Literature review

The role of Programmed Death-Ligand 1 expression in nasopharyngeal carcinoma

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ABSTRACT

Background: Nasopharyngeal carcinoma (NPC) is a malignant tumor that arises from the epithelial cell that cover surface of the nasopharynx, which has the highest incidence of all types of head and neck cancer. Cell-mediated immunity plays an important role in the growth and development of NPC. The expressions of Programmed Death-Ligand 1 (PD-L1) of NPC is still being debated and researched. **Objective:** To find out and understand the role of PD-L1 expression in NPC. **Literature review:** PD-L1 is a ligand from Programmed Death-1 (PD-1) receptors that could be expressed by cancer cells. When the PD-1/PD-L1 pathway is active, it promotes survival of cancer cells via anti apoptotic signals and inhibits the activation of signaling pathways, which are critical for survival of T cells. **Conclusion:** Various studies had found an increase of the PD-L1 expression in NPC cancer cells. PD-L1 is also a potentially important tumor immunotherapy target and can be a significant prognostic factor in NPC.

Keywords: nasopharyngeal carcinoma, programmed death-ligand 1, programmed death-1, immunotherapy

ABSTRAK

Latar belakang: *Karsinoma nasofaring (KNF) merupakan suatu tumor ganas epitelial nasofaring yang mempunyai insiden tertinggi di antara kanker kepala dan leher. Imunitas selular mempunyai peran penting terhadap pertumbuhan dan perkembangan KNF. Ekspresi* Programmed Death-Ligand 1 *(PD-L1) pada KNF masih diperdebatkan dan diteliti.* ***Tujuan:*** *Mengetahui dan memahami peran PD-L1 terhadap kejadian KNF.* ***Tinjauan Pustaka:*** *PD-L1 merupakan ligan dari reseptor* Programmed Death-1 *(PD-1) yang dapat diekpresikan oleh sel kanker. Jalur PD-1 / PD-L1 yang teraktivasi akan melindungi sel kanker melalui sinyal anti apoptosis dan menghambat aktivasi jalur-jalur pengiriman sinyal lain yang sangat penting untuk kelangsungan hidup sel T.* ***Kesimpulan:*** *Berbagai penelitian menemukan adanya peningkatan ekspresi PD-L1 pada sel kanker KNF. PD-L1 menjadi suatu target imunoterapi yang sangat penting dalam meningkatkan respon imun terhadap sel kanker dan dapat dijadikan suatu faktor prognosis pada KNF.*

Kata kunci: *karsinoma nasofaring, programmed death-ligand 1, programmed death-1, imunoterapi*

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INTRODUCTION

Nasopharyngeal carcinoma (NPC), it is also called as Cantonese cancer, is a malignancy that is different from other head and neck carcinomas, which is distinct among head and neck cancer in etiology and in racial and geographic distribution. NPC is a squamous epithelial cancer arising from the superior and lateral wall surface of nasopharynx. NPC originates in the epithelium and lacunar columnar epithelium of nasopharyngeal mucosa. The pathogenesis of NPC is closely related to environmental and genetic factors, and Epstein-Barr virus infection. NPC occurs rarely in the Western countries, but is one of the most common malignant tumors of the head and neck in the South China.[1,2]

Most of NPC patient are diagnosed in the advanced stages, often accompanied by lymph nodes metastasis. Therefore, distant metastasis and recurrence remains the obstacle for improving survival rate of NPC patients. Therefore, an effective treatment to improve the survival rate of NPC is in need. Currently, radiotherapy alone or chemo-radiotherapy is used in the treatment of NPC.[2]

Cell-mediated immunity plays an important role in the occurrence and development of the NPC, lots of studies predict important relationship between immune checkpoints, PD-1 or PD-L1 and cancer.[4] Expressions of PD-1/PD-L1 by tumor-infiltrating lymphocytes (TILs) is associated with impaired of effector function (production of cytokine and cytotoxic efficacy against tumor cells cell) and poor outcome in several tumor types. Several studies had shown that the increase of PD-L1 predicts a poor prognosis for NPC, but Lee et al.[5] found that the increase of PD-L1 expression occurred only in 25% (26 out of 104 NPC patients). But their research also showed a positive correlation between PD-L1 expression with progression-free survival (PFS) and a better loco-regional failure-free survival (LRFFS).

