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REVIEW ARTICLE

Medicine Science International Medical Journal

Medicine Science 2025;14(1):300-8

Efficacy and safety of immunotherapy for nasopharyngeal carcinoma: A systematic review and meta-analysis

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Received 08 December 2024; Accepted 11 February 2025
Available online 01 March 2025 with doi: 10.5455/medscience.2024.12.159

Abstract

Cancer immunotherapy represents a more advanced and effective treatment modality compared to traditional therapies, playing a significant role in the management of patients with nasopharyngeal carcinoma. However, the efficacy of immunotherapy can be influenced by the 'double-edged sword' nature of the immune system and the individual differences among cancer patients. To assess the efficacy and safety of immunotherapy in patients with nasopharyngeal carcinoma, we conducted a systematic review and meta-analysis of published clinical studies. Clinical research literature related to nasopharyngeal carcinoma immunotherapy was searched in the PubMed, Web of Science, Embase, and Cochrane databases up until December 2010. The literature was screened rigorously according to predefined inclusion and exclusion criteria. Quality evaluation of the included studies was conducted using the Newcastle-Ottawa Scale (NOS), and studies meeting the inclusion criteria were extracted for analysis and evaluation. The Chi-square test and I^2 statistic were utilized to assess heterogeneity, while publication bias was examined through the construction of a funnel plot and the application of the Egger test. A total of 19 studies were included in this meta-analysis, including 2,354 patients with nasopharyngeal carcinoma. The results showed that immunotherapy had a good therapeutic effects on patients with nasopharyngeal carcinoma. The 0.5-3 year PFS of patients with nasopharyngeal carcinoma who received immunotherapy was significantly improved compared to the group who did not receive immunotherapy (OR: 1.87; 95% CI 1.22-2.85) and 0.5-3 year OS were also significantly improved (OR: 1.45; 95% CI 1.23-1.74). In terms of treatment-related adverse events (AEs), the incidence of ≥ grade 3 treatment-related AEs was 27% (95% CI 25-30%), and the incidence of combination therapy was higher than that of monotherapy. In the treatment of patients with nasopharyngeal carcinoma, immunotherapy has demonstrated superior efficacy compared to chemotherapy alone. Furthermore, the expression levels of EBV DNA and PD-L1 in the serum of patients significantly influence the therapeutic outcomes.

Keywords: Nasopharyngeal carcinoma, immunotherapy, curative effect, safety, programmed cell death-ligand 1, epstein-barr virus

Introduction

Nasopharyngeal carcinoma is a malignant epithelial cell tumor that originates in the nasopharyngeal region. It is primarily classified into three subtypes: keratinized squamous cell carcinoma, non-keratinized squamous cell carcinoma, and basal-like squamous cell carcinoma. Among these, the non-keratinized subtype is the most prevalent [1]. The incidence of nasopharyngeal carcinoma has an obvious regional clustering, with a high incidence in Guangdong, Guangxi, Yunnan and Hong Kong in China [2]. The occurrence of nasopharyngeal carcinoma is associated with genetic susceptibility, Epstein-Barr virus (EBV) infection, and environmental factors. Among these, EBV infection is the primary pathogenic factor for the non-keratinized subtype of nasopharyngeal carcinoma [3]. Due to the unique anatomical location of the nasopharynx, simultaneous chemoradiotherapy is one of the primary treatment methods for nasopharyngeal carcinoma. However, following combined chemoradiotherapy, 20-30% of patients with advanced nasopharyngeal carcinoma experience recurrence or metastasis (R/M), resulting in treatment failure. With the rapid advancement and increasing adoption of immunotherapy, numerous studies have demonstrated that immunotherapy is a more effective treatment option for patients with advanced nasopharyngeal carcinoma [4].

CITATION
Li YC, Zhang CC, Li WJ, et al. Efficacy and safety of immunotherapy for nasopharyngeal carcinoma: A systematic review and meta-analysis. Med Science. 2025;14(1):300-8.

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DOI: 10.5455/medscience.2024.12.159

Cancer immunotherapy represents a more advanced and effective treatment modality compared to traditional therapies. This approach aims to enhance the immune system's ability to recognize, target, and eliminate malignant tumor cells, marking a significant milestone in cancer treatment. Current immunotherapy strategies primarily include therapeutic monoclonal antibodies (such as immune checkpoint inhibitors), tumor vaccines, cellular immunotherapy, and combination therapies [5]. With the emergence of clinical research evidence, tumor immunotherapy has demonstrated significant advantages and effects in the treatment of patients with nasopharyngeal cancer. Concurrently, various immunotherapies exhibit differences in both efficacy and safety, and individual patient characteristics can also influence the effectiveness of immunotherapy.

Programmed death receptor-1 (PD-1) and programmed death ligand-1 (PD-L1) are critical immune checkpoints within the tumor microenvironment (TME) and significantly influence the tumor immune response. PD-L1 is highly expressed on the surface of tumor cells and binds to PD-1 on T cells, thereby inhibiting the tumor-killing activity of these immune cells and facilitating tumor immune escape [6].The incidence of nasopharyngeal carcinoma is closely associated with EBV infection, which plays a significant role in the onset and progression of this cancer [4]. Consequently, the level of EBV DNA expression in patients' serum may influence the effectiveness of immunotherapy for nasopharyngeal carcinoma.

