Review Article

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Immune checkpoint blockade therapy in head and neck cancer: a review

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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 CD 28 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 chemotherapy 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].

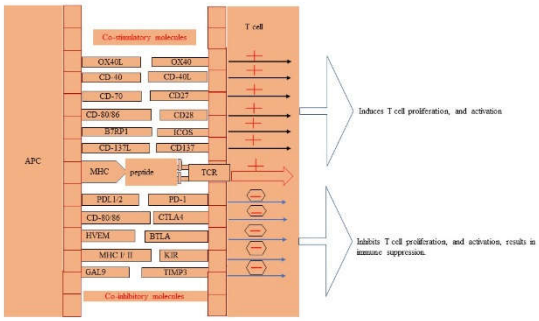

Figure: 1 Co-stimulatory and Co-inhibitory immune checkpoints overview.

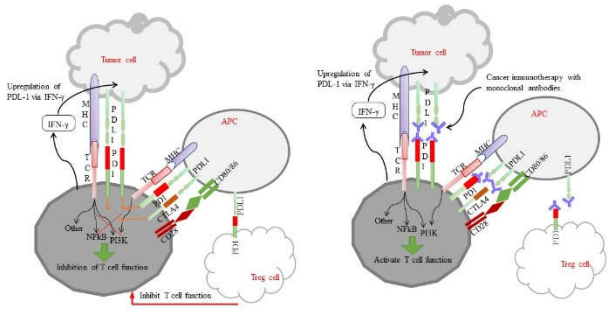

Figure: 2. PDL1 ligand binds to PD1 receptors on activated T cell, thus inhibit the T cell proliferation, activation and results immune suppression within the tumor microenvironment (a). Anti PDL-1 or Anti PD1 monoclonal antibodies inhibit PDL-1/PD1 mediated T cell suppression within the tumor microenvironment (b).

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 unregulated PDL-1 expression (Figure:3).

The first mechanism is activation of the EGFR (epidermal growth factor receptor), MAPK , PI3K (phosphoinositide 3-kinase)/Akt or JNK2 (Janus kinase 2) signal transducer and AP-1 (activator of transcription-1) signaling pathways.

The second mechanism is amplification of genes coding PD-L1 (*9p24.1*).

The third mechanism is induction of the EBV, Gastric cancer and EBV + nasopharyngeal carcinoma can result in high expression of PD-L1.

The final mechanism is epigenesis. Some microRNAs (miR-34a, miR-200, miR-513, and miR-570) have a negative correlation with PD-L1 expression.

Role of tumor cells produced cytokine on PDL-1 expression

TGF β (transforming growth factor beta)	IL 6 (interleukin 6)	IL 10 and Oncogenic VEGF
▪ Decreased cell mediated immunity ▪ Suppress STAT1 activation, results decreased APM components, thus decrease MHC class. ▪ Cell cycle arrest of activated T cell ▪ Increased T-reg cell, which secrete IL 10, CTLA 4, TGF β, acts as a positive regulator on TGF β ▪ Recruits MDSC	▪ Decreased cell mediated immunity ▪ Suppress STAT1 activation, results decreased APM components, thus decrease MHC class. ▪ Acts on STAT3 and secrete IL 10 , TGF β. ▪ Increased PDL 1 ▪ Increased HIF 1α ▪ Recruits MDSC	▪ Decreased cell mediated immunity ▪ Suppress STAT1 activation, results decreased APM components, thus decrease MHC class. ▪ Acts on STAT3 and decreased IL12, MHC class, increased T reg (IL10) ▪ Increased PDL1 ▪ Recruits MDSC

Figure 3: Mechanisms of PDL-1 upregulation via tumor cells

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-stimulating molecule [14-15,18,20]. In addition to ensuring that T cells are not overstimulated, there are negative co-stimulatory molecules that regulate T cells, and they are mainly 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 checkpoints 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 in 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.

