

Precision drugs for recurrent or metastatic nasopharyngeal carcinoma (Review)

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Abstract. Nasopharyngeal carcinoma (NPC) is a malignancy that is common in Southern China, South-East Asia and North Africa. Platinum-based chemotherapy is currently the main treatment option for the first-line therapy of recurrent and/or metastatic NPC (RM-NPC). However, the outcome of patients with advanced disease remains poor after treatment with standard chemotherapy, as patients eventually became resistant to chemotherapy. Other strategies, such as targeted therapy and immunotherapy, offer alternative options for patients due to their reported efficacy and manageable toxicities. This suggests that these modalities, either as monotherapy or in combination with chemotherapy, may serve as viable treatment options for RM-NPC. The present review provides a comprehensive summary of the clinical data of targeted therapy and immunotherapy for RM-NPC, with the aim of broadening the understanding of RM-NPC management.

Contents

1. Introduction
2. Targeted therapies
3. Immunotherapy
4. Conclusions

1. Introduction

Nasopharyngeal carcinoma (NPC) is a malignancy that is commonly observed in Southern China, South-East Asia and North Africa. NPC is closely associated with genetic factors (such as HLA genes residing at the major histocompatibility complex region on chromosome 6p21), infection with the Epstein-Barr Virus (EBV) and environmental factors (1). Radiotherapy and chemotherapy are the main therapeutic options applied for NPC treatment (1). With the advances in radiotherapy technologies and chemotherapy treatments over the past decade, the 5-year overall survival rate of patients with NPC has improved to >80% for early-stage and 50-60% for locally-advanced disease patients (2). However, relapse and metastasis remain an issue in ~30% patients after standard care (radiotherapy/chemotherapy) (1,3). Cisplatin-based chemotherapy is the standard first-line treatment method for inoperable, recurrent and metastatic NPC (4). However, responses to such regimen do not endure and tend to reach a plateau, particularly in heavily pre-treated (radiotherapy/chemotherapy) disease. Targeted therapies and immunotherapy demonstrate efficacy for recurrent and/or metastatic NPC (RM-NPC) (1).

In the present review, the evidence and potential value of targeted therapies and immunotherapy for the clinical management of RM-NPC were comprehensively summarized. The current review aimed to provide suggestions to facilitate the optimal tailoring of treatment modalities, in addition to highlighting important future research directions and gaps in the knowledge in the field.

2. Targeted therapies

Over the past decade, gene sequencing technologies have been evolving, which advanced the understanding into the molecular signaling pathways involved in tumors (5,6). This has stimulated an interest in molecular-targeted therapies. To date, a number of clinical trials have evaluated the feasibility of targeted therapies for the treatment of RM-NPC, including anti-epidermal growth factor receptor (EGFR) and anti-vascular endothelial growth factor (VEGF) (7,8).

Targeting EGFR. EGFR is highly expressed in most (>82%) NPCs and contributes to tumor development (Fig. 1) (5,6). As

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a result, a number of investigations have assessed the efficacy and toxicity of anti-EGFR monoclonal antibodies (Table I) and EGFR tyrosine kinase inhibitors (TKIs) for patients with RM-NPC (Fig. 2). Chan *et al* (7) reported that the combination of cetuximab (a monoclonal antibody targeting EGFR) and carboplatin displayed clinical efficacy in patients with RM-NPC who have already been treated with platinum-based chemotherapy. The overall response rate (ORR) was 11.7% (7/60 patients), the median progression-free survival (PFS) was 81 days, and the median overall survival (OS) was 233 days. For adverse events, 51.7% (31/60) of the cases had grade 3/4 toxicities (7). Another retrospective study evaluating the toxicity and efficacy of the combination of paclitaxel, carboplatin and cetuximab for the first-line treatment for patients with RM-NPC revealed that this regimen was feasible and potentially effective, with a 58.3% (7/12 patients) ORR and a 4.1-month PFS (8). Furthermore, the aforementioned data were confirmed by another previous retrospective study, which revealed that an anti-EGFR monoclonal antibody (nimotuzumab or cetuximab) combined with gemcitabine and platinum achieved a 10.3-month median PFS, a 42.8-month median OS and a 67.9% (57/84 patients) ORR. The most common grade 3/4 adverse events were leukopenia (35.7%; 30/84 patients) and thrombocytopenia (26.2%; 22/84 patients) (9). Furthermore, using cetuximab alongside chemoradiotherapy for the treatment of patients with RM-NPC was found to improve the survival of patients, with an ORR of 70.0% (21/30), median PFS of 12.2 months and median OS of 23.6 months (10). However, the aforementioned studies included small sample sizes, resulting in limited reproducibility. In addition, these studies did not evaluate the difference in the efficacy and safety profile between standard platinum-based chemotherapy plus monoclonal antibody and chemotherapy alone. A retrospective study revealed that there was no difference between anti-EGFR therapy plus chemotherapy (62 cases) and chemotherapy alone (248 cases) in the outcomes of patients with *de novo* metastatic NPC (11). Therefore, the use of anti-EGFR monoclonal antibodies warrants consideration for the treatment of early-stage metastatic NPCs.

