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Review Article

Current progress in immunotherapy of nasopharyngeal carcinoma

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Abstract: Nasopharyngeal carcinoma is one of the highly prevalent malignant tumors and the most common type of ear, nose, and throat cancer. The exact cause of various cancer is still unclear; however, a diversity of risk factors for the development of nasopharyngeal cancer have been reported, including genetic changes, viral infection, and environmental factors, among which, Epstein-Barr-Virus plays an important role in the oncogenesis of nasopharyngeal carcinoma. Nasopharyngeal carcinoma is highly malignant and prone to metastasis, while most of them are moderately sensitive to radiation therapy; hence, radiation therapy combined with chemotherapy is currently the standard treatment for nasopharyngeal carcinoma. However, this combination therapy tends to cause more complications and tumor recurrence, which not only increases the financial burden to patients, but also adversely affects their physical and mental health. In recent years, immunotherapy has been emerging as a new strategy to treat malignant tumors including nasopharyngeal carcinoma and has achieved favorable results. The immunotherapy for nasopharyngeal carcinoma can control or even eliminate tumor cells by inducing and enhancing the collective immune function. Currently, the main immunotherapeutic approaches for nasopharyngeal carcinoma include successive immune cell therapy, immune checkpoint inhibitors, and tumor vaccines. However, the efficacy of immunotherapy in nasopharyngeal carcinoma still require improvement. In this review, we summarized the current progress and efficacy of immunotherapy, particularly by targeting EVB, in the treatment of nasopharyngeal carcinoma.

Keywords: Nasopharyngeal carcinoma, immunotherapy, CAR-T, NK, ICIs

Introduction

Nasopharyngeal cancer occurs in the nasopharynx behind the nose and above the back of throat. It is one of the highly prevalent malignant tumors and the most common type of ear, nose, and throat cancer [1-3]. The specific pathogenesis of this cancer is still unclear but multiple risk factors have been reported, including genetic changes, viral infection, and environmental factors [4-7]. The main clinical manifestations of nasopharyngeal carcinoma include snotty blood or nasal bleeding and headache. Advanced nasopharyngeal carcinoma can lead to cachexia or even death.

The traditional treatment methods for nasopharyngeal cancer include surgery and radiotherapy, but due to the limitation of anatomical location, surgery is difficult to implement. Since nasopharyngeal cancer is more sensitive to radiation therapy, radiation therapy combined with chemotherapy is currently the preferred treatment option for nasopharyngeal cancer [8-10]. Although the efficacy of the combination treatment regimen was better than monotherapy in overall survival rate and recurrence survival rate, the adverse side effects from the combination treatment therapy were much severe, especially the acute adverse effects were significantly increased. In addition, the combination treatment therapy does not significantly reduce the incidence of distant metastasis. For example, Sun et al. retrospectively analyzed the clinical data of 123 patients with nasopharyngeal carcinoma and found that the prognosis of patients in the concurrent radiotherapy group was not significantly better than that of the

radiotherapy alone group, while the incidence of neutropenia, hemoglobin reduction, and radiation mucosal reaction was significantly increased [11].

Epstein-Barr-Virus (EBV) plays an important role in the development of nasopharyngeal carcinoma [12-14]. Almost all nasopharyngeal carcinoma subtypes, including basal-like, keratinized, and non-keratinized types, are associated with EBV [15, 16]. Depending on the cell type, EBV-infected cells undergo different latent cycles and express different viral proteins. Because viral proteins are almost exclusively expressed in malignant cells, EBVs present as ideal targets for immunotherapy to treat nasopharyngeal carcinoma [13, 17-19]. Since the blockade of CTLA-4 and PD-1 as well as CAR T-cell therapies have produced significant therapeutic responses in cancer patients, immunotherapy has revolutionized the current cancer treatment regimens. Moreover, immunotherapy can not only persistently remove the small amount of disseminated tumor cells but also improve the body immune function damaged by radiotherapy and chemotherapy, demonstrating the complementary advantages in combination with other conventional therapies [13, 20, 21].

