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Review Article

A Concise Review of Immune Checkpoint Inhibitors Immunotherapy for Head and Neck Cancer

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Abstract

Tumor cells can evade and suppress immune response through various mechanisms such as T cell activation suppression by PD-1 and/or CTLA-4. The main objective of this study is to examine the checkpoint inhibitors immunotherapy for head and neck cancer. Data were collected in numerous areas from various medical databases. The data collected and were thoroughly analyzed. Major findings of the studies were analyzed and presented in this article. Conclusions: The findings showed that immunotherapy is promising to increase survival rate and control of metastasis.

Keywords: Cancer Immunotherapy; Immune Checkpoint Inhibitors; Head and Neck Cancer; Monoclonal Antibodies Therapy; Cytokines Immunothearpy

Introduction

Head and neck (HN) cancer is a broad and heterogeneous group of malignancies that affect the oral cavity, pharynx, larynx, paranasal sinuses, nasal cavity, salivary glands, or head and neck lymph nodes. HN cancer is the sixth most frequent cancer worldwide, and while it has different histology, squamous cell carcinoma (SCC) accounts for 90% of diagnoses, HN cancer contributes to approximately 900,000 cases and over 400,000 deaths worldwide each year It has a mortality rate of 40% to 50% [1]. The traditional treatments for this cancer (surgery, radiation, and chemotherapy) have failed to improve survival while also causing considerable negative effects and poor survival rate [2-4]. Immunotherapy was first introduced in 1891 by William B. Coley, the father of father of immunotherapy. The principle of immunotherapy is that a patient's immune system can be enhanced or boosted to fight malignancies [5,6]. It is a novel and unique treatment that targets and fortifies the immune system by controlling the immunological microenvironment to eradicate tumor cells particularly when combined with immunocheckpoint inhibitors or conventional anti-tumor therapy [5]. The aim of this article is to present a concise updated review of head and neck on immune checkpoint inhibitors immunotherapy.

Materials and Methods

A systematic search was made in all peer-reviewed publications in English-language journals utilizing medical journal databases, starting year January 2000 up to September 2023. Search terms pertinent to used were "immunotherapy", "head & neck cancer", "oral cancer" "check points"; combined with Boolean operators AND and OR. The search revealed 509,146 articles. Articles titles and abstracts were screened for relevance then full-text screening performed and the most relevant ones were selected.

Results and Discussion

Immunotherapy has been identified as an effective therapeutic option for HN cancer, as the immune system can eliminate cancer cells and aid in patient recovery. Ideally, the immune system recognizes pre-malignant tumor cells and eliminates them [7]. However, it is well understood that all malignancies, including HN, are caused by the accumulation of genetic and epigenetic alterations and aberrations in cancer-related signaling pathways, resulting in cancer tumor cells developing mechanisms to halt immune recognition and response, a dynamic process known as immunoediting that leads to immune escape [7-9]. Despite the existence of immune cells and lymph nodes close to tumor cells the beginning, advancement, and