Nimotuzumab is an IgG1 humanized anti-EGFR monoclonal antibody. A multicenter, phase II study (12) explored the effects of nimotuzumab combined with cisplatin and 5-fluorouracil (PF) on patients with RM-NPC after standard chemoradiotherapy. The results indicated that ORR was 71.4% (25/35 patients), the median PFS was 7.0 months and OS was 16.3 months. However, leukopenia was also observed, which is a severe side effect (62.9% of patients had grade 3/4) (12). In another clinical trial, compared with chemotherapy alone, nimotuzumab plus chemotherapy prolonged the survival and did not exacerbate the toxicity of RM-NPC, with 7.5 vs. 8.5 months in median PFS and 25.6 vs. 48.6 months in median OS, respectively (13). Chemoradiotherapy is a treatment option for locally recurrent NPC. However, the combination of radiation and chemotherapy may increase the toxicity. Additionally, when combined with chemotherapy, patients become less tolerant to repeated irradiation (1). A previous study suggested that compared with chemoradiotherapy, radiotherapy combined with nimotuzumab achieved similar local control rates and OS for patients with RM-NPC (14). Furthermore, the nimotuzumab treatment group had a lower incidence of

acute and late toxicities (14). The addition of nimotuzumab to radiotherapy may be a promising strategy for patients who cannot tolerate chemoradiotherapy. Given that both cetuximab and nimotuzumab demonstrated clinical efficacy for RM-NPC to an extent, a retrospective study by Chen *et al* (15) aimed to determine which drug would be more effective. It was revealed that cetuximab plus palliative chemotherapy had a longer PFS time compared with nimotuzumab plus palliative chemotherapy (9.7 vs. 7.9 months), but there was no difference in the OS time (15). However, these findings need to be verified by future head-to-head randomized trials.

Gefitinib and erlotinib are TKIs that can target EGFR (16-18). However, three trials over the past decade suggested either no or limited clinical efficacy in patients who have already been heavily treated (after ≥ 2 lines of therapy) (16-18). The lack of EGFR mutations has been proposed to underly this phenomenon (19). Previous studies have reported that the degree of TKI efficacy in non-small cell lung cancer is closely associated with the EGFR mutational status (20,21).

Targeting VEGF and VEGF receptor (VEGFR). VEGF and its receptor VEGFR serve an important role in NPC, being associated with angiogenesis and metastasis (22,23). Therefore, targeting VEGF signaling has been considered potentially beneficial for patient outcome. Sorafenib, an oral multi-kinase inhibitor, offered only modest efficacy (ORR of 3.8%; 1/26 patients) for recurrent or metastatic squamous cell carcinoma of the head and neck and NPC (24). However, only a small percentage of patients (26.9%; 7/26 patients) were diagnosed with NPC in this aforementioned study (24). In addition, Xue *et al* (25) previously revealed a high ORR of 77.8% (42/54 patients), a median PFS of 7.2 months and an OS of 11.8 months after treatment with sorafenib plus PF. Compared with the OS of patients treated with PF (19.5 months) demonstrated in another previous study (26), this OS was shorter despite the higher ORR (77.8 vs. 60.2%) (25). Furthermore, 83.3% (45/54) of patients exhibited hand-foot skin reactions [18.5% (10/54) of grade 3/4] (25). Consequently, whether sorafenib can provide additional benefits for patients with RM-NPC requires further exploration, as does the difference between sorafenib plus PF and the standard dose of PF alone.

Sunitinib is another multi-kinase inhibitor of VEGFR1-3, platelet-derived growth factor receptor (PDGFR), stem cell factor receptor and fms-like tyrosine kinase receptor-3 (27). Although sunitinib demonstrated modest anticancer activity (an ORR of 10%) in patients with RM-NPC who had been previously treated with high-dose (curative) radiation, 64.3% (9/14) patients hemorrhaged (epistaxis, hemoptyses and hematemesis) [29% (4/14) in grade 3/4 and 14.3% (2/14) in grade 5] (27). Pazopanib is also a multi-kinase inhibitor of VEGFR-1, -2, and -3, platelet-derived growth factor (PDGF)-a, PDGF-b and c-kit tyrosine kinases. Pazopanib displayed promising efficacy and acceptable side effects in patients with RM-NPC who had already been heavily pre-treated (after ≥ 2 lines of therapy), as 6.1% (2/33) cases achieved partial responses (PRs) and 48.5% (16/33 patients) achieved stable disease. However, 15.2% (5/33) patients had grade 3/4 hand-foot syndrome and 1 patient succumbed to epistaxis and myocardial infarction (28).