Adoptive cell transfer therapy

Adoptive cell transfer therapy, also known as cellular immunotherapy, involves several different immunotherapy methods. Basically, in this type of therapy, the biologically active immune effector cells from patients are isolated and cultured in vitro to expand their number by thousands of times or are manipulated to enhance their cytotoxic function or to induce them to differentiate into immune effector cells with anti-tumor activity. Then, these cells are infused them back into patients to eliminate pathogens, cancer cells, and the mutated cells in blood and tissues to exert their anti-tumor effects [22].

Tumor infiltrating lymphocyte (TIL) therapy

In the early stages of cancer, the immune system plays defensive roles by attacking the tumor via mobilizing special immune cells of lymphocytes. These lymphocytes, also known as TILs, discovered by Rosenberg et al., can recognize and attack tumor and penetrate the tumor mass [23]. However, the tumor microenvironment and the expression of PD-1 can inhibit the activity of TILs, as a result, TILs are unable to effectively kill the tumor cells in tumor tissue. Therefore, growing efforts have been made to enrich certain type of lymphocytes in tumor tissues by in vitro culture methods, which are then infused back to patients to play an anti-tumor role. Moreover, combining this enrichment with PD-1 can further improve the therapeutic efficacy [24]. In a phase I clinical trial conducted by Li et al. [25], 20 patients with nasopharyngeal carcinoma were infused with in vitro-expanded autologous TILs after synchronous chemoradiotherapy, and 19 out of 20 patients exhibited complete remission with only mild adverse effects. In addition, after infusion of TILs, increased expressions of LMP-1, LMP-2 and EBNA-1-specific T cells could be detected in the blood of 65% of patients, while plasma EBV load was significantly reduced in 85% of patients. Hence, the findings from this clinical trial confirmed that adoptive cell transfer therapy with TILs produced sustained anti-tumor activity and anti-EBV immune response in patients with nasopharyngeal carcinoma.

Engineered T-cell receptor (TCR) therapy

Nevertheless, not all patients have T cells that can recognize the tumor. For these patients, an engineered TCR therapy can be applied. This approach starts with obtaining T cells from the patient first. Then, in vitro manipulation of these cells will activate and expand these anti-tumor T cells while equipping them with new T cell receptors that enable them to recognize specific cancer antigens. TCR-based adoptive therapy allows the modification of the optimal target for each patient's tumor and different types of T cells. This personalized therapy offers patients higher probability of remission. At present, the application of TCR-T in patients with nasopharyngeal carcinoma is still under clinical trials, and the specific treatment plan and efficacy need to be investigated in subsequent studies [26].

Chimeric antigen receptor (CAR) T-cell therapy

The basic principle of CAR T-cell therapy is to genetically modify the patient's own T-lymphocytes, which are then processed and cultivated to meet the requirements for therapeutic purposes before these cells are infused back to

the patients [27]. These modified T-lymphocytes can specifically recognize tumor cells that express antigenic targets, thereby activating T-lymphocytes to effectively kill tumor cells.

One example of this approach was reported by Zhao et al. [12], in which using LMP2A as the target, the authors successfully prepared LMP2A CAR T cells and confirmed by in vitro and in vivo experiments that compared with CD19 CAR T cells and T cells, LMP2A CAR T cells had a stronger cytotoxic effect on nasopharyngeal carcinoma cells, particularly, a significant targeting toxicity on LMP2A-positive nasopharyngeal carcinoma cells.

Adoptive immunotherapy with EBV-specific cytotoxic T lymphocytes (EBV-CTLs) has been proven clinically effective, but it has never been evaluated in combination with chemotherapy in the first-line treatment. One follow-up study evaluated the efficacy of adding 5-fluorouracil (5-FU) as maintenance chemotherapy to the induction chemotherapy with Paclitaxel-Gemcitabine-Carboplatin (PGC) in a cohort of nasopharyngeal carcinoma patients. While this regimen was effective, it was also highly toxic, with almost 80% of patients experiencing grade 3 to 4 neutropenia [28]. However, when using the combination of EBV-CTLs, the chemotherapy efficacy is improved with tolerable side effects. Chia et al. found that the median survival was increased to 29.9 months in patients with recurrent and/or metastatic nasopharyngeal carcinoma receiving GC-CTL regimen (gemcitabine and carboplatin (GC) followed by up to six doses of EBV-CTL), while it was only 17.7 months in those receiving PGC chemotherapy and 21.4 months in those receiving PGC-5-FU chemotherapy [22]. The two-year overall survival rates for patients receiving GC-CTL, PGC-5-FU, and PGC regimens were 62.9%, 42.9% and 29.5%, respectively, and the three-year overall survival rates were 37.1%, 25% and 16.4%, respectively, demonstrating the benefit of using CTL combination therapy. Their study also found a positive correlation between LMP2-specific T cells and survival.

