Immune checkpoint blockade therapy in head and neck cancer: a review
Dr. Shajedul Islam 1, Dr.Md.Shahed Rafi Pavel 2, Dr. Syed Taufiqul Islam 3, Dr. Nazmus Shalehin 4, Dr. Shahed Jahan Babu 5.

AFFILIATION
1. Division of Disease Control and Molecular Epidemiology.
2. Associate Professor
   Department of Dental Public Health, City Dental College, and Hospital
3. Division of Pediatric Dentistry.
4. Division of Histology
   School of Dentistry
   Health Sciences University of Hokkaido, 1757 Kanazawa Ishikari Tobetsu, Hokkaido 061-0293, Japan.
5. Associate Professor
   Department of Dental Public Health, Update Dental College, and Hospital.

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E-mail: updci@hotmail.com

* Corresponding Author
Dr. Shajedul Islam
Division of Disease Control and Molecular Epidemiology.
Health Sciences University of Hokkaido, Japan.
Email-shajedul@hoku-iryo-u.ac.jp

ABSTRACT
Head and neck cancer (HNC) is a common malignant tumor, carrying a poor prognosis, and despite advances in oncology, this rate has not improved significantly for decades. It has recently been evaluated that the immunologic checkpoint inhibitors become a novel promising strategic immunotherapy in the treatment of metastatic cancer. Therefore, our current review article will discuss the biological role and impact of the immune checkpoint inhibitor in HNC.

KEYWORDS: PD1; PDL-1; CTLA4; MHC; T cell, APC.

INTRODUCTION
HNC is a group of cancers, that arise from the mouth, nose, throat, larynx, sinuses, or salivary glands 1 and together they are the seventh most frequent cancer and the ninth most frequent cause of death from cancer in the worldwide 2. It is believed that smoking, alcohol consumption, betel quid chewing, poor oral hygiene, genetic predisposition, HPV (human papillomavirus), EBV (Epstein Barr Virus) and other virus infection seem to be associated with the progression of HNC 3,8. Over the decades, improvements have been made in the diagnosis, management and targeted therapies for malignancy. Recently it has been reported that immune checkpoint inhibitors have become a promising strategy for the treatment of the metastatic tumor. Immune checkpoint inhibitors, which target the interaction between PDL-1/PDL-2 (programmed death ligand-1/2) and PD-1 (programmed cell death-1), have been recently approved for the treatment of various malignancies and are currently being investigated in clinical trials for HNC. Data available from these trials indicate substantial activity accompanied by a favorable safety and toxicity profile in this patient population. This review article focuses on the molecular background of the immunologic checkpoint and their significance in the treatment of metastatic HNC.

An overview of immune checkpoint
T-cell activation or inhibition is mediated via co-stimulatory or co-inhibitory molecules respectively. This interaction is exerted via ligand/receptor interaction. T-cells harbor a myriad of both activating receptors such as OX-40, GITR, or CD28 and inhibitory receptors (the so-called immune checkpoints) such as PD-1 or CTLA-4 9. Activation of this immune checkpoint results in T cell deactivation (Figure:1) 10.
Tumor cells often hijacking these pathways contributes to their successful immune escape (Figure-2 a). In HNC, it has been reported that tumor cell expressed 45–80 % PDL-1 on their cell surface 11. In addition, PDL-1 was upregulated upon cancer cells exposed to therapy. It has been demonstrated that HNC patients have elevated PDL-1 expression compared to healthy controls and that chemotheraphy and radiation causes a PDL-1 upregulation in HNC patients, which lasts up to one year 12. Furthermore, upregulation of PDL-1 in HNC also induced via extrinsic secretion of IFN-γ by NK or CD8+ cells or by intrinsic oncogenic drivers 13 and EGFR/JAK2/STAT-1 axis act as such a driver pathway 13.

**Factor induces PDL-1 and PD-1 expression**

PD-1 is a member of the CD28/CTLA-4/ICOS costimulatory receptor family type-I transmembrane glycoprotein, mainly comprises an extracellular region, a hydrophobic transmembrane region, and an intracellular tyrosine residue containing region 14,17. The PD-1 receptor binds to its ligands PDL-1/2, presence in tumor cells, thus mediated inhibitory signal to the T-cells (Figure-2 a). PDL-1 is expressed in APC (antigen-presenting cell), tumor cells, TAM (tissue associated macrophage) and so on. Whereas PDL-2 is expressed on activated macrophage, dendritic cell 14.

