Journal of Cancer Research and Clinical Oncology (2023) 149:2071–2079
https://doi.org/10.1007/s00432-022-04214-8

Immunotherapy for the treatment of advanced nasopharyngeal carcinoma: a promising new era

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Received: 19 April 2022 / Accepted: 15 July 2022 / Published online: 25 July 2022

Abstract

Purpose Nasopharyngeal carcinoma (NPC) is ranked the top otorhinolaryngology malignant tumors in the world. However, the general prognosis of recurrent and metastatic (R/M) nasopharyngeal carcinomas (NPCs) remains poor, and current surgery and chemoradiotherapy do not generate satisfactory outcomes.

Methods As a new therapeutic choice, immunotherapy, especially with regard to the development of checkpoint inhibitors including PD-1 and CTLA-4 inhibitors have made considerable progress in recent years. As Epstein-Barr virus (EBV) infection is associated with increased risk of NPC, EBV-related immunotherapy may lead to a breakthrough in advanced NPCs.

Results In this review, we summarized the clinical characters of NPC, and several past and ongoing clinical trials of checkpoint inhibitors and EBV-CTLs (CTLs: cytotoxic T lymphocytes) in R/M NPC immunotherapy.

Conclusion We conclude that although the evaluated effects of new immunotherapy drugs have brought us hope on NPC treatment, further phase II-III trials with larger samples are still required to improve the proportion and scheme of drug collocation for better clinical outcomes and less drug-related safety.

Keywords R/M NPC · Immunotherapy · PD-1 · CTLA-4 · EBV

Background

Nasopharyngeal carcinoma (NPC) is a malignant tumor that occurs in the upper and side walls of the nasopharynx and is ranked among the top otorhinolaryngology malignant tumors in the world (Chen et al. 2019). The incidence rate of NPC is characterized by obvious racial differences and has the characteristics of susceptibility and regional clustering (Lee et al. 2019). Currently, the possible factors related to the occurrence of NPC mainly include genetic susceptibility(Shannon-Lowe and Rickinson 2019), environmental factors and Epstein-Barr virus (EBV) infection. It is confirmed that EBV is closely related to the occurrence and development of NPC and may play a crucial carcinogenic role under the joint action of genetic and environmental factors.

NPC can be divided into three categories based on pathological classification: keratinizing squamous cell carcinoma, non-keratinizing squamous cell carcinoma, and basal like squamous cell carcinoma. Among these, poorly differentiated non-keratinizing squamous cell carcinoma is the most common type. According to its pathological features, most NPCs have moderate sensitivity to radiotherapy, especially in stage I. However, due to the occult clinical manifestations, most cases have been diagnosed in stages II, III, and IV when found (AJCC 8th Edition) (Chen et al. 2021) even has progressed beyond the nasopharynx, usually to cervical lymph nodes (Fang et al. 2018). Notably, stage IV NPCs can account for about 10% of all cases with data showing one-year survival rate to be less than 48%, even after standard chemoradiotherapy. Surgery participation is generally low, and is mainly opted for in advanced cases with metastasis. Although the removal of tumors occurring in the nasopharynx via endoscopic skull base surgery is a practical choice,

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it does not have a satisfactory survival rate (Chan and Wei 2018).