Natural killer (NK) cell therapy

NK cells present in the human bloodstream as the first responders. They directly recognize the abnormal cells and release cytotoxic granule contents, e.g., perforin and granzyme, which are recognized by target cells before the T cells are deployed, triggering the self-destruction of cancer cells. They can also eliminate circulating cancer stem cells to prevent metastasis. Growing studies are exploring the potential of integrating these NK cells with cancer-targeting CARs [29-31]. As an example, Mei et al. studied the cytotoxic effect of the modified NK cells on human nasopharyngeal carcinoma cells and found that the modified NK cells could eliminate the nasopharyngeal carcinoma cells, and IL-2 and IL-15 treatments could up-regulate the expression of NKG2D in the modified NK cells and restore their cytotoxicity to CNE2 cells [30].

Immune checkpoint inhibitors (ICIs)

It has been well known that ICIs block the function of immune checkpoint proteins to enhance the immune response or to relieve immune suppression. Programmed death 1 (PD-1, also known as CD279) belongs to the immunoglobulin superfamily expressed on the surface of T cells and Pro-B cells and inhibits T-cell activation through binding to its ligands PD-L1 or PD-L2, whereas PD-1 pathway inhibitors, e.g., PD-L1 and PD-L2 inhibitors, inhibit PD-1 binding to ligands, thereby enhancing T-cell activity, which are particularly effective in the late phase of the immune response [32].

A study on the regulatory mechanisms of PD-L1 in EBV-positive nasopharyngeal carcinoma showed that interferon (IFN)-γ, IFN-β and EBV latent membrane protein 1 (LMP1) induced cellular PD-L1 expression [33]. In addition, PD-1 inhibitory monoclonal antibodies can enhance the cytotoxic effects of NK cells in nasopharyngeal carcinoma by mediating the expression of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), leading to antitumor effects [34]. A study by Hsu et al. revealed that anti-PD-1 antibody Pembrolizumab showed favorable antitumor activity and a manageable safety profile in patients with recurrent or metastatic nasopharyngeal carcinoma [35]. In addition, Ma et al. found that anti-PD-1 antibody Nivolumab had better anti-tumor activity without unexpected toxicity, resulting a better 1-year overall survival of patients than that previously reported from a similar population [36]. Furthermore, a study by Lee et al. showed that PD-L1 was substantially expressed in nasopha-

ryngeal carcinoma cells, and high PD-L1 expression (IHC2+) was associated with better local progression-free survival and PFS [37]. However, in contrast to this study, a study by Chan et al. showed that no prognostic value of PD-L1 expression levels was observed in patients with nasopharyngeal carcinoma [38]. The possible explanation for these different results could be different PD-L1 antibodies or scoring algorithms used in those studies and different baseline characteristics of enrolled patients.

Tumor vaccine therapy

Tumor vaccine therapy is tumor-specific active immunotherapy which includes tumor cell vaccine, tumor nucleic acid vaccine, tumor peptide vaccine, anti-idiotype antibody tumor vaccine, tumor genetic engineering vaccine, and dendritic cell vaccine. Anti-idiotype antibody (Anti-ID Abs) is a specific antibody against the antigenic determinant (idiotype) in the variable region of an antibody, which can be used as an important reference for immunogenicity analysis [39, 40]. There has been some progress in tumor vaccine therapy, mostly in basic research and clinical trial stage. The Newcastle disease virus (NDV)-modified autologous tumor cell vaccine fNDV ATV developed by the German Cancer Center has achieved promising results in a multicenter, multitumor clinical trial. NDV is an avian paramyxovirus with a multi-tissue affinity for immunostimulatory characteristics. More importantly, NDV can replicate selectively in the cytoplasm of tumor cells independent of host cell proliferation, and it is a non-pathogenic virus that can effectively and safely infect tumor cells. Currently, fNDV.ATV is usually prepared in a PBS environment, where every 10 million cells are warmed with 32HU NDV ulster for one hour, and the cellular vaccine is inactivated by 200 Gy r-radiation or MMC treatment before it can be used for intradermal injection in patients with nasopharyngeal carcinoma. T cells are accumulated locally via NDV-induced chemokines, and some T cells express T cell receptors (TCRs) which interact with TAAs peptides present as MHC-TAAs complexes on the surface of tumor cells to mediate first signal generation. Tumor cells that lack co-stimulatory molecules are not able to transmit additional co-stimulatory signals and therefore fail to activate tumor-specific T lymphocytes [41-43]. Yue et al. prepared a live vaccine with the NDV La Sota strain and inoculated the vaccine in rabbits by the spray aspiration. After being proved to be safe and effective, the vaccine was then inoculated by the same way in nasopharyngeal carcinoma patients who have undergone radiation therapy. The results showed that the 3-year recurrence rate of the treated group was significantly lower than that of the control group (4.00% vs. 26.0%).