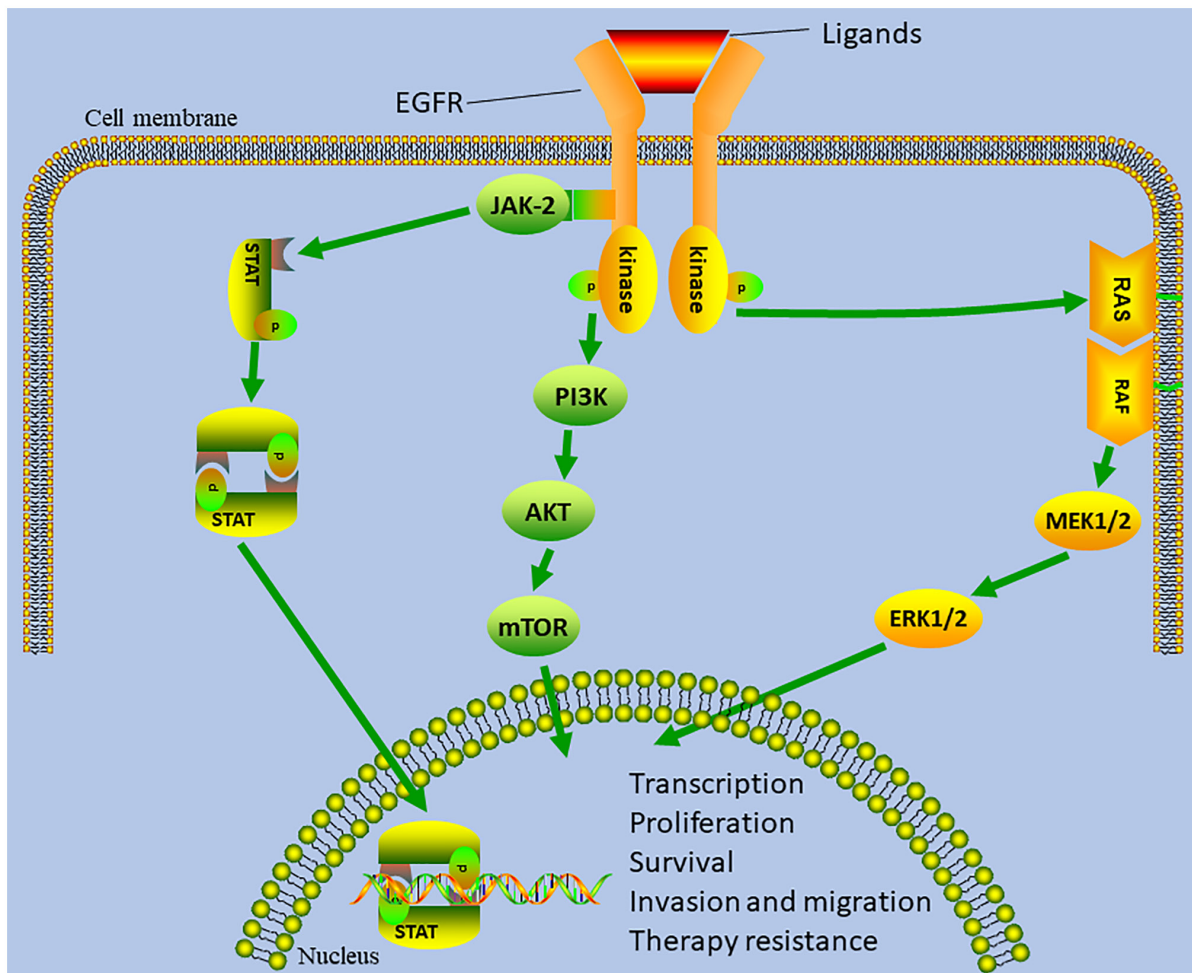


Figure 1. Downstream pathways following the activation of EGFR. Once ligands bind to the extracellular domain of the EGFR, EGFR is activated and subsequently activates downstream pathways, such as JAK/STAT, RAS/RAF/MEK/ERK and PI3K/AKT. These signaling pathways result in the proliferation, survival, invasion, migration and therapy resistance of tumor cells. EGFR, epidermal growth factor receptor; JAK, Janus kinase; p, phosphorylated.

