Pembrolizumab Efficacy in Treatment of Carcinoma of the Head and Neck Squamous Cell

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ABSTRACT
Immunotherapy acts by a system of immune modulation to destruct cells of cancer. Squamous cell carcinoma of the head and neck (HNSCC), this modality can be administered alone or combined with other therapies. Currently, immunotherapy with chemotherapy has shown better effectiveness as first-line systemic therapy. Immunotherapy drugs are divided into T-cell treatment and checkpoint inhibitors divided into chimeric antigen receptor (CAR). Pembrolizumab is categorized as checkpoint inhibitors and is currently being researched for its role in HNSCCs management. Pembrolizumab can be used the first or second-line for recurrent or metastatic (R/M) HNSCC. In addition, the side effects of Pembrolizumab are more tolerable than standard chemotherapy regimens.

Keywords: *Cancer Treatment, Head and Neck Squamous Cell Carcinoma, Immunotherapy, Pembrolizumab.*

1. INTRODUCTION

Treatment for HNSCC depends on individual factors, such as location and stage of the tumor, comorbidities, and general condition of the patients. Treatments, surgery, chemotherapy, and radiation, may be used alone or in combination, depending on tumor stage and location [1]. Most HNSCC patients came with advanced tumor progression, which was treated with a multimodality therapeutic approach. Despite advanced multimodality therapies, there have been minor improvements in generally understanding endurance (40%-60%) in the last 50 years [2]. Chemotherapy has been recommended for patients with R/M disease of HNSCC, cytotoxic-based as a standard treatment modality with average survival from 6 to 10 months with patients treated by chemotherapy only [3].

Previous research reported a high failure and low survival rate with significant toxicities associated with multimodality treatment approaches which refer to improving alternative therapeutic options. The immune system is proposed to an essential role in tumorigenesis of HNSCC. The concept of immunotherapy came from the idea that malignant cells are known as foreign bodies and can be effective for the immune system [4-5]. Several immune control mechanisms, checkpoint inhibitors, anticytotoxic T lymphocyte-associated protein 4 (anti-CTLA-4), an anti-programmed cell death protein-1 (anti-PD-1) have provided a long-lasting improved response and survival in late cancer stages. Adoptive cell transfer was also explored with engineered antigen receptor T cells or tumor-infiltrating lymphocytes (TIL) [6].

In this review, we focused on pembrolizumab in treating HNSCC. First, we described the current approach to pembrolizumab and discussed its use in clinical practice.

2. RESULTS AND DISCUSSION

2.1. The Role of Immune System in HNSCC

Malignant tumor immunosurveillance involves both innate and adaptive immune systems. Innate immunity is the first line of protection with a non-specific nature, consisting of neutrophils, natural killer (NK) cells, dendritic cells (DCs), macrophage, and monocytes, that attack and ingest pathogens. The efficacy of innate immunity declines after repeated exposures to the same antigenic structures. The adaptive immune system has a specific nature that is triggered by the innate immune response. This type of immune system may have a long-lasting effect after repeated exposures.

DCs and antigen-presenting cells (APCs) phagocytize express antigens of a tumor to major histocompatibility complex (MHC) class I or class II, the first signal at T cell proliferation. Identifying tumor antigen-specific T cells is necessary diagnostics or therapeutics with immunotherapy [6].

Several regulators for T cell activation serve as checkpoint molecules to restrict insusceptible reaction hence avoiding hyperactivation and self-initiated destruction. T cell immune checkpoint molecules are CTLA4, and PD-1 [4]. PD-1 is a “death receptor” that causes apoptosis in T cells and plays a role in preventing autoimmunity and regulating the immune response. Numerous tumors express the programmed death-ligand 1 (PD-L1), which binds to the PD-1 receptor resulting in T cells apoptosis and immune evasion [7].

Controls of the PD-1 pathway to T-cell activation are critical for self-tolerance and modulate the immune response, including amplitude and duration of the physiological immune response. However, the cancer cell may manipulate this pathway, resulting in unchecked tumor growth by the immune system. Under normal conditions, cells, PD-L2 or PD-L1, binds to PD-1 to inactive T cells. This mechanism plays a role in immune system regulation, such as overreaction avoidance. PD-L1, likewise seen in HNSCC, inactivates T cells after binding to PD-1 on T cells. The combination of TILs relates to the PD-L1 expression of tumor cells. CTLA-4 is one more safe, designated spot situated on the surface of activated CTLs that ties to the B7 ligands on APCs. CD28 receptor that addresses a stimulatory accomplice to CTLA4 can cause T-cell activation. CTLA-4 fights with the CD28 receptor to limit the B7 ligand as a stimulatory or inhibitory T cells.

Patients with solid tumors have been evaluated for immunotherapy with immune checkpoint blockade treatment [8]. PD-1/PD-L1 inhibitors can be used for R/M HNSCC treatment [9-10]. At the moment, there are two PD-1inhibitors such as Nivolumab and Pembrolizumab [11].

2.2 Pembrolizumab in HNSCC

Pembrolizumab is a monoclonal antibody binding PD-1 receptor, blocking interaction with PD-L2 and PD-L1. This interaction results in PD-1 pathway-mediated immune response inhibition and antitumor immune response. While affecting tumor cells, this could also affect normal healthy cells [12].