Chan et al. as citated by Zheng,[6] reported that overall survival (OS) and progression-free survival (PFS) had no significant correlation with PD-L1 expression in 161 NPC patients.

Recently, the research development on checkpoint blocking antibodies to PD-1 and PD-L1 had revealed a promising cancer treatment.[3] United States Food and Drug Administration (USFDA) had approved the use of Pembrolizumab, an anti PD-1 monoclonal, for the treatment of non-small cell lung cancer. Since then, Pembrolizumab had been tested in several additional tumor types, including NPC.[7] This was a more reason to investigate further the role of PD-L1 expression in NPC.

The pupose of this article is to learn and understand the role of PD-L1expression in NPC.

LITERATURE REVIEW

Cancer immunoediting

Cancer immunoediting is a dynamic interaction process involving between the tumor and the host's immune system divided into three phases: elimination, equilibrium and escape (Figure 1).[8] In the *elimination phase*, the immune system can identify and eliminate tumor cells based on their expression of Tumor-Associated Antigens (TAAs), whereas *equilibrium phase* is characterized by cancer dormancy, as cancer cells are not destroyed, but their outgrowth is restrained by the immune system. Accumulation of genetic mutations and selection of tumor cells that escape immune response lead to immune *escape*; in this phase, tumor cells can suppress, disrupt, or evade immune control.[8,9] There are different cancer infiltrating immune cell subsets including T regulator cell (Treg), Antigen Presenting Cell (APC), Myeloid Derived Suppressor Cancer cells (MDSCs), and effector T cell subsets.[10]

The immune response is triggered when T cells recognize specific TAAs expressed by tumor cells and adequately presented by antigen-presenting cells (APCs), among which dendritic cells (DCs) are the most potent. TAAs are typically the result of nonspecific mutations in the tumor that alter the structure of normal proteins, making them appear foreign to the immune system. Encounter of T cells with APCs generates multiple signals that are required for the activation, proliferation, and differentiation of T cells into highly specific cytotoxic T cells.[9]

Amplitude and quality of a T cell response are regulated by a balance of activating and inhibitory signals. Co-stimulatory or activating receptors include CD28, CD137, CD40, and OX-40, while inhibitor receptor or co-inhibitory include Programmed Death 1 (PD-1) and Cytotoxic T Lymphocyte Antigen 4 (CTLA-4).[9,11] Immune checkpoints represent immunological breaks that switch off stimulatory effects in order to avoid autoimmunity. Keymolecules involved in checkpoint pathways include PD-1 and Programmed Death Ligand 1 (PD-L1) and CTLA-4.[9]

