locally advanced and metastatic urothelial carcinoma and metastatic non-small cell lung cancer. (Tecentriuq prescribing information, 2017).

A recruiting phase 2 trial is evaluating a combination of atezolizumab and a mitogen-activated protein kinase kinase 1 (MEK1) inhibitor, cobimetinib, in patients with locally advanced cSCC (M.D. Anderson Cancer Center, NCT02721732).

Patients with locally advanced or metastatic urothelial carcinoma that were treated with atezolizumab experienced fatigue, decreased appetite, nausea, constipation, urinary tract infection, diarrhea, pyrexia. In those with metastatic non-small cell lung cancer, the most common adverse events were fatigue, decreased appetite, dyspnea, and cough. In the event of adverse reactions, withholding or discontinuing treatment is recommended (Tecentriuq prescribing information, 2017).

The recommended atezolizumab dosage is 1200 mg every 3 weeks via intravenous infusion over 60 minutes.

Incorporating emerging PD-1 inhibitors into treatment plans

As new therapeutics like cemiplimab continue to emerge, clinicians must remain aware of their safety and efficacy, and be prepared to integrate them into practice. With the recent FDA approval of cemiplimab, it is now a therapeutic option for patients with metastatic or locally advanced cSCC.

When incorporating immunotherapeutics into treatment programs, the patient's level of immunosuppression should be considered, as immunosuppression is associated with aggressive cSCC. If a patient is taking immunosuppressive drugs, dose reduction can be considered to decrease the level of immunosuppression. The NCCN Guidelines also suggest switching therapies from antimetabolites and calcineurin inhibitors to mechanistic target of rapamycin (mTOR) inhibitors (Bichakjian et al, 2018, Euvrard et al, 2012; Neuburg et al, 2007).

Patients receiving immunotherapeutics are at risk for autoimmune reactions. Because checkpoint inhibitors interfere with inhibitory mechanisms that negatively regulate the immune system, there is a possibility of immune overstimulation. Patients should be monitored for immune-mediated adverse reactions to facilitate early identification and rapid intervention, while keeping in mind that immune-related adverse effects can have a delayed onset (Puzanov et al, 2017). Depending on the severity of the reaction, corticosteroids can be administered and the therapeutic can be withheld until the condition improves to Grade 1. Treatment should be permanently discontinued for Grade 4 and some Grade 3 reactions (Libtayo prescribing information, 2018; Tecentriuq prescribing information, 2017; Keytruda prescribing information, 2018; Opdivo prescribing information, 2017).

Immunotherapies can also harm a developing fetus, so patients who are pregnant or planning to become pregnant should be made aware of this risk and encouraged to use contraception. Breastfeeding is not recommended for lactating mothers.

As future therapeutics progress through clinical trials, more options may become available, and the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®) encourages patient participation in clinical trials as a therapeutic option.

Conclusion

Checkpoint inhibitors like PD-1 and PD-L1 inhibitors are antibodies that block inhibitory interactions to relieve T cells from immunosuppression. With the recent FDA approval of cemiplimab, checkpoint inhibitors have emerged as effective options for the treatment of metastatic and locally advanced cSCC. Other investigational therapies are currently moving through clinical trials. Immunotherapies share similar adverse effects, and patients receiving these treatments should be monitored for autoimmune reactions. Clinicians should be aware of ongoing clinical trials to inform their patients and refer them, as enrollment in clinical trials is encouraged as a treatment option.

Assessment Questions

1. What measures are recommended for patients experiencing adverse events while being treated with cemiplimab?

2. Which of the following is not a common adverse effect associated with PD-1/PD-L1 inhibitors Select all.

a. fatigue
b. insomnia
c. diarrhea
d. rash
e. tremors

3. A 65-year-old male presents with a 7-month history of an enlarging mass on his right shoulder that is causing pain in and functional impairment of his right arm. cSCC was confirmed by biopsy and the mass was surgically removed by Moh's micrographic surgery. Margins were negative. No disease was detected until eight months post-surgery, when a mass was detected on the right-side axilla. The patient begins treatment with cemiplimab, but experiences a hyperimmune reaction. What steps can be taken to treat his reaction?

4. A lactating mother presents with a 2-month history of a cutaneous lesion on her hand that has been rapidly expanding. Immunohistochemistry indicates high PD-1 expression. Surgical removal of the lesion requires amputation at the wrist to achieve negative margins. The patient declines amputation, instead electing to receive treatment with cemiplimab. The patient is not taking immunosuppressive medications. What measures should be taken to ensure the safety of the patient and her nursing child?