In this study, we systematically reviewed and conducted a meta-analysis of clinical research literature related to immunotherapy for nasopharyngeal carcinoma. Our analysis comprehensively evaluated the efficacy and safety of various immunotherapeutic approaches, compared the differences among them, and examined the influence of EBV DNA levels in patient serum and PD-L1 expression in tumor tissues on treatment outcomes. This investigation elucidates the strengths and limitations of immunotherapy for nasopharyngeal carcinoma and identifies key factors that impact therapeutic efficacy, thereby providing valuable insights for the selection of optimal clinical treatment strategies for patients.

Material and Methods

Literature gathering

Literatures related to nasopharyngeal carcinoma immunotherapy were searched through PubMed, Web of Science,Embase and Cochrane databases until December 2010. Keywords included: "nasopharyngeal carcinoma", "immunotherapy", "tumor immunity", "immune checkpoint inhibitors (including various drug names)". The literature was screened strictly according to the inclusion and exclusion criteria. The inclusion criteria were: (1) studies involving patients with nasopharyngeal carcinoma; (2) studies in which immunotherapy was used; (3) clinical studies; (4) studies involving efficacy and safety evaluation; and (5) studies that have been published and are available in any of these public databases. Exclusion criteria: (1) reviews, retrospective analyses, case reports, guidelines, letters, meta-analyses; (2) literature with incomplete information or no statistical significance; (3) studies of non-nasopharyngeal carcinoma patients; (4) studies with fewer than 10 patients.

Data extraction

References that met the inclusion criteria were summarized for detailed information, including the first author, year of publication, tumor characteristics, treatment agents and approaches, median age, median progression-free survival (mPFS), and median overall survival (mOS). Data related to efficacy indicators and adverse events (AEs) were extracted from patients with nasopharyngeal carcinoma. The efficacy indicators included the objective response rate (ORR), progression-free survival (PFS), overall survival (OS), and disease control rate (DCR). Adverse event data were mainly collected for grade 3 or greater treatment-related AEs. Quality of the literature was evaluated using the Newcastle-Ottawa scale (NOS). The ORR values of nasopharyngeal carcinoma patients with different expressions of PD-L1 and EBV were also collected simultaneously after receiving immunotherapy and subsequently subjected to analysis and comparison.

Statistical analysis

Statistical analysis was performed with Rstudio 12.1.0 Software (Copyright (C) 2022 by Posit Software, PBC, USA) and forest maps were drawn. Chi-square test and I^2 statistic were used to measure heterogeneity. If $P>0.1$ or $I^2<50\%$, a fixed effects model is used if heterogeneity is significant, a random effects model is used. Publication bias was detected by drawing a funnel plot and using the Egger test.

Clinical and Research Consequences

Results

Screening for inclusion in the study

A total of 119 references were obtained through database searches. By reading titles and abstracts, 75 references were excluded, including: 15 duplicate records, 5 review articles, 17 animal models, 3 case reports, 9 in vitro experiments, 20 cell experiments, and 6 meta-analyses. After screening, a total of 44 clinical trials may meet our study criteria. We then searched and downloaded the full texts for a more detailed evaluation. Through further evaluation, we excluded 25 studies for reasons including the absence of detailed patient clinical data or the absence of specific efficacy reviews and adverse event records. The specific screening process is shown in (Figure 1). Finally, we selected 19 articles based on clinical trials of nasopharyngeal carcinoma immunotherapy for meta-analysis [7-25].

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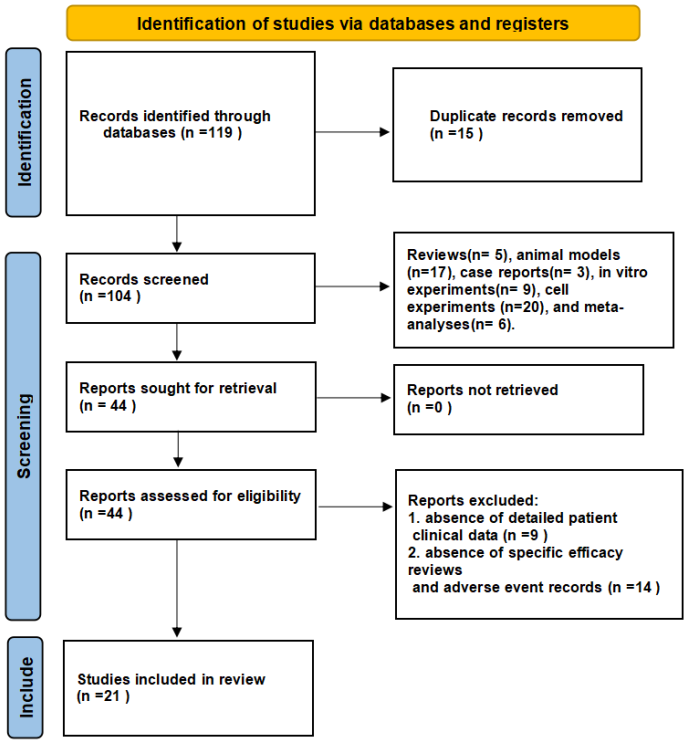

Figure 1. The PRISMA diagram of this systematic review; the retrieval processes are illustrated, covering the stages of identification, screening and inclusion of studies; note that the use of n indicates the number of studies included at each stage

Systematic review of included studies and patient characteristics

19 literature studies were screened for inclusion in our meta-analysis. (Table 1) summarizes specific information from 19 studies that included a total of 2,354 patients with nasopharyngeal carcinoma, mainly recurrent or metastatic nasopharyngeal carcinoma. Approximately 80% of the were male, with a median age range of 45-59 years. Treatment methods mainly included PD-1 immune checkpoint inhibitors (tirellizumab, pembrolizumab, carrellizumab, cardonilizumab, triplizumab, nivolumab), carrellizumab, camrelizumab, triplizumab, nivolumab), combination immunotherapy (therapeutic mab in combination with chemotherapy, radiation therapy, or cellular immunotherapy), and cellular immunotherapy.