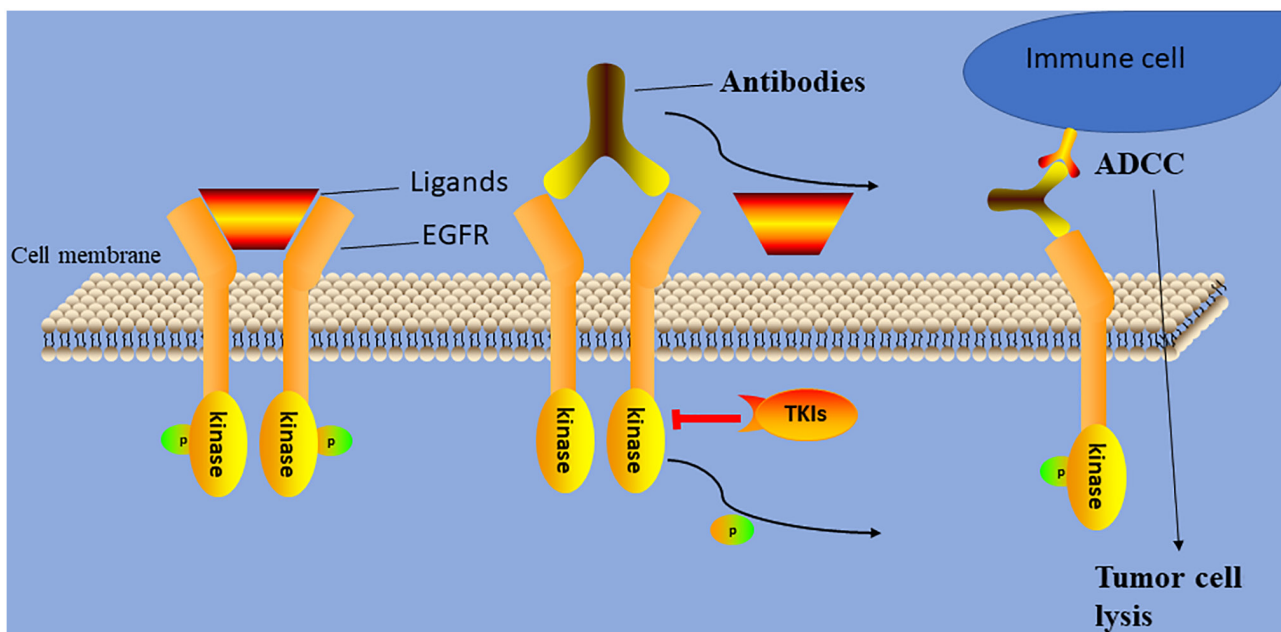


Figure 2. Mechanism of anti-EGFR therapies. Anti-EGFR antibodies can recognize and bind to the extracellular domain of EGFR, which prevents EGFR from binding to ligands. By contrast, antibodies can induce tumor cell lysis by activating ADCC. EGFR TKIs bind to the intracellular tyrosine kinase portion and block the phosphorylation of EGFR. EGFR, epidermal growth factor receptor; ADCC, antibody-dependent cell-mediated cytotoxicity; TKI, tyrosine kinase inhibitor; p, phosphorylated.

Table I. Targeted EGFR therapy for recurrent or metastatic nasopharyngeal carcinoma.

