New Horizons in the Treatment of Metastatic Head and Neck Squamous Cell Carcinoma (HNSCC): How Immunotherapies are Changing the Treatment Paradigm

A CME/CNE Approved Activity

JOURNAL of MANAGED CARE MEDICINE

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Instructions for CME/CNE: Activity is valid from October 20, 2017 to October 31, 2019.
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Read the monograph, answer the post-test, complete the evaluation form, and send completed post test and evaluation to:

By E-mail: Jeremy Williams at jwilliams@namcp.org By Fax: Jeremy Williams at 804-747-5316

By Mail: Jeremy Williams
NAMCP CME Dept.
4435 Waterfront Drive, Suite 101
Glen Allen, VA 23060

Authors:
Dr. Joshua Bauml, MD, is an Assistant Professor of Medicine in the Division of Hematology/Oncology at the Perelman School of Medicine at the University of Pennsylvania.
Dr. Robert L. Ferris, MD, PhD, is the Director of the UPMC Hillman Cancer Center.
Dr. Gary Owens, MD, is President of Gary Owens and Associates.
Dr. Tanguy Seiwert, MD, is the Associate Program Director of the Head and Neck Cancer Program at the University of Chicago.

Learning Objectives:
1. Discuss the role of immunotherapies in the treatment of metastatic head and neck squamous cell carcinoma (HNSCC).
2. Review recent clinical data on the use of immunotherapiy in the management of metastatic HNSCC.
3. Discuss the potential impact of human papillomaviris (HPV), programmed cell death ligand1 (PD-L1) status, and expression profiling on a patient's clinical response to immune checkpoint inhibitors.
4. Discuss challenges associated with disease progression in metastatic HNSCC and strategies for managing therapy beyond the first-line.
5. Assess strategies for optimal treatment switching for metastatic HNSCC patients whose disease progresses after platinum chemotherapy.
6. Identify adverse events commonly associated with immunotherapeutic agents used in the treatment of metastatic HNSCC.
7. Discuss how newer immunotherapies have affected managed care professionals in the metastatic HNSCC arena.
8. Assess important points that payers need to know about the use of immunotherapies in metastatic HNSCC.

Faculty Disclosure:
Dr. Bauml has disclosed the following relevant financial relationships: served as an advisor or consultant for Clovis, BMS, AstraZeneca, Celgene, Merck, Genentech, Guardant Health, and Boehringer Ingelheim; received grants for clinical research from Bayer, Carevive Systems, Incyte, Merck, and Novartis.
Dr. Ferris has disclosed the following relevant financial relationships: served on advisory boards at Amgen, Astra-Zeneca/Medimmune, Bristol-Myers Squibb, Pfizer, and Merck; received clinical trial/research funding from VentiRx Pharmaceuticals, Astra-Zeneca/Medimmune, and Bristol-Myers Squibb.
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All material has been peer reviewed for bias.

Planning Committee Disclosure
Bill Williams, MD; Jacquelyn Smith, RN, BSN, MA, CMCN; Jeremy Williams and Will Williams have no real or perceived financial relationships to disclose.

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Nurses who complete this activity and achieve a passing score will receive 1 hour in continuing nursing credit.

This activity has been approved by the American Board of Managed Care Nursing for 1.0 contact hours toward CMCN re-certification requirements.

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Post-Test Questions

1. Which of the following is an accurate statement about head and neck cancer?
   a. It is the twelfth most common cancer worldwide.
   b. It represents 10 percent of all cancers.
   c. Approximately 120,000 new cases and 50,000 deaths occur per year in the U.S.
   d. Around 95 percent of cases are squamous cell cancer.

2. Which of the following is NOT a risk factor for head and neck cancer?
   a. Tobacco use. b. Alcohol use.
   c. Red meat consumption. d. Viral infections.

3. Which type of high-risk human papillomaviris (HPV) has been implicated in the pathogenisis of a growing subset of HNSCC?
   a. 6 b. 16 c. 31 and 33 d. 45 and 52

4. Which of the following is an accurate statement about HPV and HNSCC?
   a. HPV is involved in the etiology of 60 to 80 percent of oropharyngeal cancer in the U.S.
   b. HPV positive (+) HNSCC is found in older patients.
   c. HPV (+) patients typically have poor prognosis compared with those with HPV negative disease.
   d. Vaccination has been shown to reduce incidence of HNSCC.

5. Which of the following has been shown to improve five-year survival for head and neck cancer?
   a. Anti-angiogenic agents.
   b. Multi-disciplinary care.
   c. Care at high volume centers.
   d. Radiation followed by immunotherapy.

6. In metastatic setting HNSCC, first-line chemotherapy results in an overall survival (OS) of _____.
   a. 2 to 4 months b. 5 to 7 months
   c. 8 to 12 months d. 14 to 18 months

7. Programmed death one (PD-1) is a cell surface receptor that plays an important role in down-regulating the immune system by _____
   a. Suppressing T cell inflammatory activity.
   b. Up-regulating regulatory T cells.
   c. Increasing the number of anergic T cells.
   d. Interfering with the inhibitory effect of regulatory T cells.