At the same time, mOS and mPFS were also counted. After summarization (Table 1), we found that mPFS and mOS were 1.9-9.2 months and 17.1-25.2 months, respectively, after treatment with immune checkpoint inhibitors alone. While mPFS in combination immunotherapy ranged from 6 to 26 months, and mOS was rarely observed (note: mOS was not observed because OS was longer than the planned follow-up time). mOS was observed in only three studies, at 14 months, 29.9 months, and 32 months, respectively. Thus, we found that patients receiving combination immunotherapy achieved longer mPFS and mOS than those treated with immune checkpoint inhibitors alone.

Table 1. Detailed information of the 21 studies included

First author	Year	Tumor characteristic	Treatment	Number of patients / control	Age (median); years	Male/Fmale	Median OS (months)	Median PFS (months)	NOS score
Yunpeng Yang	2023	R/M NPC	Tislelizumab	131/132	50	206/54	Unknown	9.2	9
A.T.C. Chan	2022	R/M NPC	Pembrolizumab	117/116	52	193/40	17..2	4.1	7
Yunpeng Yang	2021	R/M NPC	Camrelizumab	156	48	124/32	17.4	3.7	8
Qiu Yan Chen	2024	R/M NPC	Cadonilimab	23	Unknown	20/3	Unknown	3.71	8
Jian-Ying Xu	2022	R/M NPC	Toripalimab	179	46	148/31	Unknown	Unknown	8
Feng-Hua Wang	2021	R/M NPC	Toripalimab	190	Unknown	158/32	17.4	1.9	8
Caroline Even	2021	R/M NPC	Spartalizumab	82/40	51	101/21	25.2	1.9	9
Xiaozhong Chen	2020	R NPC	Penpulimab	130	Unknown	Unknown	Unknown	Unknown	7
Brigette B.Y. Ma	2018	R/M NPC	nivolumab	45	57	35/10	17.1	2.8	8
Yunyan Mo	2024	R/M NPC	Camrelizumab+apatinib	26	49	22/4	14	6	8
Yijun Hua	2021	R NPC	Toripalimab+IMRT	25	49	18/7	Unknown	18.67	8
Li Yuan	2023	R/M NPC	Camrelizumab+apatinib	40/32	45	56/16	Unknown	12.6	9
Hu Liang	2024	N3 NPC	Camrelizumab+apatinib	49	46	37/12	Unknown	Unknown	7
Hai-Qiang Mai	2023	R/M NPC	GC+Toripalimab	146/143	46	240/49	Unknown	13.2	8
Yu-Jing Liang	2023	NPC	CCRT+TILs	78/78	45	116/90	Unknown	Unknown	8
Whay-Kuang Chia	2013	R/M NPC	GC-CTL	38	57	28/10	29.9	7.6	9
Yin Li	2015	M NPC	GC+CIK	112/110	Unknown	168/64	32	21	8
Jian-jun Li	2012	M NPC	GC+CIK	30/30	Unknown	48/12	Unknown	26	8
Julian Huang	2017	R/M NPC	CTL	28	45	22/6	16.7	2.2	8

It mainly included first author, publication year, tumor characteristics, treatment method, number of patients, median age, sex ratio, mOS, mPFS, NOS score; please note that the number of patients is the experimental group compared to the control group; if the experiment has no control group, it is the total number of patients in the experimental group; unknow means no valid data

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Analysis of efficacy of immunotherapy in patients with nasopharyngeal carcinoma

ORR and DCR in patients with NPC after immunotherapy were reported in 13 of the 19 studies, among which 17 cohorts received related immunotherapy, including 11 cohorts receiving PD-1 immune checkpoint inhibitors (therapeutic mAbs) and 6 cohorts receiving combination immunotherapy. We collected the ORR and DCR of 17 cohorts and mapped the forest.

The ORR of patients with nasopharyngeal carcinoma treated with therapeutic monoclonal antibody therapy was 30% (95% CI 21-44%), I^2=93% with high heterogeneity, so a random-effects model was used (Figure 2). ORR was 72% (95% CI 64-81%) in patients with nasopharyngeal carcinoma receiving combination immunotherapy, and I^2=42% was adopted by a fixed-effects model. The overall ORR for patients receiving immunotherapy was 40% (95% CI 31-52%), I^2=93% using a random-effects model. The ORR of combination immunotherapy was better than that of therapeutic monoclonal antibodies alone, and overall the ORR of immunotherapy was better than that of chemotherapy alone (ORR was 23.3% (95% CI 15.9-32%) [8].