Dendritic cell vaccine is another antitumor immunotherapy that has been intensively studied in recent years and has shown promising therapeutic effects in multiple preliminary clinical trials of various tumors. Lin et al. loaded dendritic cells of nasopharyngeal carcinoma patients with a restricted epitope polypeptide of latent membrane antigen 2 (LMP2) and then infused the cells back into the patient [44]. Among the 16 patients tested, 9 patients showed strong cytotoxic T lymphocytes (CTLs) activity against LMP2 peptide. Also, the tumor volume decreased in 2 patients 3 months after treatment. In vitro experiments showed that CTLs activated by DC-loaded LMP2A1 1 peptide binding epitopes could effectively inhibit the growth of poorly differentiated nasopharyngeal carcinoma cell lines.

In another study by Wang et al., the bispecific and multivalent antibodies with more antigen binding would improve the immunogenicity of the vaccine. The bispecific anti-idiotype antibody vaccine G22-I50, produced through the genetic engineering approach to enhance its immunogenicity, induced a strong humoral and cell-mediated immune response, suggesting its potential application in the prevention and treatment of nasopharyngeal carcinoma [45]. The ability of bispecific antibodies to improve vaccine immunogenicity is because they can enhance the killing effect on target cells by recognizing and binding two different antigens to attach immune cells, viral molecules, and other factors to tumor cells. They can also bind different antigens on the same tumor cells to enhance their binding specificity, thus reducing side effects such as off-target toxicity. On the other hand, anti-idiotype is a strong stimulator of CD4 response. Chen Luo et al. found that three injections of PCDNA3.1-G22, an anti-idiotype antibody, induced CD4+ T helper cell activity and CD8+ cytolytic activity, thereby protect-

Table 1. Clinical studies of immunotherapy in patients with nasopharyngeal carcinoma

Authors	Immunotherapy regimen	Therapeutic effect	Safety
Li et al. [14]	Treatment with CCRT and ACT using expanded auto-TIL	The short-term CR was 69.5% in the 23 enrolled patients at the completion of CCRT and 83% (19/23, DFS >9) at 3 months after ACT when using auto-TILs.	18 exhibited DFS for longer than 12 months. Only one patient presented a residual neck lymph node 3 month after ACT.
Chia et al. [13]	GC-CTL regimen/PGC-5-FU and PGC regimens*	The median survival was 29.9 months in patients receiving GC-CTL regimen, 17.7 months in those receiving PGC chemotherapy, and 21.4 months in those receiving PGC-5-FU chemotherapy.	Our results include additional follow-up data collected in 2007 that contained 11 more deaths as compared with 15 deaths reported in the original publication.
Hsu et al. [18]	Nivolumab	Partial response and stable disease were observed in 7 and 14 patients, respectively, for an ORR of 25.9% (95% CI, 11.1 to 46.3) over a median follow-up of 20 months.	Patients had better activity, no unexpected toxicity, and better 1-year overall survival than previous data from a similar population.
Ma et al. [19]	Nivolumab	The overall ORR was 20.5%. The 1-year overall survival rate was 59% (95% CI, 44.3% to 78.5%) and 1-year progression-free survival (PFS) rate was 19.3% (95% CI, 10.1% to 37.2%).	There was no association between survival and PD-L1 expression or plasma Epstein-Barr virus DNA clearance. There was no unexpected toxicity to nivolumab.
Taylor et al. [24]	MVA recombinant cowpox vaccine	Vaccination increased EBNA-1 (EBV nuclear antigen 1) in 7 of 14 (50%) patients and increased LMP2 reactivity in 6 of 14 (43%) patients by more than 2-fold, and also increased the mass and frequency of epitope-specific CD4+ and CD8+ T cells to 120% and 420%.	EBV strain variation and HLA diversity did not alter the immunogenicity of the vaccine.