Chemoradiotherapy is the main treatment of stage-IVB NPCs, with several conventional chemotherapy regimens currently available. A combination of gemcitabine and cisplatin has been used most frequently. In this regimen, gemcitabine and cisplatin were used once every three weeks, in combination with synchronous radiotherapy, depending on the condition of the patient. This regimen has been shown to significantly improve the effect of local control of NPC by high-level evidence (Zhang et al. 2016). In a phase III trial by Zhang et al. (Zhang et al. 2016), 362 patients with recurrent and metastatic nasopharyngeal carcinoma (R/M NPC) were randomly divided into two groups: gemcitabine combined with cisplatin (GC) and fluorouracil combined with cisplatin (FC). The results of this study revealed a significantly prolonged progression-free survival (PFS) (7.0 vs 5.6 months; $p < 0.0001$) and overall survival (OS) (29.1 vs 20.9 months; $p = 0.0025$) in the GP group. According to the drug toxicity, a significantly decreased number of treatment-related grade > 3 adverse events of the GC group were reported compared to the FC group, including leucopenia (29% vs 9%), thrombocytopenia (13% vs 2%), and neutropenia (23% vs 13%). Gemcitabine combined with cisplatin has become the global standard first-line treatment for R/M NPCs. In some advanced cases, high-dose radiotherapy (RT) combined with concurrent chemotherapy is also an option; however, this regimen has only showed improved progression-free survival (PFS), while overall survival (OS) is still poor (Yin et al. 2017; Verma et al. 2017). Other regimens such as docetaxel plus cisplatin and capecitabine plus cisplatin are also used for concurrent radiotherapy and chemotherapy or postoperative adjuvant chemotherapy of NPC.

Immunotherapeutic methods for nasopharyngeal carcinoma

Palliative radiotherapy and chemotherapy, typically with platinum-based combinations remains the mainstream treatment option for NPC, but the corresponding treatment options and side effects have not improved significantly over the years (Benasso 2013). Considering the limited survival rates associated with chemotherapy regimens, there is an urgent need to develop targeted therapies for R/M NPCs, to potentially reduce toxicity and improve response duration/survival benefits.

Under normal circumstances, the immune system can recognize and destroy tumor cells in the microenvironment; however, to survive and grow, tumor cells adopt different strategies to escape the surveillance of immune cells or inhibit the normal killing of tumor cells by the human immune system, called immune escape (Bommareddy et al. 2018). The anti-tumor process is complex with multi-links and multi-steps, and can be divided as follows: 1) Tumor antigen release; 2) Tumor antigen presentation; 3) Activation of effector T cells; 4) T-cell migration to tumor tissue; 5) T-cell infiltration in tumor tissue; 6) Tumor cell recognition by T cells; 7) Clearing of tumor cells. Any abnormality in these links may lead to the failure of anti-tumor immune circulation and immune escape. Different tumors can inhibit effective recognition and killing by the immune system in different links, thereby developing immune tolerance that may even lead to the progress of the tumor itself.

Tumor immunotherapy is a new strategy to control and eliminate tumor cells by restarting and maintaining the immune cycle and restoring the normal anti-tumor immune response. It can be broadly divided into two categories: nonspecific and tumor antigen-specific (Larkin et al. 2015). Nonspecific ways include nonspecific immune stimulation and immune checkpoint blocking, while tumor antigen-specific ways include various tumor vaccines and adoptive immune cell therapy (Galluzzi et al. 2014; Ott et al. 2017). The concrete types of immunotherapies include:

Nonspecific immune stimulation

This includes lymphokine activated killer cell (LAK) therapy and cytokine mediated killer cell (CIK) therapy.

Immunosuppressive cytokines and bioactive molecules

These can inhibit the function of T cells. T cells are the main tumor-killing cells in the human immune system and can secret interleukin-2 (IL-2), interferon-γ (INF-γ), granulocyte macrophage colony stimulating factor (GM-CSF), tumor necrosis factor-α (TNF-α), and other cytokines to kill tumor cells. The activation of T cells requires two signals: a major histocompatibility complex (MHC) polypeptide signal and a costimulatory molecular signal. The signals of costimulatory molecules mainly include positive costimulatory factors (CD27, CD28, and CD137), negative costimulatory factor cytotoxic T-lymphocyte associated antigen 4 (CTLA-4) pathway, and programmed death molecule-1(PD-1)/programmed death molecule ligand 1 (PD-L1) pathway. These two inhibitory pathways may get hijacked by the tumor to fight against the immune system. Therefore, the use of positive costimulatory agonists or negative costimulatory antagonists can improve the immune killing effect on tumors. CTLA-4 has been used for targeted immunotherapy for some time.