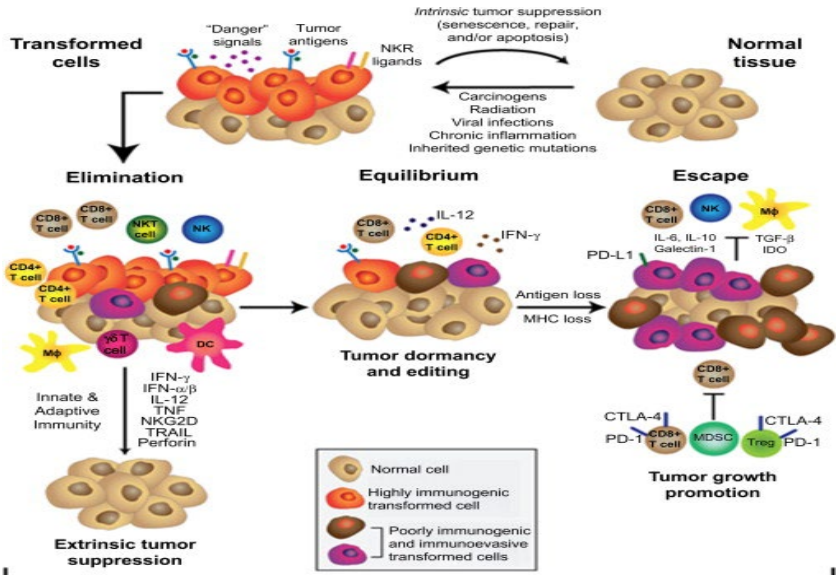

Figure 1. Cancer immunoediting[8]

Programmed death ligand 1 (PD-L1)

Programmed Death 1 (PD-1/ CD279) is a protein on cell surface which has a role of regulating the immune system response towards other human body cells through decreasing the immune system and through triggering self-tolerance by pressuring the activity of T cell. It will prevent the occurrence of autoimmune, and could also inhibit immune system to target cancer cells.[12]

PD-1 is a member of B7-CD28 family, which was expressed by T cell, B cell, monocyte, APC, dendritic cell (DC), and natural killer cell (NK) after being exposed to antigen for quite some time.[14,15] The common γ chain cytokines such as interleukin-2 (IL-2), IL-7, IL-15, and IL-21 can induce PD-1 expression on T cells. PD-1 can also be selectively induced on myeloid DCs by Listeria monocytogenes infection or by Toll-like receptor 2 (TLR2), TLR3, TLR4, or *Nucleotide-binding* ligation and oligomerization domain (NOD) ligation, but is inhibited by IL-4 and TLR9.[13]

PD-1 has a role in preventing autoimmune, through two mechanisms. First, by triggering apoptosis of antigen-specific T cell in the

lymph nodes. Secondly, by decreasing apoptotic of Regulatory T cells (Tregs).[16] In patients with different types of cancer, high levels of PD-1 expression are detected in tumor infiltrating T cells including tumor antigen-specific T cells, presumably due to chronic antigenic stimulation.[10]

PD-1 is presumed to have two ligands, which are PD-L1 (B7-H1) and PD-L2 (B7-DC), each has a different expression profile.[15] PD-L1 is constitutively expressed on T and B cells, DCs, macrophages, mesenchymal stem cells, bone marrow-derived mast cells, and various tumor cells.[13,14] PD-L1 is also very low expressed in non-hematopoietic cells including lung, vascular endothelium, fibroblastic reticular cells, liver non-parenchymal cells, mesenchymal stem cells, pancreatic islets, astrocytes, neurons, and keratinocytes.[14] PD-L2 is expressed limitedly in active dendritic cells, macrophages, bone marrow-derived mast cells, and in more than 50% peritoneal B cells. In the thymus, PD-L1 is expressed mostly in the cortex, while PD-L2 expression is confined in medullary stromal cells.[13] PD-L1 expression in cancer cells will inhibit the antitumor activity through PD-1 involvement in effector T cell.[17] The PD-L2 expression is relatively rare in cancer cells.[10]

The PD signal activation mechanism

Munn,[18] stated that numerous hypothesis mentioned the probable PD-L1 activation location. At first, the traditional model, in which PD-L1 is expressed on the tumor cell itself and directly inhibits killing of the target cell by activated PD-1 effector T cells. But, Tang et al. and Lin et al. as citated by Munn,[18] discovered in their researches that a tumor with low expression of PD-L1 was still responsive to PD-L1 checkpoint blockade, which indicated the hypothesis that PD-L1 only affects tumor cells is irrelevant. The second hypothesis stated that probably PD-L1 was expressed by DC at the first contact with naive tumor specific T cell. PD-L1 will send suppressor signal through unknown mechanism and it will make effector T cell unresponsive.[19] The third hypothesis formulate that PD-L1 will activate Treg cells indirectly through bonding with PD-1 so that Treg cells will enhances their immunosuppressive activity. The activation mechanism of Treg cells in this tumor is still unclear.[15] The fourth hypothesis affirmed that PD-L1 expressed by Antigen Presenting Cells (APC) will bind with PD-1, whereas PD-1 will send cross-inhibit signaling to CD28, to prevent the binding of B7-CD28 which could re-activate exhausted T cell (Figure 2).[18]