development of cancers remains unclear [7-9]. The augmentation of the defected immune system through immunotherapy may assist in the antitumor response. Three main types of cancer immunotherapies are used: adjuvant or nonspecific, targeted therapies, and vaccines[10]. Monoclonal antibodies are targeted immunotherapy that can turn on the immune system and are widely used [11,12]. An effective anti-tumor activity demonstrated by an unconjugated antibody and two radioimmunoconjugates targeting CD20 [11,12]. Vaccination strategies are promising in controlling and regression of tumors. They function via immune system's enhancement to detect and kill tumor cells [12,13]. Therapeutic vaccines augment the immune response to an existing tumor, while preventive vaccines, is aimed to stop the progress of cancer [13]. Cytokines are nonspecific molecular messengers that act by stimulating immune effector cells stromal cells and in proximity to the cancer to recognize and destroy the cells [14]. Many FDA approved cytokines are now used including GM-CSF, IL-7, IL-12, IL-15, IL-18 and IL-21 [4]. CAR-T cell therapy is an adoptive cell transfer [15]. It involves isolation of cancer patient- activated T cells, genetically engineered to locate and kill cancer and expanded, then transferred with stimulating growth factors to the patient [15]. Immune checkpoints are points that regulate different components of immune response. Immune check points are part of immune system to protect healthy cells, Checkpoint inhibitors have significantly advanced the field of cancer immunotherapy [10]. The Nobel Prize in Physiology and Medicine was granted in 2018 for the development of such medicines, the relevance of cancer immunotherapy became more widely recognized [16]. Tumor cells activate programmed death molecule-1 (PD-1) to escape immunosurveillance. PD-1 inhibitor is used in immunotherapy to activate the immune response to destroy the tumor cells [16]. Inhibitory checkpoint receptors (IR) expressed on activated immune cells, such as CTLA4 and its ligands CD80 and CD86, as well as programed death 1 (PD1) and its ligands PD-L1 and PD-L2, play critical roles in the tumor microenvironment (TME) [17]. The presence of these inhibitory receptors frequently indicates an exhausted T cell that has lost its physiological function, such as decreased proliferative capacity or cytolytic activity [18,19]. The immune system changes observed in HN cancer patients show that this cancer is an immunosuppressive process [20]. In general, the patients also have a lower overall number of white blood cells in their peripheral bloodstream [9,20]. A higher proportion of suppressive regulatory T cells (T reg) and tumor-infiltrating lymphocytes (TIL) within HN tumors have an even more suppressive population of T reg cells [19-22]. implying that tumors both evade and suppress the immune response. Immunotherapy for HN cancer was initially approved for recurrent/metastatic cases [23]. Notably, preoperative neoadjuvant immunotherapy for untreated OSCC has just been presented [24]. Immunotherapy is an extremely specific approach to cancer treatment in which immunologic effector mechanisms are activated to eliminate cancer cells. The expression of tumor and major histocompatibility complex (MHC) antigens on target tumor cells, cancer cell sensitivity to effector mechanisms, and enhanced and/or augmented activity of anticancer effectors are all required for a successful anticancer immunotherapeutic impact [25,26]. There are numerous viable immunological techniques to achieve these goals, one of which is immune checkpoints inhibitor (ICIs) CTLA-4 and PD1 or PDL1. Ipilimumab, the first antibody to disrupt an immunological checkpoint (CTLA4), was approved in 2011. This was shortly followed by the development of monoclonal antibodies against PD1 and PDL1 (pembrolizumab and nivolumab) (atezolizumab and durvalumab). Anti-PD1/PDL1 antibodies are among the most commonly recommended anticancer medicines. T-cell-targeted immunomodulators are being employed as the first or second lines of treatment for around 50 cancer types as single medicines or in conjunction with chemotherapies [27].

Understanding the complex balance of immune cell interactions and cell signaling has evolved greatly and has led to renewed interest in immunotherapy as a potential cure for various solid tumor forms, including HNSCC, as a result of the effectiveness of immunotherapy in the treatment of HN. Understanding the topography of HNSCC has also led to breakthroughs in the field of immunotherapy survival outcomes.

HN cancer is an excellent option for immunotherapy because immune escape plays a role in tumor development and progression. Several research groups have investigated the expression of PD-L1 in humans. SCCHN tissue samples from multiple primary sites were studied, and significant levels of PD-L1 expression were found in 46-100% of tumors [23]. As a result, T-cell checkpoint drugs that block the PDL1: PD-1 relationship and target RM-SCCHN have been explored.

Patients with recurrent disease or distant metastases have fewer treatment options and a poor prognosis; the median overall survival (OS) after diagnosis is less than a year [28,29]. Cetuximab, a monoclonal antibody targeting the epidermal growth factor receptor (EGFR), and platinum-based chemotherapy are the primary treatments for recurrent/metastatic (R/M) HNSCC [29]. There are significant unmet needs for HNSCC patients in terms of improving therapeutic efficacy and minimizing treatment-related toxicity. Cancer immunotherapy targets have been discovered as cytotoxic T-lymphocyte associated protein 4 (CTLA-4) and programmed death-1 (PD-1). ICI agent combinations have been studied. KESTREL and CHECKMATE 651 are phase III clinical trials in HNSCC patients that compare anti-PD-1/PD-L1 and anti-CTLA4 therapy to EXTREME. Both trials are proceeding, and the results are still awaiting [30]. CONDOR is a phase II trial in platinum-refractory, PD-L1-low/negative HNSCC patients evaluating durvalumab, tremelimumab (anti-CTLA4), and its combinations, this combination had no effect on PD-L1-expressing HNSCC, according to this study [31]. EAGLE is a phase III trial that compares durvalumab, durvalumab with tremelimumab, and conventional treatment in platinum resistant HNSCC. The first clinical trial combining anti-

PD1 with platinum-based chemotherapy for HNSCC was KEYNOTE 048. Pembrolizumab in combination with chemotherapy improved survival relative to EXTREME (median OS, 13.0 months versus 10.7 months, respectively; HR, 0.77; 95% CI, 0.63 to 0.93; P =.003). In terms of progression-free survival, there was no significant difference between the two arms [32]. The median duration of response in the pembrolizumab plus chemotherapy group ranged from 1.6 to 30.4 months. As a result, in platinum-sensitive HNSCC patients, KEYNOTE 048 demonstrated the advantage of anti-PD1 in conjunction with platinum-based treatment [32]. The US Food and Drug Administration authorized pembrolizumab with platinum-5FU for platinum-sensitive HNSCC on June 11, 2019.