Tumor vaccines

They are derived from autologous or allogeneic tumor cells or their crude extracts, with tumor specific antigen (TSA) or tumor associated antigen (TAA). It can attack tumor cells

by stimulating specific immune function that can overcome the immunosuppressive status caused by tumor products, enhance the immunogenicity of TAA, and improve self-immunity to eliminate tumors. According to the source, the tumor vaccines can be divided into tumor cell vaccines, gene vaccines, polypeptide vaccines, and dendritic cell vaccines.

(4) Adoptive immune cell therapy: this includes tumor infiltrating lymphocyte (TIL) therapy, T-cell receptor chimeric T-cell (TCR-T), and chimeric antigen receptor T-cell technology (CAR-T).

Both nonspecific immune stimulation and immune checkpoint monoclonal antibodies (mAbs) play an anti-tumor role by enhancing the existing immune system and cannot promote immune cells to attack tumors. The tumor vaccine attacks tumor cells by stimulating specific immune functions; however, the therapeutic effect is not particularly good. Adoptive immune effector cell therapy refers to the separation of immunocompetent cells from normal cells in tumor patients, amplification and functional identification in vitro, and transfer to patients, which enhances the number of tumor-killing immune cells, thereby allowing the direct killing of tumor cells by stimulating the body's immune response. The specificity and target of treatment are the focus of the current study and future research development direction. The use of TCR-T and CAR-T has attracted extensive clinical attention as they can express specific receptors and recognize and target specific tumor cells. These techniques have been translated from initial basic immune research to clinical application (Zeng et al. 2019; Ruhl et al. 2019; Taylor et al. 2014; Chow et al. 2019; Smalley and McArthur 2012). In NPC patients, cytotoxic cells targeting tumor cells (such as tumor infiltrating/transgenic T lymphocytes and natural killer cells) are used directly and preferentially. Anti-NPC T cells are extracted from patients and then amplified and returned to the clinic. Direct transplantation of T cells can also be achieved in the form of allogeneic transplantation. It is worth noting that EBV allogeneic T cells are mainly used in EBV dependent lymphoproliferative diseases. The immunological principle is the same: injection of T cells that can detect and kill tumor cells, which is a salvage treatment of T-cell-based combined chemotherapy in the treatment of NPC (Ostrand-Rosenberg et al. 2019).

The development of immune checkpoint inhibitors

In NPC immunotherapy, identifying immune checkpoint inhibitors has considerable potential in NPC immunotherapy. Immune checkpoint is a signaling pathway on the surface of T cells that participates in immune response. If the immune checkpoint is activated, it will inhibit the function of immune cells. To avoid being attacked by immune cells, tumor cells generally activate immune checkpoints. PD-1 and CTLA-4 are considered to be two important checkpoints of the immune system. They play a negative regulatory role in the anti-tumor immune response of T cells. Thus, it is critical to prevent tumor cells from activating immune checkpoints, so as to maintain normal immune function. The basic mechanism of PD-1 and CTLA-4 inhibitor is depicted in Fig. 1.

Programmed cell death-1 (PD-1) receptor

PD-1 receptor is currently the most studied and clinically used immunotherapy target. It is expressed on $CD4^-$ and $CD8^-$ thymocytes and induces peripheral $CD4^+$ and $CD8^+$ T cells, B cells, monocytes, natural killer T cells (NK T cells), and some dendritic cells (DC). PD-1 has two ligands, PD-L1 and PD-L2; the former is the most prominent in regulation of killing tumor cells.