PD-1 is expressed on activated T cells after induction by a T-cell antigen receptor and cytokine receptor 20. PD-1 is also expressed at low levels on double-negative (CD4–CD8–) T cells in the thymus, activated natural killer T cells, B cells, monocytes, and immature Langerhans’ cells 14,16. PDL-1 is expressed constitutively at low levels on antigen-presenting cells (APCs) and a wide variety of non-hematopoietic cell types 14,20,24. Inflammatory cytokines such as type I and type II interferons as well as TNF-α (tumor necrosis factor α) and oncogenic VEGF (vascular endothelial growth factor) can induce PDL-1 expression 14,17. On the other hand, tumor cell upregulates PDL-1 expression mainly via four mechanisms and tumor cell-derived cytokine also can upregulated PDL-1 expression (Figure-3).

**Antitumor mechanism of PDL1 and PD1**

Proper activation of T cells is dependent upon the regulation of a “dual-signal” system. At first, the signal is derived from the binding between a receptor T-cell and MHC (major histocompatibility complex) presence on APCs. The second signal arises from the co-stimulating molecules, namely, the signal mediated by the interaction between APC-expressed co-stimulatory molecules and the corresponding receptor or ligand on the T-cell surface (Figure-1, and Figure-2a). For example, CD28/B7 is an important positive co-stimulatory molecule and the one applied most extensively are CTLA4 and PD-1/PDL-1 (Fig-2 a, b) 21–23,20. When PD-1 and PDL-1 bind with each other in activated T cells, a tyrosine residue in the intracellular region of PD-1 undergoes phosphorylation. These actions lead to inhibition of the activation of downstream channels such as Akt (protein kinase B) and MAPK/ERK (mitogen-activated protein kinase). Finally, inhibition of the transcription and translation of genes and cytokines required by T-cell activation leads to the regulation of T-cell activity 14. After the invasion by tumor cells, these signal channels are used to inhibit T-cell activation so as to evade attack by the immune system. At present, inhibitors of immune checkpoint have been studied, and the ones applied most extensively are CTLA-4, PD-1, and PDL-1 monoclonal antibodies. The anti-tumor effect is realized by the inhibition of the activity of immune checkpoints, blockade of immunosuppression in the tumor microenvironment, and reactivation of the immune response of T cells to the tumor 14,16,19,21–25.
Clinical application of PDL-1/PD1 immune checkpoint inhibitors in HNC

The main PD-1-targeted drugs used to treat HNC are pembrolizumab and nivolumab, which have been used for the treatment of patients with recurrent/metastatic HNC after platinum-containing chemotherapy. Whereas, at present, the main PDL-1-targeted drug for HNC treatment is durvalumab. Several studies have been conducted on the basis of patient demographic data and revealed that these immune checkpoint inhibitor therapy has been a significant impact on the overall survival and progression-free survival 23-25,27-31.

Based on the aforementioned studies, it has been evaluated that, PD-1 immune checkpoint inhibitors pembrolizumab have significant anti-tumor activity and fewer side effects for patients with recurrent/metastatic HNC in comparison with the nivolumab. The overall survival and disease-free survival rates were significantly higher in pembrolizumab than that of nivolumab. Patients were experienced treatment-related adverse effects mainly fatigue, pruritus, nausea, reduced appetite, and rash. On the other hand, PDL-1 inhibitors had a less significant impact on the overall survival of the patients. These clinical trials demonstrated that PD-1/PDL-1-targeted drugs have obvious advantages over the traditional therapeutic method in terms of ORR (overall response rate), survival, and safety when treating recurrent/metastatic HNC. They have shown enormous potential as new types of anticancer drugs. The ORR of PD-1 as treatment of recurrent/metastatic HNC was higher than that of PDL-1.

CONCLUSION

The curative effect and safety of PD-1/PDL-1-targeted drugs using a traditional regimen to treat HNC should be explored further. Several studies have shown that PD-1/PDL-1 targeted drugs combined with radiotherapy and chemotherapy can enhance the killing of tumor cells. Hence, clinical research on PD-1/PDL-1 targeted drugs combined with traditional chemotherapy, biotherapy, radiotherapy and surgical treatment should be strengthened. Selection of drug doses, safety, and tolerability in combination therapy should be examined.

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