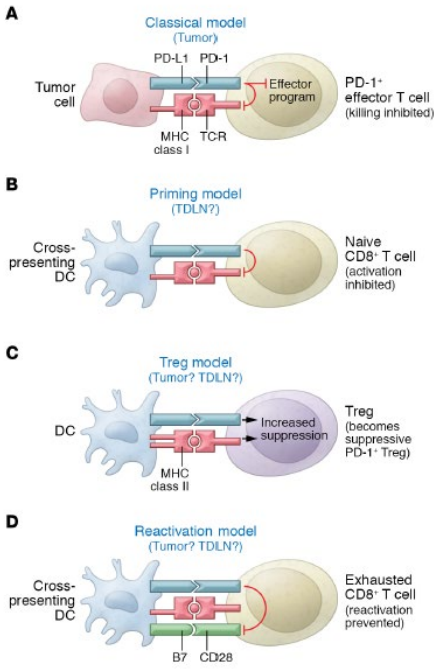

Figure 2. Hypothetical models of probable location of PD-L1 might be active[18]

There are two mechanisms of PD-L1 regulation by tumor cell, which are innate immune resistance and adaptive immune resistance (Figure 3).[11,20] Innate immune resistance happens when the increase of PD-L1 expression in tumor cells are induced by constitutive oncogenic signaling pathway.[13] Prior studies had shown that the oncogenic pathway could upregulate the increase of PD-L1, among others research by Parsa AT

et al. quoted by Fang et al.[22] stated that the loss of Phosphatase and Tensin homolog (PTEN), and the resulting activation of phosphatidylinositol-3-OH kinase (PI-3K) pathway significantly elevates PD-L1expression in glioma. It was also reported that activation from Nucleophosmin (NPM)/ Anaplastic Lymphoma Kinase (ALK) pathway could control PD-L1 expression through Signal Transducer and Activator of Transcription 3 (STAT3). Oncogenic Endothelium Growth Factor Receptor (EGFR) signaling pathway in non-small-cell lung cancer (NSCLC) may trigger PD-L1 expression and hence immune resistance. Adaptive immune resistance happens when tumor using natural physiology in inducing PD-1 ligand which usually occur to protect the tissue from infection-induced immune-mediated damage and antitumor immune response.[18] PD-L1 expression as adaptive immune resistance could be induced by Interferon gamma (IFN-ɣ) which are produced by active T cell.[13]

Activated PD-1/PD-L1 pathway controls the induction and maintenance of immune tolerance within the tumor microenvironment that will increase the survival of cancer cells through anti apoptosis signal and inhibits other pathway activating signals which are very important for the survival, proliferation, cytolytic function and cytokine production by T cells.[13,16] PD-1 engagement will inhibit T cell function and survival directly, by blocking early activation signal that are promoted by CD28, or indirectly by IL-2. CD28 and IL-2 promoted T-cell expansion and survival by stimulating anti-apoptotic, cell cycle, and cytokine genes PD-1. PD-1/PD-L1 are also prevents the induction of survival factor cell Bcl-xL, as well as expression of transcription factor associated with effector cell function, including GATA-3, T-bet and Eomes. PD-1 also alters membrane-proximal signaling events in T cell. PD-1 will inhibit the induction of PI3K activity and downstream activation of Akt. PI3 and Akt activity are key for glucose transport and glycolysis, so PD-1 mediated inhibition of this signaling molecules can hamper cell bioenergetics (Figure 4).[16] The imbalanced activation of T cell signaling pathway will impact tumor tolerance by inhibiting effector T cell and memory T cell and also trigger the differentiation towards exhausted T cell and Treg which are directed to regression and tumor rejection.[13]