Interactions between PD-1 and PD-L1 inhibit the attack of immune cells on tumor cells. First, the binding of PD-1 to PD-L1 can induce T-cell depletion. As a result, exhausted $CD8^+$ T cells lose their effector function and cannot secrete cytolytic molecules such as perforin and proinflammatory cytokines (such as interleukin-2 (IL-2), interferon-γ (IFN-γ), and tumor necrosis factor-α (TNF-α)), which inhibit their attack on tumor cells. Second, $CD4^+$ $Foxp3^+$ regulatory T cells (Tregs) are highly immunosuppressive subsets of $CD4^+$ T cells, essential for maintaining tolerance and weakening the immune response. PD-1 is also expressed on the surface of Tregs and mature B cells. Therefore, the combination of PD-1 and PD-L1 may also inhibit the immune activity of Tregs and B cells to a certain extent, weakening the anti-tumor effect of immune cells. The anti-tumor activity of

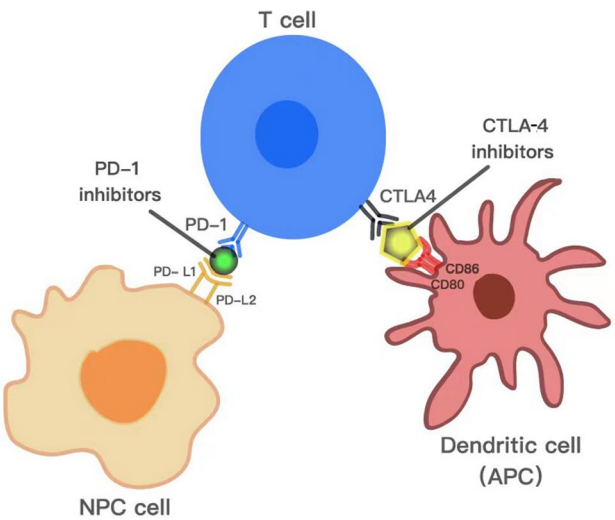

Fig. 1 The role of PD-1 and CTLA-4 inhibitors in NPC. PD-1 inhibitor can block the connection between NPC cell and T cell to decrease the deactivation of T cell induced by NPC cell. CTLA-4 inhibitors can block the connection between dendritic cell and T cell to stop inhibiting initiation of the T-cell response

PD-1$^-$ T cells can be enhanced by blocking the binding of PD-1$^-$ T cells.

PD-1 monoclonal antibodies have been developed to enhance T-cell function by blocking the binding between PD-1 and PD-L1 or PD-L2 for cancer immunotherapy. Pembrolizumab is the first Food and Drug Administration (FDA) approved PD-1 monoclonal antibody and nivolumab is a human PD-1 monoclonal antibody. These drugs can block the binding of PD-1 and PD-L1 and change the tumor microenvironment, such as T cells and IFN-γ at the tumor site. Increasing and reducing the immunosuppressive bone marrow-derived suppressor cell population is another method of inhibiting tumor cell growth. The basic mechanism of PD-1 inhibitor is depicted in Figure.

The use of PD-1/PD-L1 blockade in NPC may be enhanced by chemoradiation (Ostrand-Rosenberg et al. 2019; Manukian et al. 2019). Considering the interactions of polytherapy, anti-PD-1 checkpoint inhibitors such as PD-L1 upregulation after irradiation and chemotherapy, prompting T-cell apoptosis, and restricting the immune response upon PD-1 binding (Dovedi et al. 2017), there is still potential for adjustment in NPC immunotherapy. A comprehensive analysis of both current and ongoing PD-1/PD-L1 inhibitors trials of NPC is summarized in the following sections (summarized in Table 1).

KEYNOTE-028

In the nonrandomized, multicohort, phase IB immunotherapy study KEYNOTE-028 (NCT02054806) (Hsu et al. 2017), the effectiveness and drug-related toxicity of pembrolizumab, which is an anti-PD-1 monoclonal antibody was analyzed in PD-L1-positive R/M NPCs. A total of 27 patients received pembrolizumab, and during the 20-month median follow-up, the ORR was 25.9%, which is close to the ORR assessed by the central review (26.3%) (Hsu et al. 2017). Drug-related adverse events were also acceptable. The result of this research confirmed the anti-tumor activity and a manageable safety profile of pembrolizumab in RM-NPC patients.

