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# Mechanism and research situation of immunotherapy combined with chemotherapy in the treatment of nasopharyngeal carcinoma

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**ABSTRACT**
Nasopharyngeal carcinoma (NPC) is a malignant tumor closely related to Epstein-Barr virus (EBV) infection, which is highly cryptic and invasive. The treatment usually rely on a combination of radiotherapy and chemotherapy. Although their cure rate is high, it still have challenges of recurrence and metastasis due to the immune escape by tumor cells. Now, with the in-depth exploration of the tumor microenvironment (TME), it is found that the combination of immunotherapy and chemotherapy can improve the survival rate and quality of life of patients with recurrent, metastatic and locally advanced disease. Therefore, it is important to conduct in-depth research on the TME of NPC, especially the infiltration degree of immune cells and their immune escape mechanism. Analyzing the effects of immunotherapy and chemotherapy on the NPC tumor microenvironment and combining the latest progress in existing clinical trials will help to understand the biological characteristics of NPC, thereby optimizing treatment options and improving overall efficacy.

**KEYWORDS**
NPC; ICI; Chemotherapy; Immune escape; TME

## 1 Introduction

NPC is a malignant tumor with high incidence in Southeast Asia and southern China. The traditional treatment methods mainly include a combination of radiotherapy and chemotherapy. Radiotherapy is the basis for the treatment of nasopharyngeal carcinoma, while chemotherapy (such as gemcitabine combined with cisplatin) is used as adjuvant therapy to enhance the effect of radiotherapy and reduce the risk of recurrence. However, these methods still have some limitations in clinical use.

In recent years, the use of immune therapy to treat NPC has gradually become an emerging approach. By using the immune checkpoint inhibitors, make the body's immune system respond, then fight with tumors.

And about chemotherapy, it can directly kill tumor cells and at the same time change the TME to make it more conducive to the occurrence of immune response. Chemotherapy also promote the transformation of macrophages from M2 (promoting tumor growth) to M1 (anti-tumor), thereby enhancing the anti-tumor immune response.

The combined use of immunotherapy and chemotherapy can give full play to the advantages of both and produce a synergistic effect. At present, many clinical trials have evaluated the effects of combined chemotherapy and immunotherapy in NPC patients and achieved some positive results. These researches have shown that the combination therapy can significantly improve patients' overall survival and disease-free survival rates, showing good prospects.

This review means to summarize the current research progress on the combined use of immunotherapy and chemotherapy in NPC, analyze their mechanism and clinical effects, and provide a reference for future research.

## 2 Immune infiltration and immune escape in NPC

There is usually a large number of immune cells in the TME of NPC, including T cells, regulatory T cells (Treg), B cells, natural killer (NK) cells, macrophages, myeloid cells, etc. In normal situation, a higher degree of immune cell infiltration means that more T cells can be activated in the TME, thereby enhancing the attack on tumor cells and achieving better treatment effects.

The tertiary lymphoid structures (TLS) which present in TME can increase the infiltration of immune cells such as natural killer (NK) cells by increasing the diversity of T cell receptors (TCR) and B cell receptors (BCR) [1].

N6-methyladenosine (m6A) modification plays an important role in regulating cellular infiltration in the TME of NPCs. The two different m6A subtypes were highly consistent with immune activation and immune suppression phenotypes respectively. The low m6A subtype was shown to be associated with immune activation and a lower risk of recurrence and metastasis, exhibiting better progression-free survival (PFS). High m6A isoform was associated with activation of Wnt and NF-κB signaling pathways and lack of effective immune infiltration, predicting poor survival. M6A can be used to assess tumor immune infiltration, thereby guiding more effective immunotherapy strategies[2].

There are multiple immune escape mechanisms in NPC, among which nasopharyngeal carcinoma cells release a substance called kynurenine (Kyn) in the TME, which seriously affects the function of T cells. FLI1 protein in tumors

responds to interferon-γ (IFN-γ) released by T cells through the CBP/STAT1-IDO1 pathway, thereby producing excessive Kyn. It also leads to the exhaustion of CD8+ T cells and the differentiation of Treg cells, thus causing immune evasion[3].