Inhibitor	Type	Case numbers	Treatment	Outcomes	(Refs.)
Cetuximab (combined with chemotherapy)	Phase II	60	Cetuximab: An initial dose of 400 mg/m ² followed by weekly doses of 250 mg/m ² Carboplatin: (AUC=5); received by patients every 3 weeks up to a maximum of eight cycles	ORR (11.7%); median PFS (81 days); median OS (233 days). Grade 3/4 toxicity (51.7%)	(7)
Cetuximab (combined with chemotherapy)	Retrospective	14	Cetuximab: An initial dose of 400 mg/m ² followed by 250 mg/m ² weekly. Paclitaxel: A dose of 100 mg/m ² on day 1 and 8; Carboplatin: (AUC=2.5); received by patients on days 1 and 8, every 3 weeks	ORR (58.3%); median PFS (4.1 months). Grade 3/4 toxicity: Neutropenia (21.4%) and skin reaction (14.3%)	(8)
Cetuximab/ Nimotuzumab (combined with chemotherapy)	Retrospective	84	Cetuximab: An initial dose of 400 mg/m ² followed by 250 mg/m ² weekly. Nimotuzumab: A dose of 200 mg/m ² weekly to triweekly. Gemcitabine (1,000 mg/m ² on day 1 and 8) plus cisplatin or nedaplatin (80 mg/m ² on day 1) or carboplatin (AUC=5 on day 1)	ORR (67.9%); median PFS (10.3 months); median OS (42.8 months). Grade 3/4 toxicity: Leukopenia (35.7%) and thrombocytopenia (26.2%)	(9)
Cetuximab (combined with chemoradiotherapy)	Retrospective	30	IMRT: Median dose (60 Gy). TP/TPF (docetaxel 60-75 mg/m ² day 1 plus DDP 25 mg/m ² day 1-3±5-FU 500 mg/m ² /day with 120-h infusion), GP plus DDP (25 mg/m ² day 1-3) and PC	ORR (70%); median PFS (12.2 months); median OS (23.6 months); 2-year OS (53.3%). Grade 3/4 toxicity: Neutropenia (86.7%), anemia (26.7%) and thrombocytopenia (10%)	(10)
Cetuximab/ Nimotuzumab (combined with chemotherapy)	Retrospective	310	Cetuximab: An initial dose of 400 mg/m ² followed by 250 mg/m ² weekly. Nimotuzumab: A dose of 200 mg/m ² weekly. TP, PF, TPF and GP were received by patients every 3 weeks with five median cycles of chemotherapy (range of 2-10 cycles)	Combination group vs. control group, 3-year OS, 63.0 vs. 58.1%, P=0.485. Grade 3 skin reactions (29.0 vs. 6.9%, P<0.001) and Grade 3/4 mucositis (38.7 vs. 10.9%, P<0.001)	(11)
Nimotuzumab (combined with chemotherapy)	Phase II (NCT01616849)	35	Nimotuzumab: A dose of 200 mg/m ² weekly. Cisplatin (100 mg/m ² day 1) and 5-fluorouracil (4,000 mg/m ² continuous infusion day 1-4) were received by patients 3 times/week for a maximum of 6 cycles	ORR (71.4%); median PFS (7.0 months); median OS (16.3 months). Grade 3/4 toxicity: Leukopenia (62.9%)	(12)
Nimotuzumab (combined with chemotherapy)	Retrospective	70 (21:49)	Nimotuzumab: A dose of 200-400 mg/m ² weekly. GP, TP and PF were received by patients every 3 weeks	Combination group vs. control group: Median PFS (8.5 vs. 7.5 months), P=0.424; median OS (48.6 vs. 25.6 months), P=0.017. Toxicity: No significant difference between the two groups	(13)

Table I. Continued.

Inhibitor	Type	Case numbers	Treatment	Outcomes	(Refs.)
Nimotuzumab (combined with radiotherapy)	Retrospective	87 (32:55)	Nimotuzumab: A dose of 200 mg/m ² weekly concurrent with RT chemoradiotherapy	Nimotuzumab group vs. chemoradiotherapy group; 4-year OS; 37.1 vs. 40.7%, P=0.735. Late radiation grade 3/4 toxicity: Nimotuzumab group, 12 patients; chemoradiotherapy group, 36 patients	(14)
Cetuximab/ Nimotuzumab (combined with chemotherapy)	Retrospective	203	Cetuximab: An initial dose of 400 mg/m ² followed by 250 mg/m ² weekly. Nimotuzumab: A dose of 200 mg/m ² weekly. Chemotherapy: TP, TPF, PF or GP	ORR (67.5%); median PFS (8.9 months); median OS (29.1 months). Grade 3/4 toxicity: Leukopenia (43.4%)	(15)

Numbers presented as (n:n) represent the number of patients in different groups. AUC, area under the curve; DDP, cisplatin; ORR, objective response rate; PFS, progression-free survival; OS, overall survival; RT, radiotherapy; IMRT, intensity-modulated radiotherapy; GP, gemcitabine (1,000 mg/m² day 1 and 8) plus cisplatin (20-30 mg/m² day 1-3); PF, cisplatin (20-25 mg/m² day 1-3) plus 5-fluorouracil (800-1,000 mg/m² for 120 h); TP, docetaxel (80 mg/m² day 1) plus cisplatin (75 mg/m² day 1); TPF, docetaxel (60 mg/m² day 1) plus cisplatin (60 mg/m² day 1) plus 5-fluorouracil (500-800 mg/m² for 120 h); PC, paclitaxel 60 mg/m²/week day 1 plus carboplatin AUC = 2/week day 1.