The development of immune checkpoint inhibitors (ICIs) such as CTLA-4 antibodies (ipilimumab and tremelimumab), PD-1 antibodies (nivolumab and pembrolizumab), and PD-L1 antibodies, several forms of end-stage malignancies now have more viable therapy choices (atezolizumab, durvalumab, avelumab, and cemiplimab). ICI responders often take longer to respond. Cisplatin in conjunction with radiation (RT) was shown to be effective in HNSCC patients in the (RTOG 950163 and EORTC 2293164) investigations. Furthermore, as compared to RT alone in a global, randomized trial, cetuximab-RT dramatically enhanced survival [33]. Cetuximab-RT, on the other hand, was reported to be inferior to cisplatin-RT in two large prospective trials of patients with HPV+ HNSCC [34,35]. Prospective of HNSCC trials have investigated various RT combination strategies, however, no doublet-RT treatment has outperformed cisplatin-RT. Cisplatin/RT, on the other hand, may be associated with several delayed cisplatinrelated toxicities, such as ototoxicity, nephrotoxicity, and neurotoxicity. It is considered that PD-L1 expression is a probable mechanism that leads to RT resistance. In an animal model, PDL1 expression rose after radiation and adding an antiPD-L1 medication to RT improved efficacy [36]. In a clinical study of HNSCC patients, PD-1 expression on peripheral immune cells increased during chemoradiation [37]. These findings support the idea of combining anti-PD1/PD-L1 therapy with radiation therapy for HNSCC.

Are immune checkpoint inhibitor ICIs effective for recurrent and metastatic head and neck SCC?

The recurrent and metastatic head and neck SCC treatment plan is determined by the susceptibility to platinum agents. The EXTREME trial demonstrated that adding cetuximab, an anti-EGFR monoclonal antibody, to carboplatin-based treatment improved recurrent and metastasis head and neck SCC outcomes. Also, a combination of cisplatin (CDDP) with 5-fluorouracil prolonged survival (OS) in platinum-sensitive recurrent and metastasis head and neck SCC [29].

Combination of checkpoints inhibitor (ICIs) with other Immunotherapies

Combination immunotherapies have shown significant synergy and may lead to further treatment advancements as compared to monotherapy or existing cytotoxic regimens. Several interesting prospective therapeutic targets have been found in preclinical research, and several of these drugs are being evaluated in combination trials with anti-PD1 therapy. CTLA4 and PD1 combination has been studied in melanoma patients, validating the synergism of blocking these two agents [38].

Combining chemotherapy with anti-PD1/PD-L1 therapy has been shown to improve therapeutic efficacy in a variety of cancers, including non-small-cell lung cancer (NSCLC), small-cell lung cancer (SCLC), and breast cancer [39-42]. Chemotherapy can cause immunogenic cell death in tumors, enhance neoantigen release, and boost lymphocyte infiltration in the tumor microenvironment [43]. These findings emphasize the strength of the evidence supporting the addition of chemotherapy to ICIs in HNSCC.

One hypothesized theory for the possible benefit of radiation with immunotherapy is that triggering immunogenic cell death can potentially enhance systemic responses via an "abscopal effect," in which local therapy creates a systemic response that lasts beyond the completion of RT treatment [44]. These modifications could modify the tumor microenvironment (TME), making it more susceptible to PD1 pathway-inhibiting medications. Preclinical abscopal reactions have shown that RT and anti-PD1 treatment have cumulative effects [45]. RT has been shown to synergize with anti-CTLA4 drugs in preclinical investigations, similar to PD1 [46]. Ionizing radiation activates the adaptive immune response via a variety of pathways, any of which may be combined with immunotherapy. Furthermore, RT has been demonstrated to increase the expression of PD-L1 in tumor cells [47].