8. Which of the following is a correct statement about immune-related adverse effects (irAEs)?
   a. Almost all reactions occur within the first six months of the therapy.
   b. Corticosteroids (topical, oral, and intravenous) are the typical treatment.
   c. Seizures are a relatively common event.
   d. Patients can be educated to self-treat most reactions for one week before seeking medical care.

9. Extreme caution should be taken in treating patients who have autoimmune disease with immunotherapy.
   a. True b. False

10. As discussed in the article, which of the following is NOT a typical part of a managed care's approach to managing cancer costs?
    a. Aggressive prior authorization programs
    b. Risk shifting or sharing
    c. Contracting strategies
    d. PBM based counter detailing

Activity Evaluation and Improvement Process

(Please rate this activity on the following scale:
4 - Excellent 3 - Good 2 - Fair 1 - Poor)

1. Based on the content presented, I am better able to:

   Discuss the role of immunotherapies in the treatment of metastatic head and neck squamous cell carcinoma (HNSCC).

   4 3 2 1

   Review recent clinical data on the use of immunotherapiy in the management of metastatic HNSCC.

   4 3 2 1

   Discuss the potential impact of human papillomaviris (HPV), programmed cell death ligand1 (PD-L1) status, and expression profiling on a patient's clinical response to immune checkpoint inhibitors.

   4 3 2 1

   Discuss challenges associated with disease progression in metastatic HNSCC and strategies for managing therapy beyond the first-line.

   4 3 2 1

   Assess strategies for optimal treatment switching for metastatic HNSCC patients whose disease progresses after platinum chemotherapy.

   4 3 2 1

   Identify adverse events commonly associated with immunotherapeutic agents used in the treatment of metastatic HNSCC

   4 3 2 1

   Discuss how newer immunotherapies have affected managed care professionals in the metastatic HNSCC arena.

   4 3 2 1

   Assess important points that payers need to know about the use of immunotherapies in metastatic HNSCC.

   4 3 2 1

2. The activity met my expectations. 4 3 2 1
3. The activity and presenters were free of bias. 4 3 2 1
4. The activity was applicable to my position. 4 3 2 1
5. Do you expect that the information you learned during this activity will help you improve your skills or judgement within the next six months? (4 definitely will change - 1 definitely will not change)

   4 3 2 1

6. How confident are you in managing patients based on this activity? (4 very confident - 1 not confident)

   4 3 2 1

7. What other topics interest you? _____
8. My goal of participating in this activity was: _____

   _____

9. Did the content of the activity help in meeting your above goal?

   ☐ Yes ☐ No

10. Due to the content of this activity, I will change my practice patterns by:

    ☐ Identifying opportunities to improve treatment options for patients.
    ☐ Providing guidelines and resources on new therapies to providers.
    ☐ My practice patterns will not change.
    ☐ Other (specify): _____

11. Will the content presented increase your abilities in any of the following areas? Please check all that apply.

    ☐ Management and leadership skills.
    ☐ Business and/or financial expertise to manage the medical loss ratio.
    ☐ Exchange ideas and network with colleagues to improve patient outcomes.
    ☐ Be aware of updates of Congress, pharmaceutical, Health and Human Services and other regulatory services.
    ☐ Clear knowledge of practice of medicine, especially common disease.
    ☐ Stay updated on clinical conditions.

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(804) 527-1905
fax (804) 747-5316

EDITOR-IN-CHIEF
J. Ronald Hunt, MD

PUBLISHER
Jeremy Williams

JOURNAL MANAGEMENT
Douglas Murphy
Communications Inc.
P.O. Box 71895
Richmond, VA 23255-1895
(804) 387-7580
fax (703) 997-5842

MANAGING EDITOR
Barry Barnum
barry.barnum@douglasmurphy.com

GRAPHIC DESIGN
Douglas Murphy Communications, Inc.

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New Horizons in the Treatment of Metastatic Head and Neck Squamous Cell Carcinoma (HNSCC): How Immunotherapies Are Changing the Treatment Paradigm

Joshua Bauml, MD; Robert L. Ferris, MD, PhD; Gary Owens, MD; Tanguy Seiwert, MD

INTRODUCTION

Head and neck cancers may present in a variety of sites, including the oral cavity, pharynx, larynx, nasal cavity, paranasal sinuses, thyroid, and salivary glands. Head and neck cancer is the sixth most common cancer worldwide and represents 3 percent of all cancers.[1] Approximately 60,000 new cases and 13,000 deaths occur per year in the United States (U.S.)[2] Males are affected more than females, ranging anywhere from a 2:1 to 4:1 ratio.[2] Around 95 percent of cases are head and neck squamous cell cancer (HNSCC), but tumors can also be adenocarcinomas, mucoepidermoid, and adeno-cystic. The remainder of this article focuses on head and neck squamous cell carcinoma (HNSCC).

Risk factors for HNSCC are tobacco use, alcohol use, and viral infections. These factors increase risk anywhere from 5- to 25-fold.[3] The increase in risk from smoking is dependent on duration and amount of exposure. There is a risk with smokeless tobacco products, especially for the oral cavity and pharynx. It is often difficult to sort out alcohol use from tobacco use in terms of risk. Epstein Barr virus infection is associated with nasopharyngeal sites. Infection with high-risk human papillomavirus (HPV), primarily type 16, has been implicated in the pathogenesis of a growing subset of HNSCC. Herpes simplex, hepatitis C, immuno-deficiency, occupational exposures, and radiation have also been implicated.