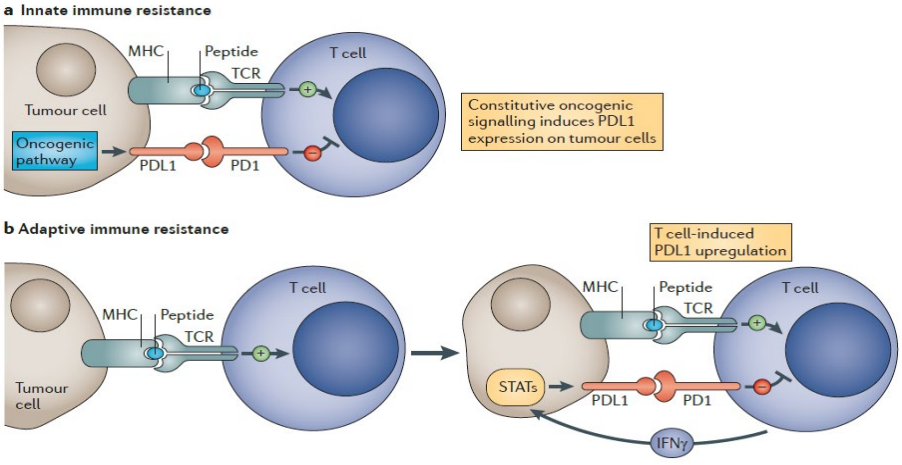

Figure 3. PD-L1 expression mechanism in tumor cell
a. Innate immune resistance, b. Adaptive immune resistance

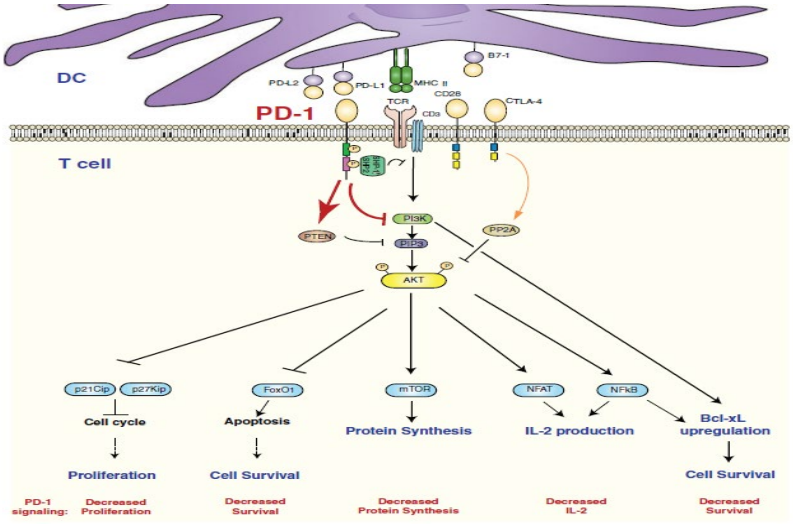

Figure 4. PD-1/PD-L1 may result in signal disturbance of T cell.[16]

The role of PD-L1 expression in naso-pharingeal carcinoma

Several studies have indicated that tumor PD-L1 expression is associated with poor prognosis, however, it remains unclear whether such an association exists in NPC.[21] Currently, the knowledge about the role of PD-1/PD-L1 in NPC prognosis is still limited.

Li et al.[21] stated that the expression of PD-L1 was assessed in tumor specimens from 120 NPC patients (71%) using immunohistochemistry (IHC). PD-L1 expression was found significantly higher in cancer cells than in adjacent non-cancerous tissues. In this study, it was also found that tumor PD-L1 expression was significantly increased in 45 patients out of 85 patients aged older than 45 years old, and in 15 patients out of 23 stage IV. The increased PD-L1 expression had no correlation with gender, smoking history, and NPC histopathological findings. He claimed that the increased tumor PD-L1 expression had a correlation with poor overall survival (OS) and disease-free survival (DFS), so that it could be used as one of NPC prognostic factors.