NCI-9742

This international, multi-center study of the Mayo Clinic Phase 2 Consortium (NCI-9742) analyzed the anti-tumor activity of Nivolumab in R/M NPCs (Ma et al. 2018). A total of 44 patients were evaluated and 9 patients (20%) received nivolumab for twelve months. The overall ORR was 20.5% (complete response), and the one-year overall survival rate was 59%, one-year progression-free survival (PFS) rate was 19.3%. The analysis showed that the proportion of NPC patients with PD-L1-positive (> 1% expression) responding to nivolumab was higher than that of PD-L1-negative ones. There was no unexpected toxicity to nivolumab. Compared to previous data, this research confirmed that nivolumab has good activity and lower toxicity in treating R/M NPCs. What's more, in the study, researchers also found human leukocyte antigen (HLA) class I proteins A and B were negatively correlated with plasma clearance of EBV DNA, and one-year PFS in patients with loss of expression of one or two HLA class I proteins was better than that of both proteins expressed (30.9% vs 5.6%). Furtherly, researchers also found that there was no association found between survival and PD-L1 expression or plasma EBV DNA clearance.

SHR-1210–101

Camrelizumab is a humanized PD-1 antibody. In the phase I clinical study (SHR-1210–101) (Fang et al. 2018), researchers presented the safety and preliminary anti-tumor activity of camrelizumab alone as second-line therapy, and combined with gemcitabine and cisplatin as first-line therapy in R/M NPCs. In this camrelizumab monotherapy trial, 31 of 93 patients (34%) had an overall response (ORR) with a median follow-up of 9.9 months, and 15 patients (16%) had treatment-related adverse events of grade 3 or 4. In the camrelizumab combination trial, 20 of 22 patients (91%) had an ORR with a median follow-up time of 10.2 months, and 20 patients (87%) had treatment-related adverse events of grade 3 or 4. The objective effective rate reached 40.6%, and the long-term benefit was obvious.

SHR-1210–104

Based on SHR-1210–101, further randomized phase 3 trial (SHR-1210–104) compared camrelizumab plus gemcitabine and cisplatin with placebo plus gemcitabine and cisplatin in the first-line treatment of R/M NPCs (Yang et al. 2021a). 263 patients were eligible and randomly assigned to the camrelizumab group ($n = 134$) or placebo group ($n = 129$), and the PFS was significantly longer in the camrelizumab group (median 9.7 months) than in the placebo group (median 6.9 months). The grade 3 or 4 adverse events of camrelizumab group are also less than placebo group. The median PFS of camrelizumab group in this study was 22.1 months, which was fully extended by 15.1 months compared with the clinical study SHR-1210–101.

POLARIS-02

In a single-arm, multi-center phase II study (ClinicalTrials.gov Identifier: NCT02915432), patients with R/M NPC received toripalimab (3 mg/kg) through intravenous infusion every 2 weeks until disease progression or unacceptable toxicity is confirmed (Wang et al. 2021). Among all 190 patients, the ORR was 20.5% with median PFS 1.9 months,

Table 1 The comprehensive analysis of both current and ongoing PD-1/PD-L1 inhibitors trials of NPC

