Review

Nimotuzumab, an Anti-EGFR Monoclonal Antibody, in the Treatment of Nasopharyngeal Carcinoma

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Abstract

Epidermal growth factor receptor (EGFR) is highly expressed in most of Nasopharyngeal carcinoma (NPC) samples and is associated with poor outcomes. Therefore, targeting EGFR may be a promising strategy to improve patient prognosis. Nimotuzumab is a humanized anti-EGFR monoclonal antibody. Recently, accumulating evidence has demonstrated that combination nimotuzumab and induction chemotherapy, radiotherapy, or concurrent chemoradiotherapy confer benefits for patients with NPC. Moreover, the side effects of such regimes are tolerable. In this review, we focus on the current data of nimotuzumab in clinical trials in the treatment of NPC.

Keywords

epidermal growth factor receptor, nasopharyngeal carcinoma, nimotuzumab

Introduction

Nasopharyngeal carcinoma (NPC) is a malignant tumor with distinctive geographical distribution, which highly prevails in Southern China and South-East Asia.[1] According to cancer statistics in 2018, about 129 000 new cases of NPC were diagnosed and more than 70% of that occurred in these areas.[2] Radiotherapy and platinum-based chemotherapy are the backbone of NPC treatment.[1] The therapeutic effect of patients has been greatly improved in the era of intensity-modulated radiotherapy (IMRT). Nevertheless, about 25% of cases develop into recurrence and metastasis after standard care.[1,3] As a result, many studies have been performed to explore complementary therapy for NPC.

Epidermal growth factor receptor (EGFR), also named HER1 or ErbB1, is a member of ErbB family consisting of HER2/neu (ErbB2), HER3 (ErbB3), and HER4 (ErbB4).[4] EFGR is a 170 kDa transmembrane receptor and contains 3 domains, including extracellular, transmembrane, and intracellular domains. The extracellular region can recognize and bind to the corresponding ligand, and the intracellular part has tyrosine kinase activity.[4] Once activated, EGFR forms homodimers or heterodimers with other ErbB family members, then phosphorylate tyrosine kinases and subsequently activate downstream signaling pathways such as RAS-RAF-ME-K-ERK, JAK-STAT and PI3K-AKT-mTOR. These signals ultimately result in tumor development and progression.[5] (Figure 1) Therefore, EGFR seems to be a promising target in tumor treatment.