REFERENCES:

1. "Head and Neck Cancers". NCI. February 1, 2013; Retrieved 29 September 2016
2. World Cancer Report. World Health Organization. 2014;
3. Van Monsjou HS, Wreesmann VB, Van Den Brekel MW, Balm AJ. Head and neck squamous cell carcinoma in young patients. Oral Oncol; 2013; 49(12), 1097-1102.https://doi.org/10.1016/j.oraloncology.2013.09.001 PMid:24103389
4. Walden MJ, Aygun N. Head and Neck Cancer. Semin. Roentgenol; 2013; 48(1), 75-86. https://doi.org/10.1053/j.ro.2012.09.002 PMid:23158052
5. Argiris A, Karamouzis MV, Raben D, Ferris RL. Head and neck cancer. Lancet Oncol; 2008; 371(9625), 1695-1709. https://doi.org/10.1016/S0140-6736(08)60728-X
6. Brakenhoff RH. Cancer. Another NOTCH for cancer. Science; 2011; 333(6046), 1102-1103. https://doi.org/10.1126/science.1210986 PMid:21868662
7. Yan Chen, Xu Ge, Ming Zhang, Jinwei Wang, Qingbo Zhao, Jianjun He and Zhenghong Wang. Epidemiology and cost analysis for patients with oral cancer in a university hospital in China. BMC Public Health; 2010; 10 196. https://doi.org/10.1186/1471-2458-10-196 PMid:20398380 PMCid:PMC2864212
8. Galbiatti AL, Padovani-Junior JA, Maniglia JV, Rodrigues CD, Pavarino EC, Goloni-Bertollo EM. Head and neck cancer: causes, prevention, and treatment. Braz J Otorhinolaryngol; 2013; 79(2), 239-247. https://doi.org/10.5935/1808-8694.20130041
9. Mellman I, Coukos G, Dranoff G. Cancer immunotherapy comes of age. Nature. 2011; 480:480–489. https://doi.org/10.1038/nature10673 PMid:22193102 PMCid:PMC3967235
10.Ovarian-cancer-trial-avelumab-pdl1-immunooncology.Accessed:13.6. 2016
11. Zandberg DP, Strome SE. The role of the PD-L1: PD-1 pathway in squamous cell carcinoma of the head and neck. Oral Oncol. 2014;50: 627–632. https://doi.org/10.1016/j.oraloncology.2014.04.003 PMid:24819861
12. Parikh F, et al. Chemoradiotherapy-induced upregulation of PD-1 antagonizes immunity to HPV-related oropharyngeal cancer. Cancer Res. 2014 https://doi.org/10.1158/0008-5472.CAN-14-1913
13. Concha-Benavente F, et al. Identification of the cell-intrinsic and -extrinsic pathways downstream of EGFR and IFN gamma that induce PD-L1 expression in head and neck cancer. Cancer Res. 2016; 76:1031–1043 https://doi.org/10.1158/0008-5472.CAN-15-2001 PMid:26676749 PMCid:PMC4775348
14. Boussiotis VA. Molecular and biochemical aspects of the PD-1 checkpoint pathway. N Engl J Med. 2016;375(18):1767–1778. https://doi.org/10.1056/NEJMra1514296 PMid:27806234 PMCid:PMC5575761
15. Zhang X, Schwartz JC, Guo X, et al. Structural and functional analysis of the costimulatory receptor programmed death-1. Immunity. 2004; 20(3):337–347. https://doi.org/10.1016/S1074-7613(04)00051-2
16. Cheng X, Veverka V, Radhakrishnan A, et al. Structure and interactions of the human programmed cell death 1 receptor. J Biol Chem. 2013;288(17):11771–11785.https://doi.org/10.1074/jbc.M112.448126 PMid:23417675 PMCid:PMC3636866
17. Yao Q, Fischer KP, Tyrrell DL, Gutfreund KS. The Peking duck programmed death-ligand 1: cDNA cloning, genomic structure, molecular characterization and mRNA expression analysis. Int J Immunogenet. 2015;42(2):111–120 https://doi.org/10.1111/iji.12175 PMid:25556810
18. Pai SI, Zandberg DP, Strome SE. The role of antagonists of the PD-1: PD-L1/PD-L2 axis in head and neck cancer treatment. Oral Oncol. 2016; 61:152–158.https://doi.org/10.1016/j.oraloncology.2016.08.001 PMid:27503244 PMCid:PMC5690560
19. Lyford-Pike S, Peng S, Young GD, et al. Evidence for a role of the PD-1: PD-L1 pathway in immune resistance of HPV-associated head and neck squamous cell carcinoma. Cancer Res. 2013;73(6):1733–1741 https://doi.org/10.1158/0008-5472.CAN-12-2384 PMid:23288508 PMCid:PMC3602406
20. Moreno BH, Parisi G, Robert L, Ribas A. Anti-PD-1 therapy in melanoma. Semin Oncol. 2015;42(3):466–473. https://doi.org/10.1053/j.seminoncol.2015.02.008 PMid:25965365
21. Pai SI, Zandberg DP, Strome SE. The role of antagonists of the PD-1: PD-L1/PD-L2 axis in head and neck cancer treatment. Oral Oncol. 2016; 61:152–158.https://doi.org/10.1016/j.oraloncology.2016.08.001 PMid:27503244 PMCid:PMC5690560
22. Pai SI. Adaptive immune resistance in HPV-associated head and neck squamous cell carcinoma. Oncoimmunology. 2013;2(5): e24065. https://doi.org/10.4161/onci.24065 PMid:23762795 PMCid:PMC3667901
23. Seiwert TY, Burtness B, Mehra R, et al. Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase 1b trial. Lancet Oncol. 2016;17(7):956–965. https://doi.org/10.1016/S1470-2045(16)30066-3
24. Chow LQ, Haddad R, Gupta S, et al. Antitumor activity of pembrolizumab in biomarker-unselected patients with recurrent and/or metastatic head and neck squamous cell carcinoma: results from the phase Ib KEYNOTE-012 expansion cohort. J Clin Oncol. 2016;34(32):3838–3845. https://doi.org/10.1200/JCO.2016.68.1478 PMid:27646946