In Zhang et al.[4] study, tumor PD-L1 expression was detected in 139 NPC patients (95%). Zhang also found that increased PD-L1 expression was associated with poor DFS. He revealed that only 37.4% of PD-1 expression in tumor infiltrating lymphocytes (TIL) and PD-1 had no correlation with life survival rate, therefore it cannot be made as NPC prognostic factor. Contrary to Zhang, a study by Hsu et al.[3] reported that PD-1 expression intratumoral CD8 T cell was significantly higher than the control tissue. This phenomenon was related to poor prognosis of overall survival (OS), progression-free survival (PFS) and locoregional failure-free survival (LRFFS) of NPC patients. Different finding was found by Lee et al.[5] reported an increase of PD-L1 expression occurred only in 25% (26 out of 104 NPC patients), and the result showed a positive correlation between PD-L1 expression and a better LRFFS and PFS. Chan et al. as citated by Zheng et al.[6] reported that the overall survival (OS) and progression-free survival (PFS) had no correlation with PD-L1 expression in 161 NPC patients.

Chen et al. as citated by Zhang[4] reported that PD-L1 expression was a characteristic of malignancy-related to virus and immunodeficiency including NPC. His study showed 89% of EBV-associated NPC cases had an increased PD-L1 expression in cancer cells. Fang et al.[22] reported that Latent

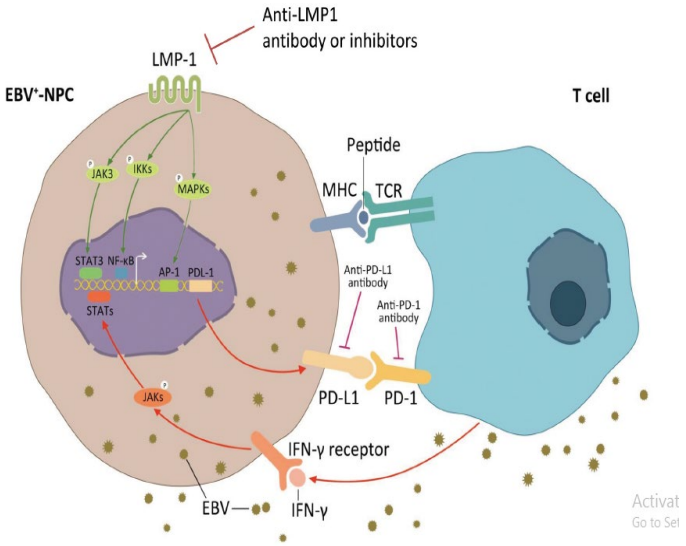

Figure 5. The mechanism of up-regulated PD-L1 expression on EBV positive nasopharyngeal carcinoma cells[22]

Membrane Protein (LMP1) and IFN-γ had induced an increased PD-L1 expression in NPC and related to DFS of NPC patients.

A study by Fang,[22] found that LMP1 as the initiator of oncogenic pathway in EBV-associated NPC, also participated in PD-L1 regulation. LMP1 remarkably increased the activity of STAT3, NF-κB, and Activator Protein 1(AP-1), altering the expression of critical proteins involved in the proliferation, anti-apoptosis, and invasion of cells and ultimately leading to tumorigenesis. Thus, the up-regulation of PD-L1 mediated by LMP1 was associated with the activation of STAT3, AP-1, and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB).