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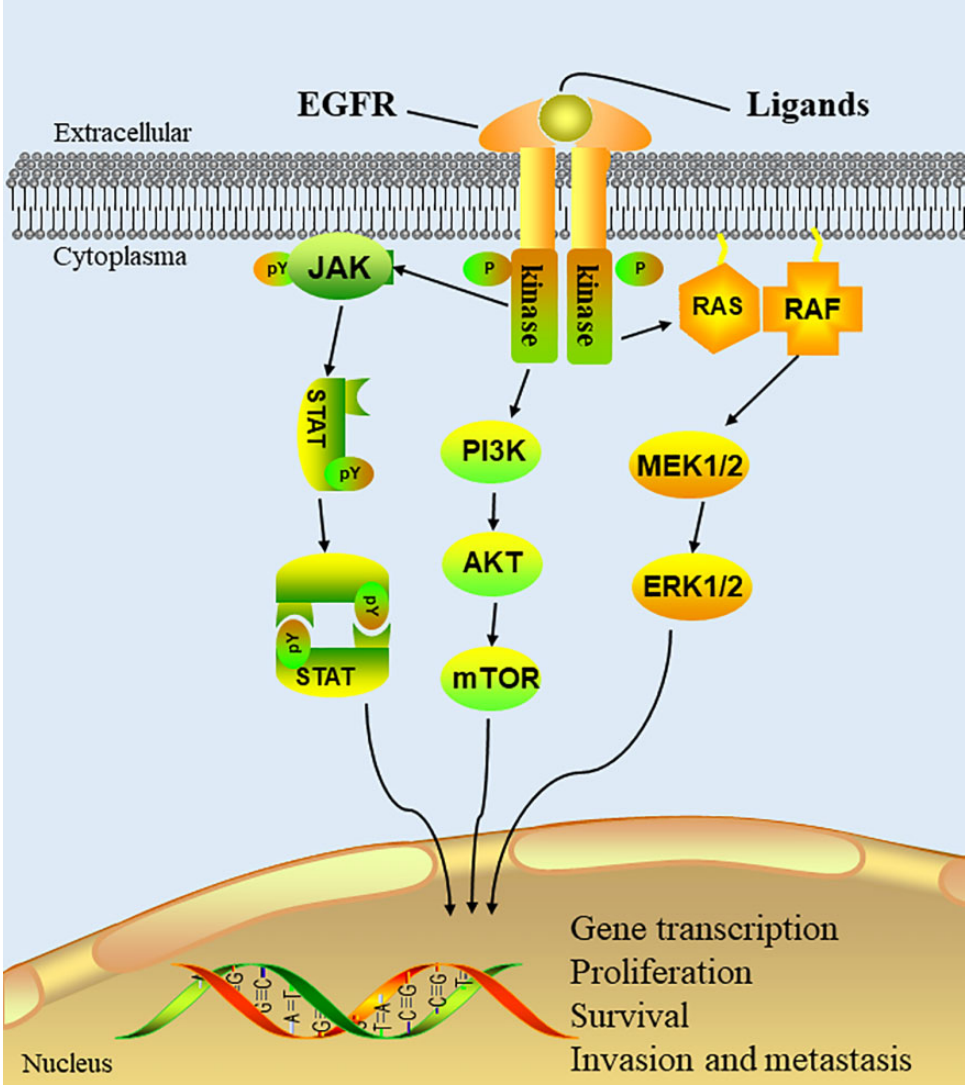

Figure 1. The signaling pathways of EGFR. EGFR is activated through the binding of ligands. Activation of EGFR phosphorylates receptor-related tyrosine kinases in cytoplasm region, and then leads to the activation of downstream pathways, which are involved in cell proliferation, survival, invasion and metastasis.

It has been reported that EGFR is highly expressed in most NPC cases and is an independent factor of poor prognosis.[6,7] As a consequence, several studies have evaluated the efficacy of EGFR-targeted therapies in NPC, including EGFR monoclonal antibodies and EGFR tyrosine kinase inhibitors. Nimotuzumab is a humanized EGFR monoclonal antibody invented in Cuba. Nimotuzumab recognizes and binds to extracellular domain of EGFR, and blocks the binding of other special ligands to EGFR and receptor autophosphorylation, ultimately leads to suppression of tumor growth.[8] (Figure 2) Accumulating evidence has revealed that nimotuzumab exert promising antitumor activity as a single agent or combination with conventional therapy.[9,10] In this review, we summarize the current clinical evidence of nimotuzumab in NPC treatment and deepen our understanding of management of the disease.

Nimotuzumab for Locoregionally Advanced NPC

COMBINATION With Concurrent Chemoradiotherapy (CCRT)

Radiotherapy combined with chemotherapy is an important strategy for locoregionally advanced NPC. To probe the effects of combination of nimotuzumab and CCRT, a number of clinical trials have been performed (Table 1). In 2016, a retrospective study enrolling 42 patients (13 patients: 100mg/week; 29 patients: 200mg/week) demonstrated that 90.5% of cases achieved complete response and 9.5% of that had partial response. Regarding to side effects, there were 6 patients with grade 3/4 mucositis, 3 patients with grade 3/4 leukocytopenia and none had skin rash.[11] These results suggested that adding