Trial	Pembrolizumab keynote-028 (Hsu et al. 2017)	Nivolumab NCI-9742 (Ma et al. 2018)	Camrelizumab SHR-1210–101 (Fang et al. 2018)		Camrelizumab SHR-1210–104 (Yang et al. 2021a)		Toripalimab NCT02915432 (Wang et al. 2021)	
			Camrelizumab monotherapy trial	Camrelizumab combination trial	Camrelizumab Plus gemcitabine and cisplatin group	Placebo plus gemcitabine and cisplatin group		
Population	Recurrent metastatic NPC	Recurrent metastatic NPC	Recurrent metastatic NPC		Recurrent metastatic NPC		Recurrent metastatic NPC	
Location	Multinational, multi-center	Multinational, multi-center	Multicenter		Multicenter		Multicenter	
Follow-up duration	Median 20 months (IQR 2.2 to 26.8 months) (Feb 20, 2015 to June 20, 2016)	Median 12.5 months (IQR 2.2 to 22.0 months) (October 28, 2015 to June 1, 2016)	Median 9.9 months (IQR 8.1–11.7) (March 31, 2016 to Sept 20, 2017)	Median 10.2 months (IQR 9.7–10.8) (April 18, 2017 to Aug 15, 2017)	Median 9.7 months (IQR 8.3–11.4) (Nov 13, 2018 to Nov 29, 2019)	Median 6.9 months (IQR 5.9–7.3) (Nov 13, 2018 to Nov 29, 2019)	Median 3.7 months (IQR, 0.2–34.8) (December 2016 to February 2019)	
NPC subtype	Type 1–6 (22.2%) Type 2/3–18 (66.7%)	Type 1–8 (17.8%) Type 2/3 (82.2%)	Undifferentiated non-keratinized 64 (69%)	Undifferentiated non-keratinized 23 (100%)	Keratinizing 1 (< 1%)	Keratinizing 1 (< 1%)	Non-keratinizing 182 (95.8%)	
			Differentiated non-keratinized 12 (13%)	Differentiated non-keratinized 0	Non-keratinizing differentiated 21 (16%)	Non-keratinizing differentiated 21 (16%)	Keratinizing 8 (4.2%)	
			Keratinized squamous carcinoma 15 (16%)	Keratinized squamous carcinoma 0	Non-keratinizing undifferentiated 110 (82%)	Non-keratinizing undifferentiated 106 (82%)		
			Unclassified 2 (2%)	Unclassified 0	Others 2 (1%)	Others 1(< 1%)		
Ethnicity	Asian 17 63% African American 2 7.4% American Indian 1 3.7% White 6 22.2% Unknown 1 3.7%	Asian 37 82.2% African American 1 2.2% Pacific Islands 1 2.2% White 4 8.9% Unknown 2 4.4%	Asian (China) 100%		Asian (China) 100%		Asian (China) 100%	
Design	Phase I	Phase II	Phase I		Phase III		Phase Ib/II	
Pt number	27	45	93	23	134	129	190	
Age	52 (18–68)	57 (37–76)	45 (38–52)	44 (34–51)	52 (40–58)	49 (40–56)	46.4 (22–71)	
Sex	M: F 21 (77.8%):6 (22.2%)	M: F 35 (77.8%):10 (22.2%)	M: F 75 (81%):18 (19%)	M: F 17 (74%):6 (26%)	M: F 113 (84%): 21 (16%)	M: F 105 (81%): 24 (19%)	M: F 158 (83.2%): 32 (16.8%)	

Table 1 (continued)