Axitinib is a second generation TKI that is effective against VEGFR (29,30). A phase II study previously assessed the efficacy of axitinib in patients with RM-NPC who had previously failed at least one line of platinum-based chemotherapy. The study revealed that treatment with only axitinib had a high clinical benefit rate, with 78.4% (29/37) patients at 3 months and 43.2% (16/37) at 6 months demonstrating an either complete response (CR), PR or stable disease. Furthermore, the incidence of hemorrhagic events was lower [17.9% (7/39) of grade 1/2] whereas that of other grade 3/4 toxicities were rare compared with the first generation TKI sunitinib (30).

Lucitanib is a novel multi-target inhibitor of fibroblast growth factor receptors 1-3, VEGFRs 1-3 and PDGFR α/β (31). A previous Phase Ib study found that lucitanib has promising anticancer activity and tolerable toxicity in patients with RM-NPC who had already been heavily pretreated. However, the tolerability and efficacy of lucitanib in patients with RM-NPC should be evaluated in further phase II/III studies (31). Given the modest efficacy in patients with RM-NPC, a further study of angiogenesis inhibitors (sorafenib and sunitinib) as a single treatment for this disease is not likely to yield beneficial results. However, these inhibitors are generally well-tolerated and easy to deliver (oral administration). Therefore, the combination of these inhibitors with other agents or radiation may yet prove be a viable option for patients with RM-NPC.

Targeting AKT. Apart from the EGFR and VEGF pathways, the PI3K/AKT signaling pathway has also been found to be activated in >40% of cases with NPC (32,33). However, MK-2206, an oral AKT inhibitor, demonstrated a limited effect on patients with RM-NPC who had already been heavily pretreated. Only 4.8% (1/21) of patients had PR, whereas the

median PFS of all patients was 3.5 months (34). The reason for this may be the activation of compensatory pathways, such as the MAPK signaling pathway (35).

3. Immunotherapy

Immunotherapy, especially immune checkpoint inhibitors, has become an intensively researched topic in the field of tumor therapy. It has been previously reported that there are various types of immune cells in NPC tissues, such as natural killer cells and T lymphocytes (36,37). However, the immunogenic effects of these cells are typically suppressed, such that the tumor cells can evade immunosurveillance (37). Therefore, the mechanisms by which tumor cells can evade this surveillance and how immune cells can be activated to destroy cancer cells have garnered the interest of researchers. Based on the findings of previous studies (38-41), cytotoxic T-lymphocyte protein 4, programmed death-1 (PD-1) (Fig. 3) and EBV are potential targets for circumventing the evasion of the immune system by tumor cells. In the present review, the prospect of targeting the aforementioned components and using EBV-related vaccines or cytotoxic T-lymphocytes (CTLs) was evaluated in the context of RM-NPC. It appears to be a valid option for patients because of the promising effectiveness and safety profile reported.

Immune checkpoint inhibitors. To date, immune checkpoint inhibitors that have been assessed for NPC are pembrolizumab, nivolumab, camrelizumab and toripalimab (Table II). In 2017, a phase Ib trial (KEYNOTE-028) preliminarily reported that pembrolizumab possessed antitumor activity in programmed death-ligand 1 (PD-L1)-positive patients

Table II. Immune checkpoint inhibitors for recurrent or metastatic nasopharyngeal carcinoma.

Inhibitor	Type	Case numbers	Treatment	PD-L >1% (%)	Outcomes	(Refs.)
Pembrolizumab	Phase I (NCT02054806)	27	Pembrolizumab 10 mg/kg IV every 2 weeks for 24 months or until disease progression	N/A	ORR (25.9%); 1-year PFS (33.4%). Grade 3/4 toxicity (29.6%)	(40)
Nivolumab	Phase II (NCT02339558)	45	Nivolumab 3 mg/kg IV every 2 weeks until disease progression	N/A	ORR (20.5%); 1-year PFS (30.9%). Grade 3/4 toxicity (22.0%)	(44)
Camrelizumab (monotherapy)	Phase I (NCT02721589)	91	Camrelizumab 1 mg/kg, 3 mg/kg, 10 mg/kg or 200 mg IV every 2 weeks until disease progression	40	ORR (34.0%); 1-year PFS (27.1%). Grade 3/4 toxicity (16.1%)	(42)
Camrelizumab (combined with chemotherapy)	Phase I (NCT03121716)	22	Camrelizumab 200 mg IV every 3 weeks for 6 cycles or until disease progression Gemcitabine. (1,000 mg/m ² on days 1 and 8) and cisplatin (80 mg/m ² on day 1)	100	ORR (91.0%); 1-year PFS (61.4%). Grade 3/4 toxicity (57.0%)	(42)
Camrelizumab (combined with chemotherapy)	Phase III (NCT03707509)	263 (134:129)	Camrelizumab (200 mg on day 1) or placebo IV, plus GP every 3 weeks for four to six cycles, followed by maintenance therapy with camrelizumab or placebo	N/A	Median PFS 9.7 vs., 6.9 months. Serious adverse events, 44.0 vs. 37.2%	(43)
Toripalimab	Phase II (NCT02915432)	190	Toripalimab 3 mg/kg IV every 2 weeks until disease progression or unacceptable toxicity	25.3	ORR (20.5%); median PFS (1.9 months); median OS (17.4 months)	(47)
Toripalimab (combined with chemotherapy)	Phase III (NCT03581786)	289 (146:143)	Median six cycles GP, followed by maintenance treatment with toripalimab or placebo	Toripalimab; 74.7%; placebo; 76.2%	Median PFS 11.7 vs. 8.0 months; grade ≥3 adverse events, 89.0 vs. 89.5%	(48)