Green et al. as citated by Zhang,[4] also demonstrated that the expression of EBV-encoded LMP1 promotes both AP-1 signaling and JAK-STAT signaling to up-regulate PD-L1. A study by Fang et al.[22] also mentioned that PD-L1 was found to be regulated by both LMP1 oncogenic pathway and inflammatory signals such as IFN-γ by initiating the synthesis of interferon regulatory factor-1 (IRF-1) a transcription factor which has two binding sites on PD-L1 promoter, through Janus Kinase (JAK)/STAT pathways. Therefore, PD-L1 may represent LMP1 mediated tumorigenesis, immune escape as well as host's antitumor immune response. The different clinical significance of PD-L1 may be determined by its predominant regulator mechanism (oncogenic pathway mediated innate immune resistance or adaptive immune resistance during antitumor response). Thus, there were two different mechanisms yet synergic in EBV-infected NPC (Figure 5).[22] Conclusively, EBV-infected NPC had higher level of PD-L1 expression at least through LMP1 mediated oncogenic pathways and immune modulation through the excretion of IFN-γ.

Larbcharoensub et al.[7] also performed a research in NPC endemic area towards 114 NPC patients, where 110 (96%) were EBV positive and 4 patients were EBV negative. PD-L1 expression was found in 78 patients with positive EBV and 3 patients with negative EBV. Ooft et al. as quoted by Larbcharoensub,[7] had a different result from his study in non-endemic area, it was found 67% EBV positive out of 96 NPC patients and it had found no correlation between PD-L1, PD-1 expression and EBV status.

Anti PD-1 and anti PD-L1 as Immunotherapy

PD-1 and PD-L1 have been reported to be important tumor immunotherapy targets. Blocking the PD-1/PD-L1 signaling pathway represents a promising immunotherapeutic strategy to enhance the ability of the immune system to target cancer cells.[21,23]

According to a study reported in 2015 European Cancer Congress, more than a fifth of patients with previously treated metastatic NPC showed a measurable response when treated with the immune checkpoint inhibitor, pembrolizumab, and two-thirds of 44 patients in the study, had some degree of reduction in target lesion size after being treated with pembrolizumab. Pembrolizumab is a highly selective humanized monoclonal IgG4-kappa isotype antibody that is designed to block the negative immune regulatory signaling of PD-1 receptor expressed by T cells. Forty one out of 44 patients screened for the study had tumors that tested positive for PD-L1 expression.[23.]

Nivolumab is an IgG4 monoclonal antibody that targets to PD-1. Nivolumab will act by blocking the interaction of T cell with PD-L1 so that T cell will release its antitumor response.[2] Clinical trial phase II on Nivolumab efficacy in recurrent and metastasis NPC is being researched. Economopoulou,[9] reported a clinical trial to investigate the efficacy of Durvalumab, an anti-PD-L1 in head and neck cancer patients, where overall response rate (ORR) was 12%, being twice as high in patients with PD-L1 expressing tumors.

PD-1/PD-L1 bond has a role in immune checkpoint in some cancers including NPC. Several studies had shown that PD-L1 expression could be a significant prognostic factor for NPC. PD-L1 could be one of very important immunotherapy targets. Blocking PD1/PD-L1 pathways could be a promising immunotherapy strategy to increase immune response towards targeting cancer cells.

Tumor PD-L1 expression was found to be a significant prognostic factor in NPC, and high PD-L1 expression may be of prognostic value for recurrence and metastasis following conventional treatments.

REFERENCE

1. Tulalamba W, Janvilisri T. Nasopharyngeal carcinoma signaling pathway: An update on molecular biomarkers. Int J Cell Biol. 2012; 212: 1-10.
2. Liu G, Sido JM, Wang M, Shen E. PD-1/PD-L1 blockade in the treatment of nasopharyngeal carcinoma. J Nasopharyng Carcinoma. 2017; 4(2): 10-13.
3. Hsu M-C, Hsiao J-R, Chang K-C,Wu Y-H, Su I-J, Jin Y-T. et al. Increase of programmed death-1-expressing intratumoral CD8 T cells predicts as poor prognosis for nasopharyngeal carcinoma. Mod Pathol. 2010; 23(10): 1393-403.
4. Zhang J, Fang W, Qin T, Yang Y, Hong S, Liang W, et al. Co-expression of PD-1 and PD-L1 predicts poor outcome in nasopharyngeal carcinoma. Med.Oncol. 2015; 32(86): 1-6.
5. Lee VHF, Lo AWI, Leung C-Y, Shek W-H, Kwong DLW, Lam K-O, et al. Correlation of PD-L1 expression of tumor cells with survival outcomes after radical intensity-modulated radiation therapy for non-metastatic nasopharyngeal carcinoma. PLos One 2016; 11(6): 1-16.
6. Zheng L, Cao C, Cheng G, Hu Q, Chen X. Cytomembranic PD-L1 expression in locoregionally advanced nasopharyngeal carcinoma. Onco Targets Ther. 2017; 10: 5483-7.
7. Larbcharoensub N, Mahaprom K, Jiarpinitnum C, Trachu N, Tubthong N, Pattaranutaporn P, et al. Characterization