* GC-CTL: Gemcitabine and Carboplatin (GC) followed by EBV-specific Cytotoxic T Lymphocytes; PGC-5-FU: Paclitaxel-Gemcitabine-Carboplatin (PGC)-5-Fluorouracil (5-FU).

ing mice against tumor cell challenge. This might explain why anti-idiotypic antibodies could elicit strong immune responses [40]. In addition, Taylor et al. conducted a dose-escalating phase IA trial in British to determine whether the MVA recombinant cowpox vaccine was broadly applicable, as it was constructed from a Chinese-derived EBV strain [46]. Their results revealed that vaccination increased EBNA-1 (EBV nuclear antigen 1) in 7 of 14 (50%) patients and increased LMP2 reactivity in 6 of 14 (43%) patients by more than 2-fold. The vaccination also increased the proportion of epitope specific CD4+ and CD8+ T cells to 120% and 420%, respectively. Most importantly, EBV strain variation and HLA diversity did not alter the immunogenicity of the vaccine, demonstrating the feasibility of using this approach in Southeast Asia, where nasopharyngeal carcinoma has the highest incidence rate.

Conclusion and prospective

Currently, immunotherapy has been widely used in the treatment of various tumors, including nasopharyngeal carcinoma (**Table 1**), and has achieved promising therapeutic effect in improving the survival and the quality of life of cancer patients [47, 48]. However, immunotherapy still has some limitations. The efficacy of immune monotherapy is relatively low, which needs to be combined with chemotherapy and radiotherapy. In addition, drug resistance is the major challenge when using immune checkpoint inhibitors, as studies have shown that resistance is observed in up to approximately 60% of patients receiving anti-PD-1 therapy [49-51].

Therefore, overcoming the acquired resistance against immune checkpoint inhibitors is an urgent unmet medical need. Furthermore, the safety of immunotherapy is also a concern. Currently, there is no definitive standard for assessing the safety of immunotherapy, which needs to be addressed.

Disclosure of conflict of interest

None.

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References

[1] Yang KY, Wei YC and Yang QY. Research progress in immunotherapy of nasopharyngeal carcinoma. Practical Oncology Journal 2021; 35: 542-546.

[2] Dai D and Hao JQ. Research progress on immunotherapy of nasopharyngeal carcinoma. Xiandai Zhongliu Yixue 2019; 27: 4308-4311.

[3] Liao ZY, Wu B and Yang KY. Current treatment of juvenile nasopharyngeal carcinoma. Zhonghua Fangshe Yixue Yu Fanghu Zazhi 2021; 41: 390-395.

[4] Huang FM. Research advances in T lymphocyte-associated tumor immunotherapy. Zhongguo Yaofang 2019; 288.

[5] Yang BQ. Status and progress of treatment for locally advanced nasopharyngeal carcinoma. Xiandai Zhongliu Yixue 2021; 29: 337-341.

[6] Yang BQ and Wang RS. Current status of locally advanced nasopharyngeal carcinoma. Neike 2018; 13: 613-615.

[7] Jain A, Chia WK and Toh HC. Immunotherapy for nasopharyngeal cancer-a review. Chin Clin Oncol 2016; 5: 22.

[8] Ni MS and Ying HM. Current status and prospects of treatment of newly-diagnosed nasopharyngeal carcinoma with distant metastasis. Zhonghua Fangshe Yixue Yu Fanghu Zazhi 2021; 30: 979-983.

[9] Raab-Traub N. Nasopharyngeal carcinoma: an evolving role for the Epstein-Barr virus. Curr Top Microbiol Immunol 2015; 390: 339-363.

[10] Xiang ZF, Hu DF, Xiong HC, Li MY, Zhang ZC, Shen ED, Li WZ and Xiang YQ. Benefit of chemotherapy in stage III nasopharyngeal carcinoma: analysis of the surveillance, epidemiology, and end results database. Oral Oncol 2021; 117: 105284.