Possible side effects of checkpoints inhibitor immunotherapy

Immunotherapy has various side effects, mostly autoimmune, like renal failure and anemia. Ipilimumab's main side effects are pneumonitis and colitis [48]. Ipilimumab's adverse effects are worse than nivolumab's. Autoimmune endocrinopathies were the most common side effect in the checkmate 141 trial, however, immunotherapy was often continued. Nivolumab caused one-third fewer grades 3 and 4 AEs than cytotoxic treatment in this trial [49].

Conclusion

Considering that only around half of patients diagnosed with head and neck cancer will survive, and since current treatment choices (surgery, radiation, and chemotherapy) have failed to increase survival rates while still being associated with substantial side effects, it's evident that something needs to change. A thorough understanding of immunotherapy as a treatment option for head and neck cancer, as well as its combination with other treatment modalities, is critical for patients seeking to enhance their quality of life. This mini literature review was prompted by the desire to learn more about the role of immunotherapy in head and neck cancer treatment, Also, it's fascinating to learn more about a field that's constantly developing and expanding.

Conflict of Interest

The authors declare that they have no competing interests.

Bibliography

1. Mandal R., *et al*. "The head and neck cancer immune landscape and its immunotherapeutic implications". *JCI Insight* 1.17 (2016).
2. Almangush A., *et al*. "Prognostic biomarkers for oral tongue squamous cell carcinoma: A systematic review and meta-analysis". *British Journal of Cancer* 117.6 (2016).
3. Rivera C., *et al*. "Prognostic biomarkers in oral squamous cell carcinoma: A systematic review". *Oral Oncology* 2 (2017).
4. Nandini DB., *et al*. "Novel therapies in the management of oral cancer: An update". *Disease-a-Month* 66 (2020).
5. Tan S., *et al*. "Cancer immunotherapy: Pros, cons and beyond". *Biomedicine and Pharmacotherapy* 124 (2020).
6. McCarthy EF. "The toxins of William B. Coley and the treatment of bone and soft-tissue sarcomas". *Iowa Orthopedic Journal* (2006): 26.
7. Hanahan D and Weinberg RA. "Hallmarks of cancer: The next generation". *Cell* 144 (2011).
8. Beatty GL and Gladney WL. "Immune escape mechanisms as a guide for cancer immunotherapy". *Clinical Cancer Research* 21 (2015).
9. Whiteside TL. "Immunobiology of head and neck cancer". *Cancer and Metastasis Reviews* 24 (2005).
10. Lee L., *et al*. "Immune Checkpoint inhibitors: An introduction to the next-generation cancer immunotherapy". *Journal of Clinical Pharmacology* 56 (2016).
11. Weiner LM., *et al*. "Monoclonal antibodies for cancer immunotherapy". *The Lancet* 373 (2009).
12. Kimiz-Gebologlu I., *et al*. "Monoclonal antibodies in cancer immunotherapy". *Molecular Biology Reports* 45 (2018).
13. Tojjari A., *et al*. "A Comprehensive Review on Cancer Vaccines and Vaccine Strategies in Hepatocellular Carcinoma". *Vaccines* 11 (2023).
14. Lee S and Margolin K. "Cytokines in cancer immunotherapy". *Cancers* 3 (2011).
15. Akhoundi M., *et al*. "CAR T cell therapy as a promising approach in cancer immunotherapy: challenges and opportunities". *Cellular Oncology* 44 (2021).
16. Huang PW and Chang JWC. "Immune checkpoint inhibitors win the 2018 Nobel Prize". *Biomedical Journal* 42 (2019).
17. Zitvogel L and Kroemer G. "Targeting PD-1/PD-L1 interactions for cancer immunotherapy". *OncoImmunology* 1 (2012).
18. Yi JS., *et al*. "T-cell exhaustion: Characteristics, causes and conversion". *Immunology* 129 (2010).
19. Jie HB., *et al*. "Intratumoral regulatory T cells upregulate immunosuppressive molecules in head and neck cancer patients". *British Journal of Cancer* 109.10 (2013).
20. Tie Y., *et al*. "Immunosuppressive cells in cancer: mechanisms and potential therapeutic targets". *Journal of Hematology and Oncology* 15 (2022).
21. Whiteside TL. "Immunobiology of head and neck cancer". *Cancer Metastasis Review* 24.1 (2005): 95-105.
22. Strauss L., *et al*. "The frequency and suppressor function of CD4+CD25 highFoxp3+ T cells in the circulation of patients with squamous cell carcinoma of the head and neck". *Clinical Cancer Research* 13.21 (2007): 6301-6311.
23. Zandberg DP and Strome SE. "The role of the PD-L1: PD-1 pathway in squamous cell carcinoma of the head and neck". *Oral Oncology* 50 (2014).
24. Schoenfeld JD., *et al*. "Neoadjuvant Nivolumab or Nivolumab plus Ipilimumab in Untreated Oral Cavity Squamous Cell Carcinoma: A Phase 2 Open-Label Randomized Clinical Trial". *JAMA Oncology* 6.10 (2020).
25. Tímár J., *et al*. "Molecular pathology of tumor metastasis III. Target array and combinatorial therapies". In: *Pathology and Oncology Research* (2003).
26. Whiteside TL. "Immunobiology and immunotherapy of head and neck cancer". *Current Oncology Reports* 3 (2001).
27. Yokota T., *et al*. "Immunotherapy for squamous cell carcinoma of the head and neck". *Japanese Journal of Clinical Oncology* 50 (2020).
28. Sklan A and Collingridge D. "Treating head and neck cancer: for better or for worse?" *The Lancet Oncology* 18 (2017).
29. Vermorken JB., *et al*. "Platinum-Based Chemotherapy plus Cetuximab in Head and Neck Cancer". *New England Journal of Medicine* 359.11 (2008).
30. Kao HF and Lou PJ. "Immune checkpoint inhibitors for head and neck squamous cell carcinoma: Current landscape and future directions". In: Head and Neck (2019).
31. Siu LL., *et al*. "Safety and Efficacy of Durvalumab with or Without Tremelimumab in Patients with PD-L1-Low/Negative Recurrent or Metastatic HNSCC: The Phase 2 CONDOR Randomized Clinical Trial". *JAMA Oncology* 5.2 (2019).