NK cells in the TME mainly play the role of observing and destroying tumor cells and virus-infected cells. They have a unique ability to target tumor cells in the absence of major histocompatibility complex class I (MHC I). This suggests that when tumor cells lack or down the regulation of MHC I molecules, they are able to evade attack by CD8+ T cells, which rely on MHC I molecules to recognize infected or cancerous cells. However, in this situation, NK cells can still identify and eliminate these tumor cells that lack MHC I expression, thus playing an important role in anti-tumor immunity. NK cells are also affected by immune checkpoints. When immune checkpoints such as PD-1 are activated, the activity of NK cells can be regulated, making them unable to effectively attack tumor cells, resulting in immune escape[4].

Macrophages in the TME can promote tumor immune suppression by releasing itaconate (ITA) and binding to the ten-eleven translocation-2 (TET2) gene. In addition, human CD34+ hematopoietic stem cells were transplanted into immune deficient mice as a model, and it was found that ITA can promote immune escape by affecting the immune response in the mice, causing NPC cells to proliferate and spread faster in the mice[5].

Furthermore, tumors with fibroblast-like malignant cells have been found to have much more immune evasion capabilities. And the tumor nests can repair epithelial cells (EP) and make it difficult for immune cells to recruit these non-malignant epithelial cells, thereby forming immune isolation and enhancing the tumor's immune evasion ability in the tumor nest[6]. Among them, CAFs with CXCL1+_FAP+ phenotype are independent prognostic factors for locally advanced nasopharyngeal carcinoma(LANPC) may become the new potential biomarkers for anti-PD-1/PD-L1 immune therapy[7].

In recent research, it was found that a G protein-coupled receptor APLNR can not only inhibit the growth and metastasis of NPCs, but also participate the immune escape in NPC. This research has shown that APLNR may inhibit immune escape by increasing the amount of IFN-γ secretion and the number of T cell infiltration, reducing the apoptosis of immune cells. When APLNR was used in combination with PD-L1, significant NPC growth restriction was found in nude mice[8].

These mechanisms have complex immune response characteristics in TME, and immune cells work together with the various pro-inflammatory and anti-inflammatory molecules they secrete, cross-talking with tumor cells to form an immune suppressive state, allowing tumor cells to evade immune surveillance and cause immune escape. These mechanisms have an important impact on the therapeutic effect. Researching the TME of NPC is of great significance and plays a certain role in promoting the current standard treatment of NPC combined with immunotherapy.

## 3 Effects of immunotherapy on the TME of NPC

Immune therapy is a method of fighting cancer by stimulating the body's own immune response. It is currently divided into immune checkpoint inhibitor therapy (ICI), adoptive immunotherapy and active immunotherapy.

ICI therapy has received the most attention in recent years, among which PD-1 and PD-L1 have been reasearched more. ICI therapy blocks the inhibitory signals between tumor cells and T cells, restoring T cell activity and thus enhancing the anti-tumor response. Moreover, it can not only activate existing immune cells, but also increase the number of new immune cells, such as increasing the number of B cells and NK cells in tumor microenviroment, increasing the degree of immune infiltration, forming a more powerful anti-tumor microenvironment, and thus improving the therapeutic effect. Immunotherapy can also reduce the expression of some factors that cause immune suppression to overcome the state of immune suppression, thereby restoring the function of effector T cells.

In a phase II trial with only one experimental group and no control group study showed that when a PD-1 IgG1 antibody without Fc gamma receptor (FcγR) binding activity was used to treat metastatic nasopharyngeal carcinoma, 28.0% of patients responded positively to penpulimab treatment and exceeded the expected trial success threshold, which can be considered that this type of immune single drug has met the expected standards[9]. The results of another retrospective research demonstrated that the addition of PD-1 inhibitors to chemotherapy alone (IC) has the potential to be an effective treatment for LANPC. Use the PD-1 inhibitors together showed higher survival rates, while immune-induced toxicity was within an acceptable range[10].The use of another immune checkpoint, CTLA-4, has been shown to enhance the therapeutic effect of subsequent PD-1 in advanced NPC. Specifically, after treatment with the CTLA-4 blocker ipilimumab, CD4+ and CD8+ T cells showed increased activation and infiltration, and reduced malignant components[11].

Immunotherapy has good prospects in NPC, but the response rate is not really high. In-depth research on the specific effects of immunotherapy on the TME of NPC will help improve patients' response rate to immunotherapy.