[11] Sun XM, Chen CY, Han F and Lu TX. Comparison of concurrent chemoradiation and chemotherapy for stage II nasopharyngeal carcinoma based on IMRT with long-term efficacy of radiotherapy alone. Zhonghua Fangshe Yixue Yu Fanghu Zazhi 2017; 26: 376-379.

[12] Zhao LR, Luo BT and Chen XY. Research advances in the latent membrane protein 2A encoded by EBV in nasopharyngeal carcinoma. Shandong Yiyao 2013; 53: 102-104.

[13] Zhang N. Effects of EB virus and host immune in the pathogenesis of nasopharyngeal carcinoma and the progress of relative immune therapy. Linchuang Zhongliuxue Zazhi 2017; 22: 184-188.

[14] Pathmanathan R, Prasad U, Sadler R, Flynn K and Raab-Traub N. Clonal proliferations of cells infected with Epstein-Barr virus in preinvasive lesions related to nasopharyngeal carcinoma. N Engl J Med 1995; 333: 693-698.

[15] Zhang B, Miao T, Shen X, Bao L, Zhang C, Yan C, Wei W, Chen J, Xiao L, Sun C, Du J and Li Y. EB virus-induced ATR activation accelerates nasopharyngeal carcinoma growth via M2-type macrophages polarization. Cell Death Dis 2020; 11: 742.
[16] Trumper PA, Epstein MA, Giovanella BC and Finerty S. Isolation of infectious EB virus from the epithelial tumour cells of nasopharyngeal carcinoma. Int J Cancer 1977; 20: 655-662.
[17] Yang ZH, Dai Q, Gu YJ, Guo QX and Gong L. Cytokine and chemokine modification by Toll-like receptor polymorphisms is associated with nasopharyngeal carcinoma. Cancer Sci 2012; 103: 653-658.
[18] Severa M, Giacomini E, Gafa V, Anastasiadou E, Rizzo F, Corazzari M, Romagnoli A, Trivedi P, Fimia GM and Coccia EM. EBV stimulates TLR- and autophagy-dependent pathways and impairs maturation in plasmacytoid dendritic cells: implications for viral immune escape. Eur J Immunol 2013; 43: 147-158.
[19] Shen Y, Zhang S, Sun R, Wu T and Qian J. Understanding the interplay between host immunity and Epstein-Barr virus in NPC patients. Emerg Microbes Infect 2015; 4: e20.
[20] Xu TT, Xing X, Guan XY, Wang XS and Hu SC. Correlation between PD-L1 expression and prognosis in Epstein-Barr virus-associated nasopharyngeal carcinoma. Zhongliuxue Zazhi 2020; 26: 849-855.
[21] Lyford-Pike S, Peng S, Young GD, Taube JM, Westra WH, Akpeng B, Bruno TC, Richmon JD, Wang H, Bishop JA, Chen L, Drake CG, Topalian SL, Pardoll DM and Pai SI. 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: 1733-1741.
[22] Chia WK, Teo M, Wang WW, Lee B, Ang SF, Tai WM, Chee CL, Ng J, Kan R, Lim WT, Tan SH, Ong WS, Cheung YB, Tan EH, Connolly JE, Gottschalk S and Toh HC. Adoptive T-cell transfer and chemotherapy in the first-line treatment of metastatic and/or locally recurrent nasopharyngeal carcinoma. Mol Ther 2014; 22: 132-139.