Numbers presented as (n:n) represent the number of patients in different groups. N/A, non-applicable; ORR, objective response rate; PFS, progression-free survival; OS, overall survival; GP, gemcitabine and cisplatin; IV, intravenous; PD-L, programmed death ligand.

with RM-NPC (40). It was then revealed that 25.9% (7/27) patients obtained a PR over a median follow-up time of 20 months whereas 51.9% (14/27) patients had stable disease. However, 29.6% (8/27) cases suffered from grade 3-5 toxicities, including hepatitis (7.4%; 2/27 patients) and pneumonia (7.4%; 2/27 patients), whilst 1 patient succumbed to sepsis (40).

Camrelizumab (SHR-1210) is another antibody against PD-1 (42). Camrelizumab monotherapy as a second-line

therapy for patients with RM-NPC resulted in a 34.1% (31/91) ORR with a median follow-up of 9.9 months. Grade 3/4 toxicity occurred in 16.1% (15/93) of patients (42). Furthermore, the addition of camrelizumab to gemcitabine and cisplatin (GP) as a first-line therapy was also evaluated in patients with RM-NPC (42). During the median follow-up period of 10.2 months, 90.9% (20/22 cases) achieved an ORR. However, grade 3/4 adverse events were common, such as neutropenia (57.1%; 12/21 patients), anemia (47.6%; 10/21 patients),

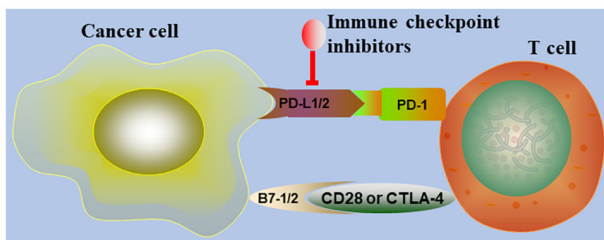


Figure 3. Mechanisms of immune checkpoint inhibitors. The immunosuppressive ligands of tumor cells bind to the corresponding receptors and suppress the immune responses of tumor-infiltrating lymphocytes. Immune checkpoint inhibitors can block this interaction and stimulate antitumor immunity. PD, programmed death; PD-L, PD ligand; CTLA-4, cytotoxic T-lymphocyte protein 4.

leucopenia (47.6%; 10/21 patients) and thrombocytopenia (30.4%; 7/23 patients). Fortunately, these severe toxicities are reversible and manageable (42). Because of the promising activity in this phase I trial, camrelizumab plus GP was also explored in patients with RM-NPC in a randomized phase III trial. This trial revealed that PFS in the camrelizumab group was longer compared with that in the placebo group (median 9.7 vs. 6.9 months). The incidence of the most common grade ≥ 3 adverse events was similar between the two groups (43). Additionally, another phase II study (44) revealed that nivolumab monotherapy could lead to an ORR of 20.5% (9/44) (CR of 2.3% and PR of 18.2%) in patients with RM-NPC who had already been heavily pretreated. The 1-year OS and PFS was 59 and 19.3%, respectively. In addition, the 1-year PFS of patients that expressed both human leukocyte antigens A and B was lower compared with patients who do not (5.6 vs. 30.9%). By contrast, the expression of PD-L1 was not associated with the survival of patients. A number of patients had grade 3 toxicities (22.7%; 10/44 patients) (44). The preliminary efficacy of nivolumab in pre-treated patients with RM-NPC, with an ORR of 12.5% (4/32 patients), was also confirmed by another study (45). The aforementioned data suggest that nivolumab is a potentially useful treatment method for patients with RM-NPC. However, additional randomized trials are warranted.