We summarized the DCR and drew the forest map (Figure 3). It was found that the DCR of NPC patients treated with therapeutic monoclonal antibody therapy was 55% (95% CI 45-69%), I^2=94%, with high heterogeneity, so the random effects model was adopted. The DCR of NPC patients receiving combined immunotherapy was 89% (95% CI 81-97%), I2=75% using the random effects model. The DCR for all immunotherapy patients was 65% (95% CI 57-74%), I^2=94% using the random-effects model. The DCR of combination immunotherapy was superior to that of therapeutic mAb alone.

We also did a summary analysis of PFS and OS, Compared with the control group, the PFS rates of nasopharyngeal carcinoma patients receiving immunotherapy at 0.5, 1, 2, and 3 years were 60.0% (295/492) vs 62.5% (263/421), 53.5% (381/712) vs 46.8% (299/639), 46.0% (307/668) vs 25.6% (157/614), 45.3% (86/190) vs 41.0% (77/118), respectively. Results showed (Figure 4) that patients with nasopharyngeal carcinoma who received immunotherapy had a significant improvement in PFS of 0.5 to 3 years compared to those who did not receive immunotherapy (OR: 1.87; 95% CI: 1.22-2.85; p<0.01).

Compared with the control group, the OS rates of nasopharyngeal carcinoma patients receiving immunotherapy at 0.5, 1, 2, and 3 years were 88.4% (237/268) vs 64.7% (139/215), 77% (479/621) vs 78.1% (439/562), 56.2% (349/621) vs 47.7% (286/562), and 49.1% (112/228) vs 42.7% (94/220), respectively. Results showed (Figure 5) that patients with nasopharyngeal carcinoma who received immunotherapy had a significant improvement in OS of 0.5-3 years compared to those who did not receive immunotherapy (OR: 1.45; 95% CI: 1.23-1.74; p<0.01).

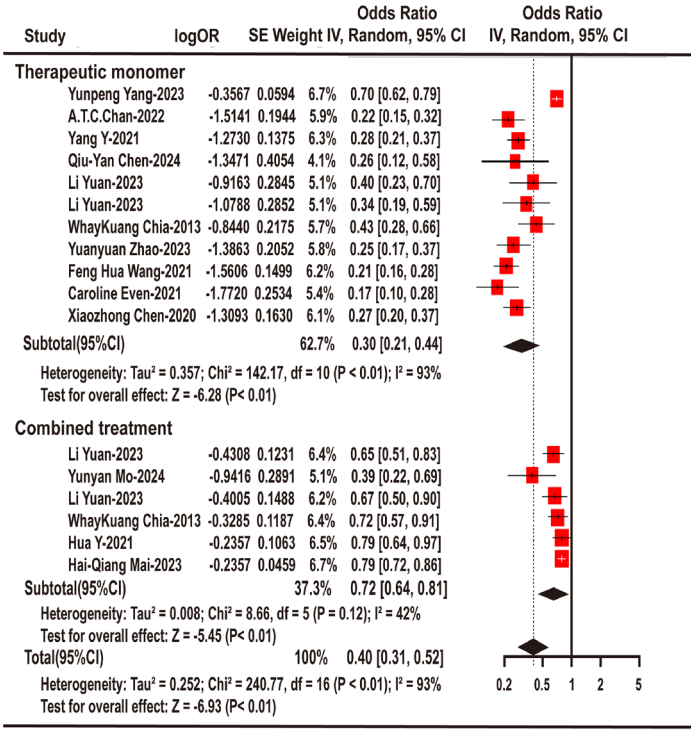

Figure 2. Forest plot of objective response rate (ORR) in patients with nasopharyngeal carcinoma; SE: standard error, IV: inverse variance methods; If P>0.1 or I^2<50%, a fixed-effects model is used, and if heterogeneity is significant, a random-effects model is used

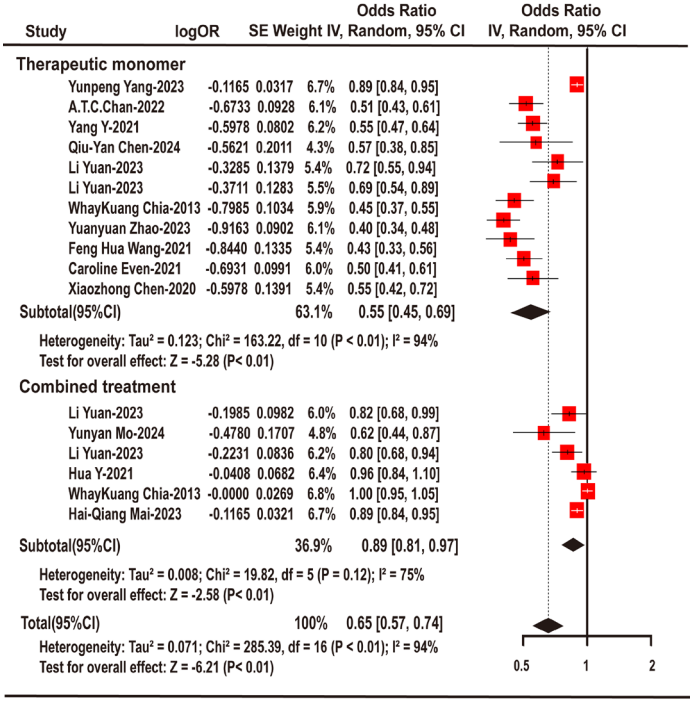

Figure 3. Forest chart of disease control rate (DCR) in patients with nasopharyngeal carcinoma; SE: standard error, IV: inverse variance methods; If P>0.1 or I^2<50%, a fixed-effects model is used, and if heterogeneity is significant, a random-effects model is used