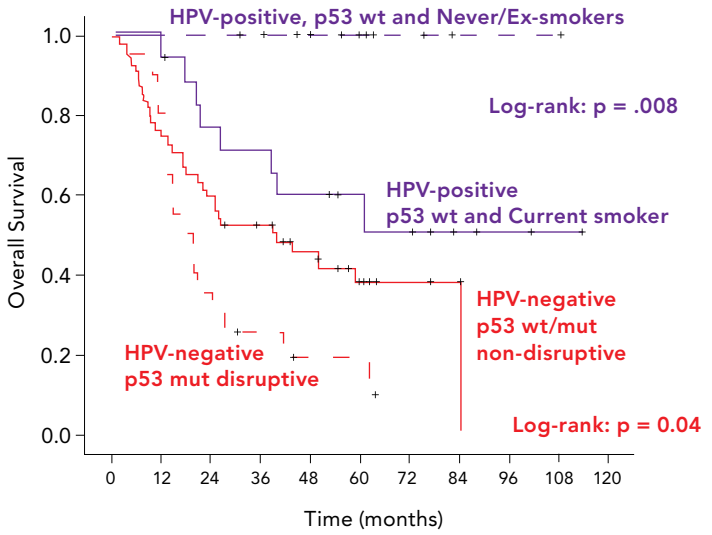
HPV is involved in the etiology of 60 to 80 percent of oropharyngeal cancer in the U.S.[4] Ninety percent of HPV(+) cases are due to HPV16.[5] Oropharyngeal HPV-related cancer cases have been dramatically increasing, whereas cases of HPV-related cervical cancer have declined.[6] HPV positive (+) HNSCC is found in younger patients who typically have a better performance status and prognosis with generally smaller primary tumors and large cystic lymph nodes compared with those with HPV negative (-) disease. The metastatic pattern of spread is distinct for HPV(+) compared to HPV(-) cancers. Patients with HPV(+) HNSCC and a less than 20 pack- year smoking history have the best prognosis compared with those with HPV(-) disease and a greater than 20 pack-year smoking history (2-year overall survival [OS] is 95% vs 63%).[7] Thus, HPV(-) tobacco-related HNSCC and HPV(+) HNSCC are two distinct clinical entities.

There is one FDA approved HPV vaccine available (Gardasil®9) on the market, and it covers HPV16. A second HPV vaccine (Cervarix®) was available but was withdrawn from the U.S. market in 2016 because of low use. HPV vaccination is recommended for women ages 9 to 26 and men 9 to 21 (up to 26 for men who have sex with men) and is FDA indicated to prevent the following diseases: cervical, vulvar, vaginal, and anal cancer and precancerous/dysplastic lesions caused by types 16, 18, 31, 33, 45, 52, and 58 and genital warts (condyloma acuminata) caused by HPV types 6 and 1.[8] It is important to note that, at this time, the vaccine does not have a specific indication for preventing oropharyngeal cancer related to HPV16 or other types.

HPV vaccination has been shown to significantly reduce the presence of HPV infection in both male and female young adults an average of 4.1 years after vaccination.[9] In 2015, about 63 percent of U.S. girls and 50 percent of boys received at least one HPV shot, according to data from the CDC's National Immunization Survey–Teen.[10] Thus, there are a significant number of preventable cases of HPV infection still occurring, particularly in men.

At this time, the persistence of vaccine effect is not known, nor is the time from infection to cancer. Prospective, long-term data is needed to prove that vaccination decreases the incidence of HPV(+)

Exhibit 1: Understanding Genetics Improves Prognostics[15]



HPV = human papillomavirus
wt = wild type
mut = mutation

HNSCC. Because of the other proven benefits in terms of other cancers, clinicians should not wait until this prospective data are available to encourage HPV vaccination. Education of teens, young adults and their parents is critical to increasing vaccination rates.

Presentation/Staging

The clinical presentation of HNSCC is highly dependent on the site of the tumor. The most frequent presenting complaint of nasopharyngeal carcinoma is a neck mass due to regional lymph node metastasis, which occurs in nearly 90 percent of patients.[11] Oral cavity tumors may present as mouth pain or non-healing mouth ulcers. Up to two-thirds of patients with primary tongue lesions have cervical lymph node involvement. Oropharyngeal tumors cause dysphagia, pain, obstructive sleep apnea or snoring, bleeding, or a neck mass. Persistent hoarseness is the initial complaint for laryngeal cancer and later symptoms may include dysphagia, referred otalgia, chronic cough, hemoptysis, and stridor. Common presenting symptoms of sinus tumors include epistaxis and unilateral nasal obstruction.

Unfortunately, cases of HNSCC present with metastatic disease due to the somewhat "silent" nature of early disease. Like other solid tumors, initial disease staging is based on the tumor site, metastases, and nodes. Work-up approaches include biopsy/excision, fine needle aspiration, and advanced imaging modalities (CT, MRI, PET etc.). A component of the initial staging evaluation for patients with new or recurrent HNSCC is the search for distant metastases which occur in 2 and 26 percent of cases.