of PD-L1 and PD-1 expression and CD8 + tumor-infiltrating lymphocyte in Eipstein-Barr virus-associated nasopharyngeal carcinoma. Am J Clin Oncol. 2018; 00(00): 1-7.

8. Schreiber RD, Old LJ, Smyth MJ. Cancer immunoediting: Integrating immunity's roles in cancer suppression and promotion. Science. 2011; 331: 1565-70.
9. Economopoulou P, Kotsantis I, Psyrri A. Checkpoint inhibitors in head and neck cancer: Rationale, clinical activity, and potential biomarkers. Curr Treat Options Oncol. 2016; 17: 40-52.
10. Zou W, Wolchok JD, Chen L. PD-L1 (B7-H1) and PD-1 pathway blockade for cancer therapy: Mechanisms, response biomarkers and combinations. Sci Transl Med. 2016; 8(328): 1-34.
11. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Publ Gr. 2012; 12(4): 252-64.
12. Syn NL, Teng MWL, Mok TSK, Soo RA. De-novo and acquired resistance to immune checkpoint targeting. Lancet Oncol. 2017; 18(12): e731-e741.
13. Bardhan K, Anagnostou T, Boussiotis VA. The PD1 : PD-L1/2 pathway from discovery to clinical implementation. Frontiers in Immun. 2016; 7(article 550): 1-17.
14. 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(7): 627-32.
15. McDermott DF, Atkins MB. PD-1 as a potential target in cancer therapy. Cancer Med. 2013; 2(5): 662-73.
16. Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. Immunological Reviews. 2010; 236: 219-42.
17. Iwai Y, Ishida M, Tanaka Y, Okazaki T, Honjo T, Minato N. Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. Proc Natl Acad Sci. 2002; 99(19): 12293-7.
18. Munn DH. The host protecting the tumor from the host - targeting PD L1 expressed by host cells. J Clin Invest. 2018; 128(2): 570-2.
19. Schietinger A, Philip M, Krisnawan VE, Schell TD, Garbi N, Greenberg PD. Tumor-specific T cell dysfunction is a dynamic antigen-driven differentiation program initiated early during tumorigenesis. Immunity. 2016; 45: 1-13.
20. Zhu Q, Cai M-Y, Chen C-L, Hu H, Lin H-X, Li M, et al. Tumor cells PD-L1 expression as a favorable prognosis factor in nasopharyngeal carcinoma patients with pre-existing intratumor-infiltrating lymphocytes. Oncoimmunology. 2017; 6(5): 1-10.
21. Li Y-F, Ding J-W, Liao L-M, Zhang Z-L, Liao S-S, Wu Y, et al. Expression of programmed death ligand-1 predicts poor outcome in nasopharyngeal carcinoma. Mol Clin Oncol. 2017: 7: 378-82.
22. Fang W, Zhang J, Hong S, Zhan J, Chen N, Qin T, et al. EBV-driven LMP1 and IFN-Y up-regulate PD-L1 in nasopharyngeal carcinoma: Implications for oncotargeted therapy. Oncotarget. 2014; 5(23): 12189-202.
23. Jain A, Chia WK, Toh HC. Immunotherapy for nasopharyngeal cancer a review. Chinese Clin Oncol. 2016; 5(2): 1-10.