[23] Rosenberg SA, Packard BS, Aebersold PM, Solomon D, Topalian SL, Toy ST, Simon P, Lotze MT, Yang JC, Seipp CA, et al. Use of tumor-infiltrating lymphocytes and interleukin-2 in the immunotherapy of patients with metastatic melanoma. A preliminary report. N Engl J Med 1988; 319: 1676-80.
[24] Donia M, Kjeldsen JW, Andersen R, Westergaard MCW, Bianchi V, Legut M, Attaf M, Szomolay B, Ott S, Dolton G, Lyngaa R, Hadrup SR, Sewell AK and Svane IM. PD-1(+) polyfunctional T cells dominate the periphery after tumor-infiltrating lymphocyte therapy for cancer. Clin Cancer Res 2017; 23: 5779-5788.
[25] Li J, Chen QY, He J, Li ZL, Tang XF, Chen SP, Xie CM, Li YQ, Huang LX, Ye SB, Ke M, Tang LQ, Liu H, Zhang L, Guo SS, Xia JC, Zhang XS, Zheng LM, Guo X, Qian CN, Mai HQ and Zeng YX. Phase I trial of adoptively transferred tumor-infiltrating lymphocyte immunotherapy following concurrent chemoradiotherapy in patients with locoregionally advanced nasopharyngeal carcinoma. Oncoimmunology 2015; 4: e976507.
[26] Lamers C, van Brakel M, Berrevoets C, Joode K, van der Veldt A, Sleijfer S and Debets R. Adoptive therapy with TCR gene-engineered T cells to treat patients with MAGE-C2-positive melanoma and head and neck cancer. Cytotherapy 2020; 22: S128.
[27] Jogalekar MP, Rajendran RL, Khan F, Dmello C, Gangadaran P and Ahn BC. CAR T-cell-based gene therapy for cancers: new perspectives, challenges, and clinical developments. Front Immunol 2022; 13: 925985.
[28] Leong SS, Wee J, Rajan S, Toh CK, Lim WT, Hee SW, Tay MH, Poon D and Tan EH. Triplet combination of gemcitabine, paclitaxel, and carboplatin followed by maintenance 5-fluorouracil and folinic acid in patients with metastatic nasopharyngeal carcinoma. Cancer 2008; 113: 1332-1337.
[29] Liou AK, Soon G, Tan L, Peng Y, Cher BM, Goh BC, Wang S and Lim CM. Elevated IL18 levels in Nasopharyngeal carcinoma induced PD-1 expression on NK cells in TILS leading to poor prognosis. Oral Oncol 2020; 104: 104616.
[30] Mei JZ, Zhou J, Guo KY and Wei HM. Low expression of MHC class I-related chain A and B reduces NK cell-mediated lysis in nasopharyngeal carcinoma drug-resistant cell line CNE2/DDP. Zhongguo Zhongliu Shengwu Zhiliao Zazhi 2006; 13: 349-352.
[31] Zheng Y, Cao KY, Ng SP, Chua DT, Sham JS, Kwong DL, Ng MH, Lu L and Zheng BJ. Complementary activation of peripheral natural killer cell immunity in nasopharyngeal carcinoma. Cancer Sci 2006; 97: 912-919.
[32] Hosseinzadeh R, Feizisani F, Shomali N, Abdelbasset WK, Hemmatzadeh M, Gholizadeh Navashenaq J, Jadidi-Niaragh F, Bokov DO, Janebifam M and Mohammadi H. PD-1/PD-L1 blockade: prospectives for immunotherapy in cancer and autoimmunity. IUBMB Life 2021; 73: 1293-1306.
[33] Makowska A, Braunschweig T, Denecke B, Shen L, Baloche V, Busson P and Kontny U. Interferon β and Anti-PD-1/PD-L1 checkpoint blockade cooperate in NK cell-mediated killing of nasopharyngeal carcinoma cells. Transl Oncol 2019; 12: 1237-1256.