Treatment

A multidisciplinary approach is desirable for managing HNSCC. Involved providers may include surgeons, medical oncologists, radiation oncologists, dentists, speech/swallowing pathologists, dieticians, and rehabilitation therapists. Care at high volume centers has been shown to improve survival. A large randomized trial (Radiation Therapy Oncology Group 0129) found a significantly better five-year overall survival rate for those treated in high volume centers compared with those treated at centers with historically low accrual (69% vs 51%).[12]

Positive prognostic factors in metastatic HNSCC include good ambulatory performance status (Eastern Cooperative Oncology Group [ECOG] 0 or 1 versus 2), poorly differentiated histology, response to chemotherapy, HPV (+) status, and presence of certain genetic mutations. Negative prognostic factors include weight loss, poor performance status, prior radiation therapy, active smoking, and significant comorbidity burden.

HPV(+) HNSCC is genetically distinct from HPV(–) disease, but both tumor types have a high mutational burden.[13] Those with smoking-related disease typically have cell cycle suppressor mutations (p53, p16) and HPV(+) disease has viral oncogenes E6 and E7 which inhibit p53, among many

other mutations in each type.[14] As shown in Exhibit 1, HPV status, smoking history, and p53 mutation status can be used to predict prognosis.[15]

Tumor suppressor gene p16 mutation status is another prognostic biomarker. Over 60 percent of oropharyngeal SCC is p16(+), but the number varies widely depending upon the clinical population studied. Patients with p16(+) tumors have an improved prognosis over those who have wild-type tumors, but 20 percent of p16(+) testing is false positive. Overall, p16 is a prognostic, not predictive biomarker.

Patients with localized (Stage I and II) HNSCC are generally managed with either surgery or radiation therapy (RT) alone. Patients with more advanced (Stage III, IVA, and IVB) disease are typically managed with a multimodality approach, including both RT and chemotherapy.

There has been a large unmet need in the treatment of recurrent or metastatic HNSCC. Salvage surgery or radiation therapy is used for selected patients with curative intent. For the majority of patients, the only option has been chemotherapy, which is only palliative.

For those with good performance status, doublet cytotoxic chemotherapy regimens, generally with a platinum-based regimen, results in improved response over single-agent therapies but no improvement in survival.[16,17] The addition of anti-angiogenic therapy, cetuximab, to cisplatin plus fluorouracil increases overall survival compared with cisplatin plus fluorouracil. Cetuximab alone has not been shown to increase survival. For patients with poor performance status or significant comorbidities, cisplatin or carboplatin-based combinations are generally contraindicated. Typically, single-agent therapy (e.g., carboplatin, paclitaxel, cetuximab) is used in these cases. Other agents that can be used when platinum-based combinations are not indicated include pemetrexed, docetaxel, and anti-angiogenic agents.

The available chemotherapy regimens are very toxic, and the outcomes remain disappointing. In the metastatic setting, progression-free survival (PFS) is seven to 11 months and overall survival (OS) is 14 to 18 months with first-line chemotherapy. Second-line therapies are even less effective; thus, supportive care needs are extensive and multidisciplinary management is critical.

Immunotherapy

Immunotherapy as a treatment option is becoming a reality in many cancers, including HNSCC. Immunotherapy is an established component of the treatment of hematologic malignancies through allogeneic stem cell transplantation. Success in solid tumors has lagged behind, with a few exceptions. Response has been thought to be limited to "immune responsive" tumors. Early immunotherapy efforts that focused on directly stimulating the immune system resulted in very high rates of toxicity.

Cancer has long been known to be partially a disease of immune tolerance, which is an unresponsiveness of the immune system to self-antigens. In the case of cancer, the immune system does not recognize the self-antigens on the cell surface or the tumor has learned how to hide the antigens to prevent immune system detections.

One way the body prevents itself from attacking normal tissue is through suppression of self-reactive T cells by regulatory (or suppressor) T cells. Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), among other molecules, plays a role in maintaining self-reactive T cells from becoming activated (anergic). Regulatory T cells use CTLA-4 to remove B7 molecules from the surface of antigen-presenting cells to prevent activation of self-reactive T cells. Anti-CTLA-4 immunotherapy agents such as ipilimumab interfere with the inhibitory effect of regulatory T cells. Ipilimumab, while already approved for several cancers, is under investigation for HNSCC.

Inhibitory receptors provide a second mechanism to maintain tolerance. Programmed death one (PD-1) is a cell surface receptor that plays an important role in down-regulating the immune system by suppressing T cell inflammatory activity. As an immune checkpoint, PD-1 guards against autoimmunity through a dual mechanism of promoting apoptosis (programmed cell death) in antigen-specific T cells in lymph nodes and simultaneously reducing apoptosis of regulatory T cells. PD-1 inhibits the immune system which prevents autoimmune disease but it can also prevent the immune system from killing cancer cells.[18]

PD-1 is the receptor on T cells and is up-regulated on T cells after activation. PD-1 receptors interact with its ligands (PD-L1 and PD-L2). PD-L1 is found on both immune and nonimmune cells in peripheral tissues, including tumor cells. PD-L2 is mostly found on immune cells in response to inflammatory stimuli. In contrast, CTLA-4 and its ligands are only found on immune cells. Blocking the PD-1/PD-L1 pathway reactivates T cells to identify tumor cells.