32. Burtness B., *et al*. "Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study". *The Lancet* 394.10212 (2019).

33. Bonner JA., *et al*. "Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival". *Lancet Oncology* 11.1 (2010).

34. Gillison ML., *et al*. "Radiotherapy plus cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (NRG Oncology RTOG 1016): a randomised, multicentre, non-inferiority trial". *The Lancet* 393.10166 (2019).

35. Mehanna H., *et al*. "Radiotherapy plus cisplatin or cetuximab in low-risk human papillomavirus-positive oropharyngeal cancer (De-ESCALaTE HPV): an open-label randomised controlled phase 3 trial". *The Lancet* 393.10166 (2019).

36. Twyman-Saint Victor C., *et al*. "Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer". *Nature* 520.7547 (2015).

37. Sridharan V., *et al*. "Definitive chemoradiation alters the immunologic landscape and immune checkpoints in head and neck cancer". *British Journal of Cancer* 115.2 (2016).

38. Wolchok JD., *et al*. "Nivolumab plus Ipilimumab in Advanced Melanoma". *New England Journal of Medicine* 369.2 (2013).

39. Gandhi L., *et al*. "Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer". *New England Journal of Medicine* 378.22 (2018).

40. Socinski MA., *et al*. "Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC". *New England Journal of Medicine* 378.24 (2018).

41. Horn L., *et al*. "First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer". *New England Journal of Medicine* 379.23 (2018).

42. Emens LA., *et al*. "Atezolizumab and nab-Paclitaxel in Advanced Triple-Negative Breast Cancer: Biomarker Evaluation of the IMpassion130 Study". *Journal of the National Cancer Institute* 113.8 (2011).

43. Wang Q., *et al*. "Immunogenic cell death in anticancer chemotherapy and its impact on clinical studies". *Cancer Letters* 438 (2018).

44. Demaria S and Formenti SC. "Can abscopal effects of local radiotherapy be predicted by modeling T cell trafficking". *Journal for ImmunoTherapy of Cancer* 4 (2016).

45. Sharabi AB., *et al*. "Radiation and checkpoint blockade immunotherapy: Radiosensitisation and potential mechanisms of synergy". *The Lancet Oncology* 16 (2015).

46. Kang J., *et al*. "Current clinical trials testing the combination of immunotherapy with radiotherapy". *The Journal for ImmunoTherapy of Cancer* 4.1 (2016).

47. Deng L., *et al*. "Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice". *Journal of Clinical Investigation* 124.2 (2014).

48. Bertrand A., *et al*. "Immune related adverse events associated with anti-CTLA-4 antibodies: Systematic review and meta-analysis". *BMC Medicine* 13.1 (2015).

49. Ferris RL., *et al*. "Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck". *New England Journal of Medicine* 375.19 (2016).