## 4 Effect of chemotherapy on TME of NPC

Chemotherapy is one of the important ways of treating NPC and is often used in combination with radiotherapy. In

recent years, it has been found that chemotherapy can eliminate tumor cells by direct killing, and on the other hand, it can stimulate the body's immune system to respond, affecting TME and thus affecting tumor progression. Reasearchers have shown that gemcitabine plus cisplatin (GP) chemotherapy can activate innate-like B cells (ILBs), which are in close contact with T cells in tertiary lymphoid organ-like structures lacking germinal centers, forming an anti-tumor immune response. DNA fragments induced by chemotherapy activate type I interferon-dependent signaling through the STING pathway, increasing MHC I expression in cancer cells. Furthermore, if the number of ILBs increases after chemotherapy, the patient will respond better to chemotherapy and have a better prognosis[12]. It can also improve the immune suppressive state by reducing the proportion of suppressive cells and changing the polarization state of macrophages[13].

Now the chemotherapy methods for treating NPC are mainly divided into neoadjuvant chemotherapy, synchronous chemotherapy and metronomic chemotherapy. Induction chemotherapy improves the effectiveness of subsequent treatment by reducing tumor burden before primary treatment. Concurrent chemotherapy increases local drug concentrations to enhance the killing effect of radiation on tumors and regulates TME to make it more sensitive to radiotherapy.

Metronomic chemotherapy refers to multiple chemotherapy sessions at certain time intervals to reduce side effects on the patient himself and is often used to control tumor growth. It is also important to study the order of chemotherapy use. The effectiveness of tislelizumab together with neoadjuvant chemotherapy and concurrent chemoradiotherapy in the treatment of LANPC was analyzed based on the existing data. The research found that neoadjuvant chemotherapy had better therapeutic efficacy and tolerability than standard treatment[14].

## 5 Current situation of immunotherapy combined with chemotherapy in the treatment of NPC

The immunotherapy and chemotherapy both reshape the TME of NPC. Since GP-induced chemotherapy can produce immunomodulatory effects on LANPCs and consume immune suppressive cells in the TME, such as MDSCs and regulatory lymphocytes, the combination of them can work together[15]. Based on the results of single-cell transcriptional profiling, immunochemotherapy reshapes T cell phenotype and promotes the maturation of CD8+ T cells. And in patients who failed to achieve complete remission, high expression of immune checkpoint genes and reduced tumor antigen activity were observed, suggesting that this may be associated with drug resistance[16].

Now there are many clinical researches which use them together for observation. Sintilimab is a monoclonal antibody targeting programmed death receptor 1 (PD-1). In a phase III clinical trial NCT03700476 initiated by the team of Academician Ma Jun from the Cancer Center of Sun Yat-sen University, patients in the experimental group received sintilimab combined with standard treatment (gemcitabine and cisplatin induction chemotherapy plus concurrent chemoradiotherapy), while patients in the control group received standard treatment only. In this research, they found that the incidence of grade 3 to 4 adverse events in the experimental group was 74%, higher than 65% in the control group, and the event-free survival rate in the experimental group was 86%, higher than 76% in the control group. This result proves that the addition of sintilimab can improve event-free survival, and although it has more adverse risks associated with it, they are still within controllable range. But long-term follow-up is still needed to prove whether this regimen can become the standard treatment for LANPC patients[17].

In a phase III clinical trial NCT05211232 conducted by Professor Mai Haiqiang's team, patients with recurrent or metastatic NPC were treated with gemcitabine-cisplatin followed by PD-1 inhibitor toripalimab or placebo. The result showed that the progression-free survival (PFS) and overall survival (OS) of PD-1 were significantly prolonged, and the incidence of adverse events was similar. However, the incidence of immune-related adverse events after discontinuation of PD-1 monoclonal antibody was higher than that after discontinuation of placebo[18].

The 2024 ASCO meeting demonstrated the use of adjuvant carrelizumab as a treatment for LANPC, showing that carrelizumab improved PFS and PS compared with standard treatment when used as adjuvant therapy[19]. This suggests that the order of use of immunotherapy is also worth exploring.

## 6 Conclusion and Outlook

Immunotherapy and chemotherapy both have a significant impact in the TME of NPC. Current research results show that the combined use of them can improve the limitations of traditional treatments for NPC by enhancing antigen presentation, overcoming immunosuppression, and consolidating treatment effects. It can improve patient prognosis and provide new directions for future treatments.

However, the cell crosstalk mechanism in NPC TME has not been fully explained, and the effects of immunotherapy and chemotherapy on TME need to be explored. The timing, order of use, dosage and safety of the two still need to be determined. The combined use of them are still in the stage of continuous improvement.

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