Both pembrolizumab (Keytruda®) and nivolumab (Opdivo®) target PD-1. Pembrolizumab has been studied in recurrent or metastatic HNSCC in two non-randomized trials with an overall response rate of 16 to 18 percent and median OS of

Exhibit 2: **Treatment Options for Recurrent, Unresectable, or Metastatic HNSCC[23]

	Combination Systemic Therapy	Single-agent Systemic Therapy
Non-nasopharyngeal HNSCC	Cisplatin or carboplatin/5-FU/cetuximab (category1) Cisplatin/cetuximab Cisplatin or carboplatin/docetaxel/cetuximab Cisplatin or carboplatin/paclitaxel/cetuximab	Afatinib* (2B) Cetuximab Nivolumab* (1A) Pembrolizumab*
Nasopharyngeal HNSCC	Carboplatin/cetuximab Cisplatin/gemcitabine Gemcitabine/vinorelbine	Gemcitabine
Non-nasopharyngeal HNSCC or Nasopharyngeal HNSCC	Cisplatin or carboplatin/docetaxel or paclitaxel Cisplatin/5-FU	Capecitabine Carboplatin Cisplatin Docetaxel 5-FU Methotrexate Paclitaxel

** Without surgery or radiotherapy options, category 2A unless otherwise noted
* If disease progression on or after platinum-containing chemotherapy

eight months.[19,20] In one of the trials, approximately 50 percent of the patients had tumor reductions.[20] It is important to note that response rates in clinical trials of immunotherapy are a poor outcome measure. Durability of response is probably a better measure; approximately 20 percent of patients have a very long- lasting response to immunotherapy. Pembrolizumab appears active in both HPV(+) and (-) tumors.

Nivolumab has been compared to chemotherapy (docetaxel, methotrexate, or cetuximab) in recurrent or metastatic HNSCC.[21-22] An overall response rate of 13.5 percent was seen with nivolumab treatment compared to 5.8 percent for chemotherapy. Although the response rate was only 13 percent, there was a major impact on survival with immunotherapy. Median OS was 7.5 months with nivolumab treatment versus 5.1 months for chemotherapy. The one-year survival rate was 36 percent with immunotherapy compared with 16.8 percent with chemotherapy. Higher OS was seen in those with PD-L1 expression greater than or equal to 1 percent in those with HPV(+) compared with HPV(-) disease.[22]

Pembrolizumab and nivolumab are both FDA approved for the treatment of HNSCC after disease progression on platinum-based chemotherapy. The available treatment options for treating metastatic disease are shown in Exhibit 2.[23]

Biomarkers for Selecting Immunotherapy

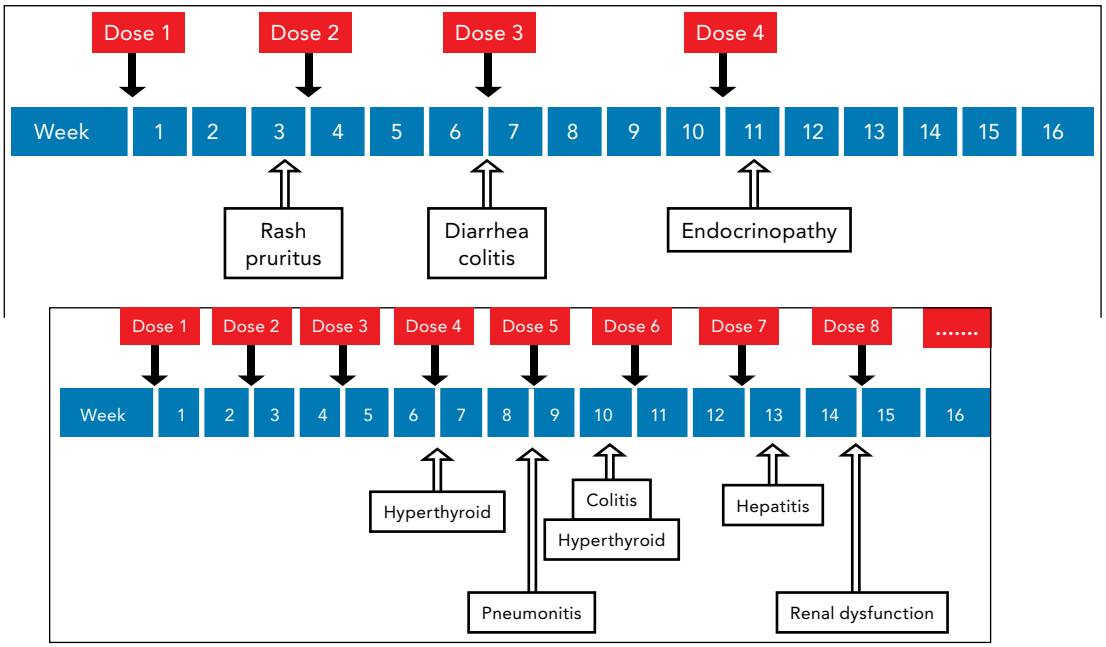
Measurement of tumor expression of PD-L1 has been used to predict response to immunotherapy in some cancers, but requiring measurement was not part of the FDA approvals for pembrolizumab or nivolumab for HNSCC. There are definitely limitations to using PD-L1 as a biomarker. It is heterogeneous, dynamic, and the definition of "negative" is a moving target due to assays and measurement cutoff differences.[24] The predictive value of the PD-L1 assay may be improved by counting immune and tumor cells. Currently, PD-L1 testing is not used for immunotherapy treatment selection in HNSCC clinical care.