Trial	Pembrolizumab keynote-028 (Hsu et al. 2017)	Nivolumab NCI-9742 (Ma et al. 2018)	Camrelizumab SHR-1210–101 (Fang et al. 2018)		Camrelizumab SHR-1210–104 (Yang et al. 2021a)		Toripalimab NCT02915432 (Wang et al. 2021)
			Camrelizumab monotherapy trial	Camrelizumab combination trial	Camrelizumab Plus gemcitabine and cisplatin group	Placebo plus gemcitabine and cisplatin group	
Treatment regime	Pembrolizumab 10 mg/kg IV every 2 weeks for 24 months or disease progression	Nivolumab 3 mg/kg IV every 2 weeks until disease progression	intravenously at escalating doses of 1 mg/kg, 3 mg/kg, and 10 mg/kg, and a bridging dose of 200 mg per dose once every 2 weeks	six cycles of camrelizumab 200 mg (day 1), gemcitabine 1 g/m^2 (day 1 and 8), and cisplatin 80 mg/m^2 (day 1) every 3 weeks followed by camrelizumab 200 mg maintenance once every 3 weeks	camrelizumab (200 mg on day 1) or matching placebo intravenously, plus gemcitabine and cisplatin (gemcitabine 1000 mg/m^2 on days 1 and 8; cisplatin 80 mg/m^2 on day 1) intravenously every 3 weeks for four to six cycles, followed by maintenance therapy with camrelizumab or placebo		Toripalimab 3 mg/kg once every 2 weeks via intravenous infusion
Clinical response (partial/complete)	25.9% (11–46)	20.5% (10–35)	31% (34; 24–44)	20% (91; 72–97)	87·3% (80·5–92·4)	80·6% (72·7–87·1)	39 (20.5%)
PD-L1	Positive: 27 (100%)	Positive:18 (40%); Negative: 27 (60%)	unknown		unknown		Positive: 48 (25.3%) Negative: 134 (70.5%) Unknown: 8 (4.2%)
Previous radiotherapy (%)	N/R	82.2	82 (88%)	18 (78%)	92 (69%)	85 (66%)	98 (51.6%)
Previous chemotherapy cycles > 2 (%)	19 (70.4%)	27 (61.4%)	93 (100%)	0	27 (20%)	29 (22%)	92 (48.4%)
Treatment related adverse event grade 3 or 4	8 (29%)	10 (22%)	15 (16%)	20 (87%)	59 (44%)	48 (37%)	30 (15.8%)
Drug-related adverse events	rash (25.9%), pruritus (25.9%), pain (22.2%), hypothyroidism (18.5%), and fatigue (18.5%)	4 (10.3)	Elevated conjugated bilirubin concentration (3%) stomatitis, anemia, and abnormal liver function (2%)	neutropenia (57%), anemia (48%), leucopenia (48%), thrombocytopenia (30%), edema (9%), hyponatremias (9%), hypochloremias (4%), and rash (4%)	blood cell count (66% vs. 70%), decreased neutrophil count (64% vs 66%), anemia (40% vs 44%), decreased platelet count (40% vs 40%)		hypothyroidism (23.7%), hyperthyroidism (2.6%), abnormal liver function (1.6%), interstitial lung disease (1.6%), dermatomyositis (0.5%), and autoimmune myocarditis (0.5%)

Table 1 (continued)

Trial	Pembrolizumab keynote-028 (Hsu et al. 2017)	Nivolumab NCI-9742 (Ma et al. 2018)	Camrelizumab SHR-1210–101 (Fang et al. 2018)		Camrelizumab SHR-1210–104 (Yang et al. 2021a)		Toripalimab NCT02915432 (Wang et al. 2021)
			Camrelizumab monotherapy trial	Camrelizumab combination trial	Camrelizumab Plus gemcitabine and cisplatin group	Placebo plus gemcitabine and cisplatin group	
drug-related death	1 (3.7%)	1 (2.6%)	0		5 (4%) vs 1 (< 1%)		4 (2.1%)

median OS 17.4 months, and median DOR 12.8 months. The ORRs were 27.1% and 19.4% in PD-L1 negative and PD-L1 positive cases, respectively. Patients with > 50% decreased plasma EBV-DNA copy number had significantly better ORR than those with < 50% decreased, 48.3% vs 5.7%. This study demonstrated a manageable safety profile and durable clinical response of toripalimab in patients with chemo-refractory advanced NPC.

Cytotoxic T-lymphocyte antigen 4 (CTLA-4)

CTLA-4 is a transmembrane protein expressed on the surface of activated T cells. It acts by inhibiting initiation of the T-cell response, resulting in the reduction of activated T cells and the formation of memory T cells. Tumor cells can activate CTLA-4 to inactivate the activated T cells, allowing immune escape (Yang et al. 2021b). Several preclinical studies have noted that blocking CTLA-4 can restore T-cell activity and prolong the survival time of memory T cells to restore the body's immune function and improve the tumor control rate. Therefore, a specific monoclonal antibody against CTLA-4 has been developed (Peggs et al. 2009). The basic mechanism of CTLA-4 inhibitor is depicted in Figure.