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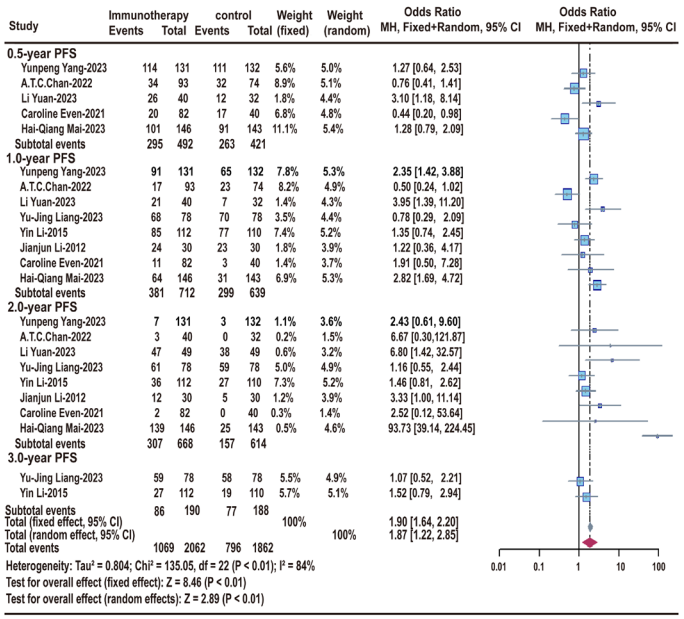

Figure 4. Forest plots of 0.5, 1, 2, and 3 year progression-free survival rates between immunotherapy and control patients with nasopharyngeal carcinoma; MH: Mantel and Haenszel method; If P>0.1 or I^2<50%, a fixed-effects model is used, and if heterogeneity is significant, a random-effects model is used

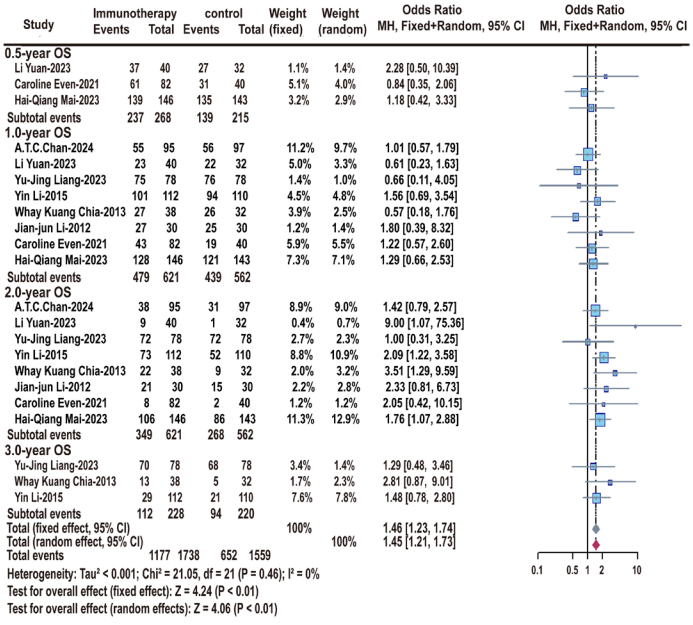

Figure 5. Forest charts of 0.5, 1, 2, and 3 year overall survival rates between immunotherapy and control groups for nasopharyngeal carcinoma patients; MH: Mantel and Haenszel method; If P>0.1 or I^2<50%, a fixed-effects model is used, and if heterogeneity is significant, a random-effects model is used

Safety analysis of immunotherapy in patients with nasopharyngeal carcinoma

A total of 1376 patients in 19 studies reported treatment-related AEs of any grade. We mainly collected the incidence of treatment-related AEs of grade 3 or higher and divided AEs into three groups based on immunotherapies: therapeutic monoclonal antibodies, combination immunotherapy, and cellular immunotherapy. The incidence of treatment-related AEs with grade 3 or higher was 18% (95% CI 13-24%), 43% (95% CI 18-70%), and 4% (95% CI 1-10%), respectively. Pooled analysis found that the incidence of grade 3 or higher treatment-related AEs in patients with nasopharyngeal cancer receiving immunotherapy was 27% (95% CI 25-30%) (I^2=96%, P<0.01), using a random-effects model (Figure 6). Overall, the incidence of AEs of 27% for immunotherapy was lower than 42.8% for chemotherapy alone [8].