Tumor mutational burden or mutational load (TMB, TML), tumor gene expression profile (GEP), and neoepitope load (NL) all appear to be better biomarkers of response to immunotherapy than PD-L1 levels.[25,26] TMB has the advantage of likely being relatively fixed, but this must be confirmed. None of these tests are currently being used widely to predict immunotherapy response.

ImmuneRelated Adverse Events with Immunotherapy

Activation of the immune system against tumors can result in a novel spectrum of immune- related adverse events (irAEs) against normal tissues. These occur in certain organ systems (skin, endocrine

Exhibit 3: Time Course of irAEs[27]



system, liver, gastrointestinal tract, nervous system, eyes, respiratory system, hematopoietic cells, and musculoskeletal) and are similar to the symptoms seen with autoimmune diseases.

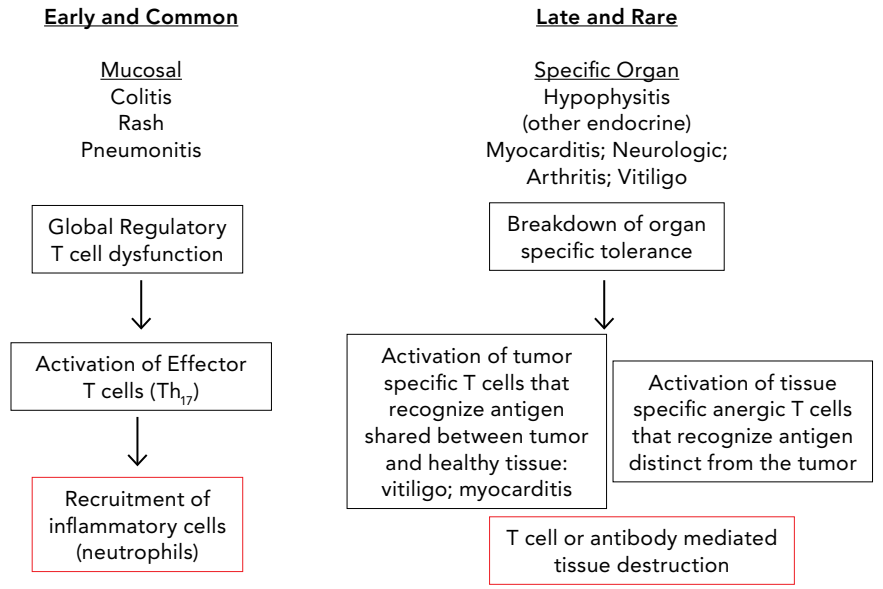
These adverse events may be unfamiliar to clinicians, especially emergency department personnel, can be serious, can result in death, require prompt recognition and treatment, and require a multi-disciplinary approach to management. Patients receiving immunotherapy need significant education on recognition of irAEs and the need for seeking medical help early. Health care providers also need to be educated on these to allow prompt recognition. Because the patient has cancer, clinicians thinking about typical chemotherapy adverse events will be led down the wrong treatment path. Clinicians need to know and understand that these adverse events are autoimmune type responses and will likely require immune suppressive therapies for management.

Immune-RelatedAdverse Events can occur both early and late in treatment (Exhibit 3).[27] There are probably different mechanisms for the early and late irAEs (Exhibit 4). Most occur within the first three months of treatment starting but may occur after the final dose. Some are dose dependent. Serious (Grade 3-4) toxicity occurs in approximately 10 percent of reactions overall.[28] Treatment includes corticosteroids, mycophenolate mofetil (CellCept®), and tumor necrosis factor inhibitors (infliximab, adalimumab, and others). With mild reactions, immunotherapy can be continued. For moderate to severe reactions, most clinicians will stop immunotherapy. Reinitiating the immunotherapy will depend on the particular reaction that occurred. For example, with a moderate rash, immunotherapy may be able to be restarted once the rash has resolved.

A mild but transient maculopapular rash with or without symptoms (pruritus, burning, tightness) is one of most common irAEs, occurring in about 15 percent of patients. The rash is considered mild if it covers 10 to 30 percent of the total body surface area (TBSA). If the rash is bothersome or limiting activities of daily living, it is treated with topical corticosteroids and antihistamines. Moderate dermatologic toxicity is a diffuse, non-localizing rash that covers 30 to 50 percent of TBSA. This is treated the same as a bothersome mild rash. Systemic corticosteroids should be considered if there is no improvement in one week. Severe dermatologic toxicity is rash with blisters, dermal ulceration, or necrotic, bullous or hemorrhagic areas. Stevens Johnson syndrome/toxic epidermal necrolysis is the most severe dermatologic toxicity that occurs with immunotherapy. It must be treated with systemic corticosteroids which are tapered over one month following improvement.