[34] Lei XM, Qu JQ and Tan T. Progress in clinical trials of PD-1 inhibitor monoclonal antibody for nasopharyngeal carcinoma. Tianjin Yiyao 2022; 50: 220-224.
[35] Hsu C, Lee SH, Ejadi S, Even C, Cohen RB, Le Tourneau C, Mehnert JM, Algazi A, van Brummelen EMJ, Saraf S, Thanigaimani P, Cheng JD and Hansen AR. Safety and antitumor activity of pembrolizumab in patients with programmed death-ligand 1-positive nasopharyngeal carcinoma: results of the KEYNOTE-028 study. J Clin Oncol 2017; 35: 4050-4056.
[36] Ma BBY, Lim WT, Goh BC, Hui EP, Lo KW, Pettinger A, Foster NR, Riess JW, Agulnik M, Chang AYC, Chopra A, Kish JA, Chung CH, Adkins DR, Cullen KJ, Gitlitz BJ, Lim DW, To KF, Chan KCA, Lo YMD, King AD, Erlichman C, Yin J, Costello BA and Chan ATC. Antitumor activity of nivolumab in recurrent and metastatic nasopharyngeal carcinoma: an international, multicenter study of the Mayo clinic phase 2 consortium (NCI-9742). J Clin Oncol 2018; 36: 1412-1418.
[37] Lee VH, Lo AW, Leung CY, Shek WH, Kwong DL, Lam KO, Tong CC, Sze CK and Leung TW. 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: e0157969.
[38] Chan OS, Kowanetz M, Ng WT, Koeppen H, Chan LK, Yeung RM, Wu H, Amler L and Mancao C. Characterization of PD-L1 expression and immune cell infiltration in nasopharyngeal cancer. Oral Oncol 2017; 67: 52-60.
[39] Coelho M, Gauthier P, Pugnière M, Roquet F, Pèlegrin A and Navarro-Teulon I. Isolation and characterisation of a human anti-idiotypic scFv used as a surrogate tumour antigen to elicit an anti-HER-2/neu humoral response in mice. Br J Cancer 2004; 90: 2032-2041.
[40] Luo C, Wang JJ, Li YH, Hu JY and Li GC. Immunogenicity and efficacy of a DNA vaccine encoding a human anti-idiotype single chain antibody against nasopharyngeal carcinoma. Vaccine 2010; 28: 2769-2774.
[41] Miles SA and Sandler AD. CpG oligonucleotides for immunotherapeutic treatment of neuroblastoma. Adv Drug Deliv Rev 2009; 61: 275-282.
[42] Chulpanova DS, Kitaeva KV, Tazetdinova LG, James V, Rizvanov AA and Solovyeva VV. Application of mesenchymal stem cells for therapeutic agent delivery in anti-tumor treatment. Front Pharmacol 2018; 9: 259.
[43] Smeets E, Meiler S and Lutgens E. Lymphocytic tumor necrosis factor receptor superfamily co-stimulatory molecules in the pathogenesis of atherosclerosis. Curr Opin Lipidol 2013; 24: 518-524.
[44] Lin S, Pan J, Han L, Guo Q, Hu C, Zong J, Zhang X and Lu JJ. Update report of nasopharyngeal carcinoma treated with reduced-volume intensity-modulated radiation therapy and hypothesis of the optimal margin. Radiother Oncol 2014; 110: 385-389.
[45] Wang JJ, Liu YH and Li GC. Induction of protective and therapeutic anti-cancer immunity by using bispecific anti-idiotype antibody G22-I50 for nasopharyngeal carcinoma. Int Immunopharmacol 2015; 28: 1026-1033.
[46] Taylor GS, Jia H, Harrington K, Lee LW, Turner J, Ladell K, Price DA, Tanday M, Matthews J, Roberts C, Edwards C, McGuigan L, Hartley A, Wilson S, Hui EP, Chan AT, Rickinson AB and Steven NM. A recombinant modified vaccinia ankara vaccine encoding Epstein-Barr Virus (EBV) target antigens: a phase I trial in UK patients with EBV-positive cancer. Clin Cancer Res 2014; 20: 5009-5022.
[47] Outh-Gauer S, Alt M, Le Tourneau C, Augustin J, Broudin C, Gasne C, Denize T, Mirghani H, Fabre E, Ménard M, Scotte F, Tartour E and Badoual C. Immunotherapy in head and neck cancers: a new challenge for immunologists, pathologists and clinicians. Cancer Treat Rev 2018; 65: 54-64.
[48] Gavrielatou N, Doumas S, Economopoulou P, Foukas PG and Psyrri A. Biomarkers for immunotherapy response in head and neck cancer. Cancer Treat Rev 2020; 84: 101977.
[49] O'Donnell JS, Long GV, Scolyer RA, Teng MW and Smyth MJ. Resistance to PD1/PDL1 checkpoint inhibition. Cancer Treat Rev 2017; 52: 71-81.
[50] Shergold AL, Millar R and Nibbs RJB. Understanding and overcoming the resistance of cancer to PD-1/PD-L1 blockade. Pharmacol Res 2019; 145: 104258.
[51] Sui H, Ma N, Wang Y, Li H, Liu X, Su Y and Yang J. Anti-PD-1/PD-L1 therapy for non-small-cell lung cancer: toward personalized medicine and combination strategies. J Immunol Res 2018; 2018: 6984948.