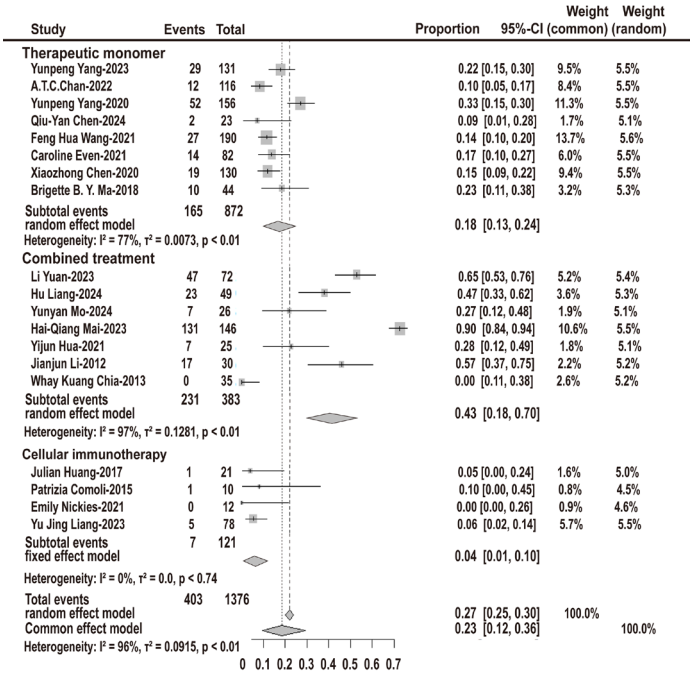

Figure 6. Forest map of the incidence of treatment-related grade ≥3 adverse events for nasopharyngeal carcinoma in patients; Total: The total number of patients receiving immunotherapy; Events: the number of grade 3 or greater adverse events; Proportion:the proportion of grade 3 adverse events; If P>0.1 or I^2<50%, a fixed-effects model is used, and if heterogeneity is significant, a random-effects model is used

Analysis of related factors affecting the efficacy of immunotherapy for nasopharyngeal carcinoma

7 of the 19 studies evaluated the expression status of PD-L1 in tumor tissues of patients, including a total of 608 patients with nasopharyngeal carcinoma, of whom 383 were PD-L1 positive and 225 were PD-L1 negative. The ORR for patients with PD-L1 positive nasopharyngeal carcinoma undergoing immunotherapy was 37% (95% CI 27-51%), (I^2=69%, P<0.01). In contrast, the ORR for patients with PD-L1 negative status was recorded at 23% (95% CI 19-28%), (I^2=1%, P<0.01) as illustrated in (Figure 7). These results suggest that PD-L1-positive nasopharyngeal carcinoma patients receiving immunotherapy have better ORR than PD-L1-negative patients.

DOI: 10.5455/medscience.2024.12.159

6 studies evaluated plasma EBV DNA levels in patients with nasopharyngeal carcinoma, including a total of 668 patients, of whom 440 had high EBV DNA levels and 228 had low EBV DNA levels. The results showed (Figure 8) that after immunotherapy, the ORR was 19.5% (86/440) in patients with higher EBV DNA levels and 53.9% (123/228) in patients with nasopharyngeal cancer with lower EBV DNA levels. Patients with higher EBV DNA levels had a poorer ORR after immunotherapy compared to patients with lower EBV DNA levels (OR: 0.36; 95% CI: 0.19-0.89; p<0.01).

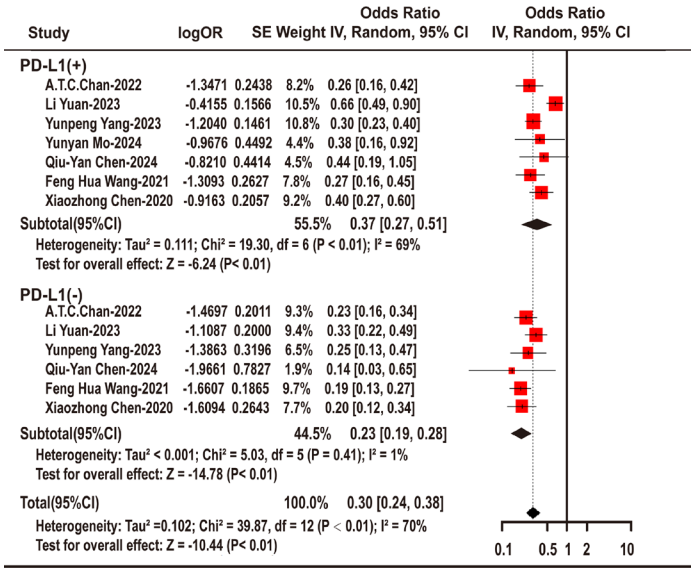

Figure 7. ORR of PD-L1 expression in patients with nasopharyngeal carcinoma; SE: standard error; IV: ınverse variance methods; If P>0.1 or I^2<50%, a fixed-effects model is used, and if heterogeneity is significant, a random-effects model is used

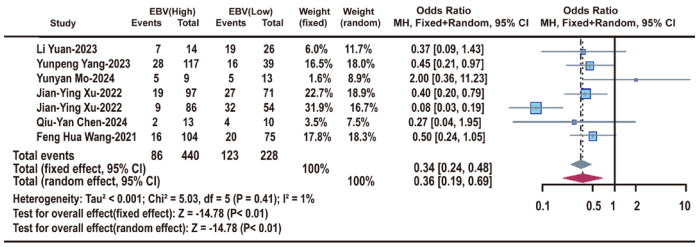

Figure 8. ORR expressed by EBV in patients with nasopharyngeal carcinoma; MH: Mantel and Haenszel method; Total: The total number of patients receiving immunotherapy; Events: Objective remission number; If P>0.1 or I^2<50%, a fixed-effects model is used, and if heterogeneity is significant, a random-effects model is used

Publication bias detection

To detect publication bias, we generated funnel plots of OS and ORR (Figure 9). Visual examination of the shape of the funnel plot shows that both funnel plots are relatively symmetrical and normally distributed. According to the funnel plot, there was no significant publication bias in this study. At the same time, the Egger test was adopted to evaluate publication bias in nasopharyngeal carcinoma patients receiving immunotherapy, and it was found that the P value of Egger test was greater than 0.05 in all groups, with no statistical difference, so there was no significant publication bias in relevant results, as shown in (Table 2).