Diarrhea and colitis are also relatively common early irAEs, occurring in about 20 percent of patients. For diarrhea/colitis, it is considered mild if

Exhibit 4: Early and Late irAEs may Occur by Distinct Mechanisms



the patient is having less than four bowel movements above baseline per day. Treatment is symptomatic with oral hydration and a bland diet. Corticosteroids are not helpful and should not be used. Moderate colitis is four to six bowel movements above daily baseline and includes abdominal pain, and blood or mucus in stool. Patients should have stool studies for various infections done and a CT scan to check for perforation. Systemic corticosteroids should be given if moderate symptoms have been present for one week or more. Severe colitis (seven bowel movements above baseline/day and may include peritoneal signs, ileus or fever) is an urgent situation requiring hospital admission for intravenous hydration, stool studies, and ruling out intestinal perforation. Systemic corticosteroids are given if there is no perforation. Corticosteroids can be held until stool studies are available (24 hours) if the patient is clinically stable. When unstable, high-dose corticosteroids (intravenous methylprednisolone 125 mg daily x 3 days) should be given to evaluate responsiveness. Empiric antibiotics should be considered for fever or leukocytosis. Infliximab can be given if there is no response to corticosteroids. Mycophenolate mofetil can also be considered for select patients.

Pneumonitis is the other early and relatively common adverse event. It occurs in about 4 percent of patients and is also treated with corticosteroids.

Hepatitis can occur with immunotherapy. Patients treated with immunotherapy should avoid alcohol, acetaminophen, and other known liver toxins while being treated. Grade 2 toxicity (AST/ ALT 2.5-5 times upper limit of normal [ULN[, Bilirubin 1.5-3 times ULN) is treated with corticosteroids. After a response, the steroids are then tapered over one month. Grade 3 or greater toxicity requires hospital admission and intravenous methylprednisolone 125mg/day. Mycophenolate mofetil can be considered.

Endocrinopathies occur in less than 10 percent of those treated with PD-1 inhibitors. Hypophysitis manifests as fatigue, headaches, and visual field defects. It can be diagnosed with laboratory testing and imaging. Corticosteroids orally or intravenously are given as treatment. Hypothyroidism, hyperthyroidism, new onset diabetes with diabetic ketoacidosis, and adrenal insufficiency can also occur.

Pancreatitis, renal insufficiency, vitiligo, episcleritis, uveitis, conjunctivitis, red cell aplasia, thrombocytopenia, hemophilia A, Gullian-Barre syndrome, myasthenia gravis, posterior reversible encephalopathy syndrome, aseptic meningitis, bronchiolitis obliterans, and transverse myelitis are other rare irAEs.[29,30]

The Future of Immunotherapy

There is a need to improve the number of patients who benefit from immunotherapy. Combination immunotherapy is a possible option for improving responses. The combination of PD-1 and CTLA-4 blockade has been studied in NSCLC but not in HNSCC.[31] An issue with combination therapy is the overlap in the irAEs, including dermatitis, colitis, and hypophysitis. Unique irAEs may also occur

with combination therapy. Erythema nodosum-like panniculitis has been reported in two patients treated with ipilimumab and nivolumab.[32] Whether the risk of irAEs outweighs the possible benefits of taking the brakes off the immune system in two different ways is yet to be determined.

There are more than 30 immunotherapy agents or combinations being studied for HNSCC that are in Phase II or later trials. A number of these agents are likely to make it to market in the next few years. Several new classes of agents are being studied in combination with anti-CTLA-4 and anti-PD-L1 therapies.

Another question about immunotherapy that needs to be answered is whether a history of autoimmunity prevents use in HNSCC. In one small series of ipilimumab treatment in patients with melanoma and a preexisting autoimmune disease, 27 percent of the patients had worsening of their underlying autoimmune disease when immunotherapy was started, but the exacerbations were successfully managed with corticosteroids.[33] Anti-PD-1 therapy resulted in worsening of the underlying autoimmune disease (psoriatic arthritis), but also had a therapeutic response for the patient's melanoma in one unpublished case. A case report of exacerbation of myasthenia gravis secondary to pembrolizumab has also been reported.[34] Until there is more data on the use of immunotherapy in HNSCC, extreme caution should be taken in treating patients with recent or ongoing autoimmune conditions, particularly any type of inflammatory bowel disease. One patient death from immune-related colitis in someone with pre-existing inflammatory bowel disease has been reported.[33]

Research is ongoing examining whether immunotherapy can be given earlier in the disease process. Studies are also ongoing using immunotherapy in combination with chemotherapy, RT, and as neoadjuvant treatment. In the neoadjuvant setting, early trials of immunotherapy are showing benefits. The neoadjuvant use of immunotherapy may allow better immune surveillance and less T cell exhaustion.

A therapeutic HPV vaccine is also under investigation. This HPV DNA vaccine targets HPV 16/18, and immune responses were seen in HNSCC. A Phase 1b/2a trial of combination HPV vaccine and durvalumab, an investigational immunotherapy, in recurrent metastatic HPV(+) HNSCC is ongoing.

Overall Conclusions on Immunotherapy

Immunotherapy is active in HPV(+) and HPV(-) HNSCC. The effect may be primarily on overall survival. Immunotherapy is active in heavily pretreated populations and is generally well tolerated. The serious irAEs have to be monitored for and managed appropriately. Biomarkers to predict response are not yet used in HNSCC clinical practice.