KEYNOTE-012 phase trial reported that Pembrolizumab monotherapy had a better curative effect in 60 HPV-positive HNSCC patients with positive expression of PDL-1. The response duration was 53 weeks, and the mean overall survival was 13 months. This study revealed that there were no medication-related deaths, showing that pembrolizumab was tolerated [12].

KEYNOTE-055 in the phase II trial shows that the PD-L1 positive rate was 82%, the mOS was eight months, and the mPFS was 2.1 months. This study concludes that pembrolizumab was not dependent on HPV or PD-L1 expression [13].

KEYNOTE-040 trial in phase III, pembrolizumab was given after and during platinum-based therapy of R/M HNSCC. The mean overall survival was 6.9 and 8.4 months [14].

KEYNOTE-048 in phase III trial proved that pembrolizumab with or without chemotherapy vs. EXTREME was analyzed for R/M HNSCC curative treatment. Patients receiving EXTREME protocol had a better ORR (36 vs. 17%) with a higher incidence of AE grade 3 (83 vs. 55%) than pembrolizumab for monotherapy. Pembrolizumab monotherapy improved OS above EXTREME protocol in the PD-L1-positive patients. PD-1 antibody combined with chemotherapy reported a better survival rate in PD-L1 negative patients [15].

Pembrolizumab monotherapy as the first-line therapy improved OS in the PD-L1 CPS pf 20 or more, CPS of 1 or more patients. Pembrolizumab is safer than cetuximab with chemotherapy for first-line treatment for R/M HNSCC. Pembrolizumab combined with platinum-based and 5-fluorouracil (5-FU) for first-line treatment significantly improve OS in CPS of 1 or more and PD-L1 CPS of 20 more vs. cetuximab with chemotherapy. For PDL-L1 R/M HNSCC, pembrolizumab can be used for first-line therapy [15]

Guidelines 2021 version 3 from National Comprehensive Cancer Network (NCCN) states that pembrolizumab can be used as systemic therapy for non-nasopharyngeal cancer patients. Pembrolizumab/platinum based/5-FU or pembrolizumab (for tumors that express PD-L1 with CPS >1 can be used for first-line treatment in patients with metastatic unresectable or recurrent (with no surgery or RT option). Subsequent-line therapy if disease progression on or after platinum therapy. Pembrolizumab is used for systemic treatment in R/M progression or after platinum-based chemotherapy of nasopharyngeal cancer [16].

Pre-treatment preparation is noteworthy to avoid the severity of toxicity and variations in how symptoms and signs may be associated with the administration of ICI monotherapy. History of infectious, autoimmune, endocrine, and organ-specific disease should be noted. Any dermatological lesion should be observed,

including type and the extent of lesions. Supporting examinations such as blood test (metabolic, blood count, TSH, and T4 level, HbA1c, fasting lipid profile and infectious disease including hepatitis B, CMV, and HIV), pulmonary function test such as baseline O_2 saturation, ECG, Troponin I, and T is recommended before therapy initiation.

Pembrolizumab for rationale therapy can be administered on cycle treatment day 1 of each 3-week cycle. The dose of pembrolizumab is 200 mg using an IV infusion for 30-minute. A window between less than 5 minutes and more for 10 minutes is allowed (infusion time is 30 minutes -5 min/+10 min). For patients administered pembrolizumab with chemotherapy, the pembrolizumab first followed by the platinum and 5-FU infusions [17].

Each cycle for day one will be administered platinum-based (Cisplatin or Carboplatin). Carboplatin is given for AUC 5 with a duration of 60 minutes. Cisplatin is provided for 100 mg/m2 for 60 minutes. Administered 5-FU with dose 1.000 mg/m2/day for day 1-4 of each treatment cycle [17].

A gradual dose reduction is performed if the severity of toxicity is found and is associated with platinum-based, 5-FU, or pembrolizumab alone. The dose cannot be increased again if there is a reduction before. Dosage modifications should consider in the previous cycle. The amount of Pembrolizumab should not be modified for toxicity [17].

Table 1. Dose Modifications for Trial Medications [17]

Drug	Dose level 0	Dose level-1	Dose level-2	Dose level-3
Cisplatin	100 mg/m2	80 mg/m2 (20% decrease)	64 mg/m2 (20% decrease)	Discontinue
Carboplatin	AUC 5	AUC 4 (20% decrease)	AUC 3 (20% decrease)	Discontinue
5-FU	1000 mg/m2/day	800 mg/m2/day (20% decrease)	640 mg/m2/day (20% decrease)	Discontinue

Standard Toxicity Criteria should evaluate the tolerability and safety of pembrolizumab in R/M HNSCC for Adverse Events (CTCAE) measures for events of clinical interests (ECIs), serious adverse events (SAEs), and immune-related adverse events (irAEs). Most irAEs are reversible and improve with pembrolizumab discontinuation, corticosteroid administration, and other supportive care [17].

Patients should be follow-up using the Response Evaluation Criteria in Solid Tumours (RECIST) criteria. During follow-up, imaging should be done every six weeks for the first year and every nine weeks after one year [17].

3. CONCLUSION

Pembrolizumab was approved for the first-line choice for R/M HNSCC and second-line therapy for platinum-refractory R/M HNSCC.

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