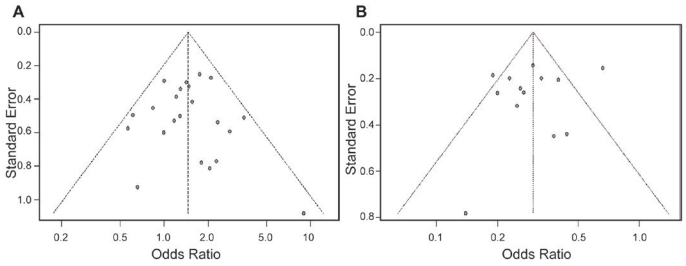

Figure 9. Funnel plot of publication bias; **A.** 0.5-3 years overall survival; **B.** objective response rate

Table 2. Results of publication bias

Effect size	Egger's test (P)
ORR	0.4072
DCR	0.0756
PFS	0.1752
OS	0.6732
Grade≥3 AEs	0.9279

ORR: objective response rate, DCR: disease control rate, PFS: progression-free survival, OS: overall survival, AEs: adverse events

Discussion

According to WHO statistics published in 2022, there are 120,000 new cases of nasopharyngeal cancer worldwide each year, resulting in 73,482 deaths [26]. The incidence of nasopharyngeal carcinoma exhibits significant regional clustering and ethnic differences. In China, it is more prevalent in the southern regions, with an incidence of approximately 30 per 100,000 in males and 13 per 100,000 in females. The incidence in men is about 2.3 times higher than that in women [4]. Among these cases, the treatment of recurrent/metastatic nasopharyngeal carcinoma presents a considerable challenge. The primary salvage treatments for patients with recurrent/metastatic nasopharyngeal carcinoma include radiotherapy, chemotherapy, and surgery. However, the efficacy and prognosis of these methods for patients with recurrent or metastatic nasopharyngeal carcinoma (R/M NPC) remain suboptimal. Following salvage intensity-modulated radiation therapy (IMRT), patients with advanced recurrent NPC exhibit a poor prognosis, with a 5-year survival rate of merely 30%. Moreover, radiation-induced damage during therapy can lead to significant sequelae, contributing to 46-70% of deaths attributed to radiotherapy complications [27]. Gemcitabine in combination with cisplatin (GP) and fluorouracil in combination with cisplatin are the primary systemic therapies for patients with recurrent or metastatic nasopharyngeal carcinoma, yielding median OS rates of 22.1 months and 18.6 months, respectively [28]. The prognosis following chemotherapy for nasopharyngeal carcinoma remains unsatisfactory. Given the unique anatomy of the nasopharynx, there are limited surgical options available.

DOI: 10.5455/medscience.2024.12.159

Additionally, nasopharyngeal carcinoma cells exhibit high radiosensitivity and sensitivity to chemotherapy. Consequently, the primary treatment approach for patients with this condition involves a combination of radiotherapy and chemotherapy [29]. Although combined chemoradiotherapy has demonstrated a favorable prognostic effect, with a 5-year survival rate of 85-90%, its efficacy remains limited, as recurrence or metastasis occurs in 8-10% of patients undergoing this treatment [30]. With the continuous advancement of modern medical practices, researchers have achieved significant improvements and breakthroughs in the clinical treatment of advanced nasopharyngeal carcinoma. However, the outcomes remain unsatisfactory, and substantial challenges persist in the clinical management of this condition. There is an urgent need for new therapeutic strategies to enhance the efficacy and prognosis for patients with advanced nasopharyngeal carcinoma. The growing popularity and rapid development of tumor immunotherapy have created greater opportunities for the treatment of this malignancy.

Immunotherapy has opened new avenues for the treatment of various refractory cancers, representing a significant advancement in the field of tumor clinical treatment. Cancer immunotherapy encompasses tumor vaccines, cellular immunotherapy, immune checkpoint inhibitors, combination therapies, and other modalities [31]. Inhibitors of the PD-1/PD-L1 immune checkpoint are the most commonly utilized immunotherapies for the treatment of nasopharyngeal cancer, having received approval in China in 2021 for the management of recurrent or metastatic (R/M) nasopharyngeal cancer [32]. Currently, various immunotherapies have been employed in the treatment of advanced nasopharyngeal carcinoma, leading to significant advancements in both efficacy and safety. However, there are notable differences in therapeutic efficacy and safety among different immunotherapies and therapeutic agents. Our meta-analysis further demonstrated that the ORR for immunotherapy was 40% (95% CI 31-52%), which is superior to that of chemotherapy alone, where the ORR was 23.3% (95% CI 15.9-32%) [8]. In comparison to patients who did not receive immunotherapy, those with nasopharyngeal carcinoma (NPC) who underwent immunotherapy exhibited significant improvements in both PFS and OS over a period of 0.5 to 3 years. The odds ratios (OR) were found to be 1.87 (95% CI: 1.22-2.85; $p<0.01$) for PFS and 1.45 (95% CI: 1.23-1.74; $p<0.01$) for OS. Additionally, we observed that the ORR for NPC patients receiving combined immunotherapy was 72% (95% CI: 64-81%), which was notably higher than the ORR of 30% (95% CI: 21-44%) for those treated with the PD-1 immune checkpoint inhibitor alone. A similar trend was also evident in the DCR. Through statistical analysis of the occurrence of grade 3 or higher adverse events following treatment, we found that combined immunotherapy demonstrated a greater efficacy advantage. However, the incidence of grade 3 or higher adverse events was higher compared to that of PD-1 immune checkpoint inhibitors and cellular immunotherapy administered alone. Consequently, while immunotherapy presents a promising approach for treating patients with advanced nasopharyngeal carcinoma, further in-depth research is necessary to optimize treatment selection and manage adverse events effectively, thereby achieving enhanced therapeutic outcomes while ensuring patient safety.