25. Ferris RL, Blumenschein G, Fayette J, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. N Engl J Med. 2016;375(19):1856–1867.https://doi.org/10.1056/NEJMoa1602252 PMid:27718784 PMCid:PMC5564292
26. Ibrahim R, Stewart R, Shalabi A. PD-L1 blockade for cancer treatment: MEDI4736. Semin Oncol. 2015;42(3):474–483. https://doi.org/10.1053/j.seminoncol.2015.02.007 PMid:25965366
27. Bauml J. Preliminary results from KEYNOTE-055: Pembrolizumab after platinum and cetuximab failure in head and neck squamous cell carcinoma (HNSCC). J Clin Oncol. 2016: ASCO meeting abstracts: 34(Suppl): abstract 6011.
28. Cohen RB. Preliminary results for the advanced salivary gland carcinoma cohort of the phase 1b KEYNOTE-028 study of pembrolizumab. J Clin Oncol. 2016; ASCO meeting abstracts: 34(Suppl): abstract 6017.
29. Segal NH. Safety and efficacy of MEDI4736, an anti-PD-L1 antibody, in patients with a squamous cell carcinoma of the head and neck (SCCHN) expansion cohort. J Clin Oncol. 2015: ASCO meeting abstracts: 33(Suppl): abstract 3011.
30. Fury M, Ou SI, Balmanoukian A, et al. Clinical activity and safety of medi4736, an anti-PD-L1 antibody, in patients with head and neck cancer. Ann Oncol. 2014:25(Suppl 4): iv341 https://doi.org/10.1093/annonc/mdu340.3
31. Segal NH. Preliminary data from a multi-arm expansion study of MEDI4736, an anti-PD-L1 antibody. J Clin Oncol. 2014: ASCO meeting abstracts: 32(5s, Suppl); abstract 3002.
32. Jie HB, Srivastava RM, Argiris A, et al. Increased PD-1+ and TIM-3+ TILs during cetuximab therapy inversely correlate with response in head and neck cancer patients. Cancer Immunol Res. 2017;5(5):408–416. https://doi.org/10.1158/2326-6066.CIR-16-0333 PMid:28408386 PMCid:PMC5497750