Toripalimab is a humanized IgG4 monoclonal antibody against PD-1 (46). The POLARIS-02 study revealed that toripalimab yielded a manageable safety profile and a ORR of 20.5% (39/190) in patients with chemorefractory metastatic NPC (47). Furthermore, the addition of toripalimab to GP chemotherapy as a first-line treatment for patients with RM-NPC provided superior PFS compared with GP alone (median PFS of 11.7 vs. 8.0 months), which also had a manageable safety profile (48). Intensity-modulated radiotherapy (IMRT) is another treatment option for patients with recurrent NPC (rNPC) who are unsuitable for local surgery (1). A previous study revealed that 19 patients with rNPC (79.2%; 19/24) achieved an overall response and the 12-month PFS was 91.7% (22/24) after treatment with a combination of toripalimab and IMRT. This strategy appeared to be tolerable, with a grade ≥ 3 acute skin reaction (8.0%; 2/25) and mucositis (4.0%; 1/25) (49). In light of these clinical findings, toripalimab has been approved by the National Medical Products Administration of China for heavily pretreated patients with RM-NPC.

Other approaches of immunotherapy. Given that EBV serves a crucial role in NPC progression, vaccines encoding part of an EBV component or EBV-related adoptive and active T lymphocytes were proposed treatment options before the emergence of immune checkpoint inhibitors (1). Chia *et al* (50) explored the ability of a dendritic cell vaccine against the EBV antigens, namely latent membrane proteins 1 and 2, which are expressed in NPC cells. Although no adverse events were observed, there was limited efficacy for patients with metastatic NPC, as the ORR was found to be 6.3% (1/16 patients) for 7.5 months, the median PFS was 1.92 months and the 1-year OS was 18.8% (3/16 patients) (50). AdE1-LMPpoly, an adenoviral vector-based vaccine encoding EBV nuclear antigen-1, possessed the property of stimulating a T lymphocyte response in the majority of RM-NPC cases (51). After the adoptive transfer of responsive T lymphocytes to patients, the median time to progression was 136 days and 71.4% (10/14) patients obtained stable disease from 38 to 420 days (51). Therefore, AdE1-LMPpoly may provide benefit for patients with NPC.

EBV-specific CTL (EBV-CTL) therapy was also evaluated in NPC. In 2010, of the 15 recurrent/refractory EBV-positive NPC cases, 5 patients achieved CRs and 2 patients had PRs, but no patients suffered from severe toxicities after treatment with EBV-CTLs. In addition, of the 8 recurrent patients who were in remission at the time of EBV-CTL application, 5 cases were disease-free from 17 to 75 months after treatment (52). In another study, despite an ORR of 4.8% (1/21 patients with CR), the patient was kept in remission for >8 years after EBV-CTL infusion. The median PFS and OS were 2.2 and 16.7 months, respectively. However, 2/21 cases that previously failed chemotherapy became sensitized to chemotherapy drugs again (53). As a consequence, investigating how to increase the efficacy and predict patient response to EBV-CTL treatment may form another direction for future studies. Furthermore, a combination of EBV-CTLs and chemotherapy as a first-line therapy could benefit patients. A phase II trial (54) found the ORR to be 71.4% (25/35) (8.6% of CR, 62.8% of PR) in a total of 35 patients, and the 2-year OS rate was 62.9%, which was higher compared with that following chemotherapy monotherapy (29.5%) in a previously published study (1).

4. Conclusions

Platinum-based chemotherapy has been the standard treatment of RM-NPC for over a decade. Although chemotherapy agents and treatment modalities have advanced during this time, the efficacy has reached a plateau. Furthermore, the strategy of how to select a second- or third-line treatment after the failure of first-line treatment remains unclear. Therefore, the survival of patients with RM-NPC, especially in heavily pretreated (after ≥ 2 lines of therapy) patients with NPC, remains poor. As understanding into the molecular mechanisms underlying tumor progression deepens, precision therapies (including targeted therapy and immunotherapy) have emerged over the past years. For targeted therapy, anti-EGFR monoclonal antibodies and inhibitors against VEGF/VEGFR have demonstrated benefits for patients with RM-NPC, where the associated adverse events are also reversible and manageable. However, future large randomized trials are required before the wider clinical application

of such targeted therapy. At present, EGFR-TKIs are not recommended for further large-scale studies in patients with RM-NPC due to the limited efficacy in previous investigations. In addition, immunotherapy is emerging as an option for RM-NPC in tumor therapy. Immune checkpoint inhibitors and adoptive EBV-CTL monotherapy or in combination with chemotherapy have demonstrated promising outcomes in patients with RM-NPC. However, additional studies are warranted to consolidate these findings in the future. In addition, searching for biomarkers that can accurately predict the response to adoptive EBV-CTL therapy may be a next research step.

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Authors' contributions

RL contributed to the study design and prepared the manuscript. The author has read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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