Among the various pathogenic factors associated with nasopharyngeal carcinoma, EBV infection plays a significant role, accounting for the majority of cases across all non-keratinized nasopharyngeal carcinoma subtypes. Furthermore, EBV infection may synergistically enhance the occurrence and progression of nasopharyngeal carcinoma in conjunction with other pathogenic factors [1]. Given the close relationship between EBV and nasopharyngeal carcinoma, we conducted a comprehensive analysis of EBV DNA levels in the serum of patients and the efficacy of immunotherapy. Our findings indicate that patients with elevated EBV DNA levels exhibited a lower ORR to immunotherapy compared to those with lower EBV DNA levels (OR: 0.36; 95% CI: 0.19-0.89; $p<0.01$). This suggests that EBV infection not only facilitates the malignant progression of the tumor but also adversely impacts the effectiveness of tumor immunotherapy, serving as a critical factor influencing both the occurrence and treatment of nasopharyngeal carcinoma. Consequently, the expression level of EBV DNA should be thoroughly considered in the management of nasopharyngeal carcinoma, and appropriate treatment strategies should be developed. Furthermore, we posit that addressing nasopharyngeal carcinoma from the standpoint of EBV infection presents a promising avenue for research, including the potential development of an EBV vaccine.

Immune escape is a critical mechanism underlying tumor development. PD-1 serves as a significant immunosuppressive molecule and is one of the key immune checkpoints. Its overexpression contributes to the immune evasion of tumors and is closely associated with tumor occurrence, progression, and poor prognosis [33,34]. PD-L1, a ligand of PD-1, is expressed on both tumor cells and immune cells, whereas PD-1 is primarily expressed on activated T cells. Upon binding to PD-1, PD-L1 inhibits T cell effector functions by inducing T cell exhaustion and apoptosis, thereby leading to an immunosuppressive state [35]. Studies have demonstrated that the PD-L1/PD-1 signaling pathway plays a crucial role in T cell-mediated tumor immune responses. Therapeutic blockade of the PD-1/PD-L1 pathway has been shown to elicit tumor responses in certain patients with tumors [36]. In this study, we conducted a comprehensive analysis of PD-L1 expression in tumor tissues from patients and evaluated the efficacy of immunotherapy. Our findings indicate that PD-L1-positive nasopharyngeal carcinoma patients who received immunotherapy exhibited a higher ORR of 37% (95% CI: 27-51%) compared to PD-L1-negative patients, who had an ORR of 23% (95% CI: 19-28%). Thus, PD-L1 serves as a signal of immune escape in nasopharyngeal carcinoma (NPC) tumors and may also be utilized as a significant biomarker for guiding immunotherapy.

DOI: 10.5455/medscience.2024.12.159

In summary, tumor immunotherapy has demonstrated promising efficacy and safety in the treatment of nasopharyngeal carcinoma. However, variations in the efficacy and safety profiles of different immunotherapies warrant further investigation and refinement. Additionally, given the individual variability in cancer presentations, therapeutic responses to immunotherapy may differ among patients. Consequently, clinical treatment should take into account these individual differences, and treatment strategies should be tailored to each patient's specific circumstances. Current research on immunotherapy for nasopharyngeal carcinoma is not yet fully developed, resulting in a lack of sufficient evidence to conduct a more detailed group study. We will continue to monitor the relevant evidence regarding immunotherapy for nasopharyngeal cancer in future studies to provide more detailed and comprehensive analytical recommendations.

Conclusion

In the treatment of nasopharyngeal carcinoma, immunotherapy has demonstrated greater efficacy compared to chemotherapy alone. The use of PD-1 checkpoint inhibitors in conjunction with other chemotherapeutic agents, radiation therapy, or cellular immunotherapy has proven to be more effective than utilizing these methods independently; however, this combination may be linked to a relatively high incidence of adverse events. Additionally, elevated levels of EBV DNA in the serum of patients can hinder the effectiveness of immunotherapy. Conversely, patients exhibiting high expression of PD-L1 tend to experience improved outcomes with immunotherapy.

Conflict of Interests

The authors declare that there is no conflict of interest in the study.

Financial Disclosure

This work was supported by the National Natural Science Foundation of China (grant nos. 82460724 and 82260485); Yunnan Applied Basic Research Project-Kunming Medical University Union Foundation (grant nos. 202201AY070001-013); The program Innovative Research Team in Science and Technology in Kunming Medical University(grant nos. CXTD202202) ; Yunnan Ten Thousand Talents Plan Young and Elite Talents Project(grant nos. YNWR-QNBJ-2019-056); Basic research project of Science & Technology Department of Yunnan Province in 2020 (grant nos. 202001AT070056).

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DOI: 10.5455/medscience.2024.12.159

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