Managed Care Issues in Oncology

Oncology is poised to be one of the largest growth areas in medicine today. New cancer case numbers in the U.S. are increasing, mainly due to our aging demographic, whereas cancer deaths are decreasings, mainly due to the impact of early detection and new treatments. Therefore, cancer has become a chronic disease for many patients. National expenditures for cancer care are projected to increase by 27 percent by 2020 based on our aging and growing population.[35]

Immunotherapy is a major cost driver in cancer care today. In his keynote address at the American Society of Clinical Oncology Annual Meeting in 2015, Dr. Leonard Saltz estimated that the widespread use of immunotherapy agents could cost the United States $174 billion annually.[36] Payers have seen projections that estimate the cost of individual immunotherapy agents in the range of $250,000 to over $1 million per year per patient, depending on tumor type and dosing. Payers view this cost as representative of cancer care cost overall and often use the term "unsustainable." Historically, payers had limited tools to manage oncology costs and often those tools were relatively blunt instruments. Payers are not the only ones involved now as employers who are paying for the care are demanding cost control actions as well.

Until the new century arrived, payer management of cancer care was limited to a few management activities, including limited prior authorizations, case management of catastrophic cases, site of care shifts to outpatient treatment, and management of the cost of infusion therapies through average sales price based reimbursement. Cancer management today includes aggressive prior authorization programs, risk shifting or sharing, and contracting strategies. Aggressive prior authorization programs only allow approval for FDA labeled indications and may restrict medication access to cases identical to populations studied in the clinical trials or to selected genetic subtypes using genetic markers. Use of a particular agent may be limited to only payer approved centers or groups. Risk shifting or sharing includes increased contracting with accountable care organizations (ACOs) and other risk-bearing entities, increased use of pathways, risk or value-based contracting with oncology groups, and contracting with centers of excellence. Contracting strategies include aggressive contracting for preferred agent positioning, closed formularies even on the medical

side, and outcomes-based contracting.

Many large payers have adopted new programs to try to manage oncology costs. In July 2015, Anthem introduced its Cancer Care Quality Program, which is a pathway-based program with embedded quality measures. United has started offering bundled payments based on a three-year pilot study in five practices that demonstrated a 34 percent reduction in cost. Cigna is focusing on improved access and care coordination.

The Center for Medicare and Medicaid Services (CMS) Oncology Care Model (OCM) is impacting cancer care in the wider community. The program aims to provide higher quality, more highly coordinated oncology care at the same or lower cost. Under the OCM, physician practices have entered into payment arrangements with financial and performance accountability for episodes of care surrounding chemotherapy administration to cancer patients. The practices participating in OCM have committed to providing enhanced services to Medicare beneficiaries, such as care coordination, navigation, and national treatment guidelines for care. As of September 2017, 192 practices and 14 payers are participating in the OCM.[37]

There has been much discussion in the payer community about the role of value or outcomes-based contracting. There have been 16 risk-sharing pharmacy contracts announced publicly between 2015 and 2017. Examples include hepatitis C, diabetes, and high cholesterol.[38] To date, there are no risk-sharing contracts publicly announced for use of immunotherapies across multiple cancer types including HNSCC, but this may occur in the future.

There are numerous operational and legal issues that must be considered for a risk or value-based contract. Legal considerations include pricing regulations, FDA regulations on economic claims, and anti-kickback statues. Operational considerations include choosing relevant outcomes (overall survival, progression-free survival, overall response rate, or duration of response), availability of data of sufficient detail, and time frame. Patient factors also need to be considered. Quality of life should be a consideration in HNSCC where survival is typically not long. Once it arrives, value-based contracting for immunotherapy agents will likely cross the spectrum of multiple types of cancer.

Conclusion

HNSCC accounts for only about 3 percent of all cancers in the U.S. It is a highly aggressive tumor type that is often only found after it has become metastatic. Despite advances and innovations in multimodality treatment and a better understanding of head and neck carcinogenesis, survival rates of locally metastatic HNSCC have not substantially improved, and the prognosis for recurrent/metastatic disease remains poor. Chemotherapy, with or without anti-angiogenic agents, provides limited success with survival typically less than one year for metastatic disease. Checkpoint inhibitor immunotherapy is an option for patients with progressive disease after their initial chemotherapy regimen. These agents have been shown to delay progression and at least one agent has shown improved overall survival. But there is a significant cost with these agents that payers are now struggling to manage. Old methods of management of cancer costs are being replaced with newer reimbursement models and value-based contracting. Because of the growing interest in new agents and success of the treatment of metastatic HNSCC with immune checkpoint inhibitors, payers will need to better understand this disease and the emerging treatments to better manage cost and access to appropriate care.

Joshua Bauml, MD, is an Assistant Professor of Medicine in the Division of Hematology/Oncology at the Perelman School of Medicine at the University of Pennsylvania.

Robert L. Ferris, MD, PhD, is the Director of the UPMC Hillman Cancer Center.

Gary Owens, MD, is President of Gary Owens and Associates.

Tanguy Seiwert, MD, is the Associate Program Director of the Head and Neck Cancer Program at the the University of Chicago.

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