Currently, two CTLA-4 inhibitors, ipilimumab and tremelimumab, have been approved by the FDA for the adjuvant treatment of advanced melanoma (Larkin et al. 2019). Clinical research of the two drugs in renal cancer, prostate cancer, and lung cancer has also been promising. Early clinical studies demonstrated that the two mAbs were safe and effective either alone or in combination with IL-2, PD-1/PD-L1 inhibitors, or chemotherapy.

Immunotherapy of Epstein-Barr virus-positive nasopharyngeal carcinoma

Almost all NPC cells express EBV antigen; however, outcomes for patients with metastatic or locally recurrent EBV-positive NPC are poor. It has been confirmed that EBV plays an etiological role in the occurrence of NPC, is related to cell transformation, proliferation and dedifferentiation, and can induce NPC in cooperation with cancer promoters. In NPC clinical histological samples, the prevalence of PD-L1 expression ranges from 89 to 95% (Chen et al. 2013; Jiang et al. 2019). It was also reported that EBV synergistically upregulates the expression levels of PD-L1 with interferon-γ in NPC cells in vitro by latent membrane protein 1 (LMP1) (Fang et al. 2014). This feature of NPC makes EBV-positive patients potentially more suitable for immunotherapy. Even though the specific mechanism of EBV dependent promotion of PD-L1 expression to induce immune escape has not been fully clarified, this is a very attractive research direction for NPC immunotherapy.

In clinical studies, adoptive transfer of EBV-specific cytotoxic T lymphocytes (EBV-CTLs) as single-agent therapy has shown clinical benefit in phase I and phase II clinical trials; however, its evaluation as the first-line treatment in combination with chemotherapy is lacking. In a phase II clinical trial (Chia et al. 2014), adoptive immunotherapy with EBV-CTLs was evaluated in combination with chemotherapy of gemcitabine and carboplatin (GC scheme), in EBV-positive R/M NPCs. In this trial, 38 patients were enrolled and 35 received GC and EBV-CTL. The data showed that there were 3 cases of complete response (CR) and 22 cases of partial response (PR) and the favorable response rate was 71.4%. The two- and three-year overall survival rates were 62.9% and 37.1%, respectively. This study achieved a satisfactory survival outcome in patients with advanced NPC, setting the stage for a future randomized study of chemotherapy with EBV-CTL.

Conclusion and perspective

While notable advances have been made in our understanding of R/M NPC, which accounts for approximately 10% of all cases, poor outcomes persist. Although immunotherapy is a new therapy method, it has great potential in the treatment of R/M NPC. Most clinical trials have centered on the development of several anti-PD-1 checkpoint inhibitors and have shown improved outcomes. By comparison, the results of clinical trials on anti-CTLA-4 are insufficient to support its effectiveness and require further exploration. Due to the close association between NPC incidence and EBV infection, active immunotherapy against EBV, especially the development of a tumor vaccine, is another promising direction and results from systemic clinical trials are required. Several ongoing clinical research trials investigating NPC immunotherapy are being performed and will bring more conclusive results. For example, a randomized interventional clinical trial (ClinicalTrials.gov Identifier: NCT01744587) has enrolled 353 participants to study EBV reactivation and the effect of Epigallocatechin gallate (EGCG) on virus reactivation in remission NPC patients in China. Another single-arm, open-label, multi-center, phase II study (ClinicalTrials.gov Identifier: NCT03866967) in China aims to performed to analyze the effectiveness of a new anti-PD-1 drug AK105 on 153 metastatic NPC patients. In the future, an increasing number of clinical trials are expected to verify the efficacy of more reliable immunotherapeutic drugs or schemes.

Acknowledgements We would like to thank Editage (www.editage.cn) for English language editing.

Author contributions Writing–original draft preparation SW, SC and QZ; writing–review & editing, SW, SC and YL; supervision, YL.

Funding Project supported by Hainan Province Clinical Medical Center.

Declarations

Competing interests The authors declare no competing interests.

Conflict of interest The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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