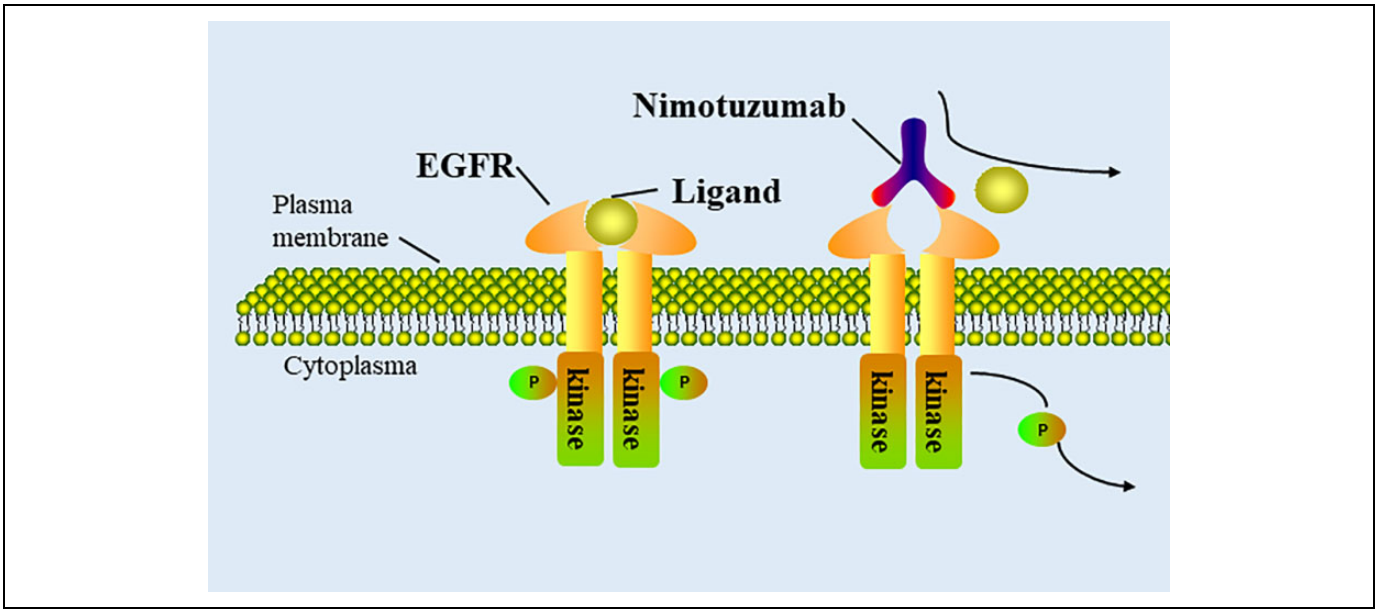

Figure 2. The roles of nimotuzumab in tumor cells. Nimotuzumab can recognize and bind to extracellular domain of EGFR, which prevents the binding of ligands to receptor. Hence, EGFR signaling pathways is inhibited and this impairs tumor growth.

Table 1. The Studies of Combination Nimotuzumab and CCRT in Locoregionally Advanced NPC.

References	Type	Treatment	Cases	Outcomes
11	Retrospective	Nimotuzumab plus cisplatin-based CCRT with and without IC, adjuvant chemotherapy	42	ORR (100%); 2-year LRFS (96.4%), DMFS (93.1%) and OS (96.6%). Grade 3/4 mucositis (14.3%); hematology toxicity (7.1%); no skin rash.
12	Prospective phase II	IC and nimotuzumab plus CCRT	23	2-year PFS (83.5%) and OS (95.0%). Grade 3/4 mucositis (34.8%); grade 3 neutropenia (26.1%); no acne-like rash.
13	Retrospective	IC and nimotuzumab plus CCRT	39	3-year LRF (92.1%), DMF (82.5%), PFF (77.6%) and OS (86.8%). Grade 3 mucositis (15.8%); no skin rash.
15	Prospective phase II	Nimotuzumab plus CCRT	49	ORR (100.0%); 3-year OS (89.7%), DMFS (87.8%), LRC (97.9%) and PFS (85.7%). Grade 3 mucositis (8.2%); grades II xerostomia (20.4%).
14	Retrospective	31 patients received nimotuzumab plus CCRT versus 62 patients received CCRT	93	Nimotuzumab plus CCRT versus CCRT (5-year OS; 96.8% vs. 82.3%; $P = 0.001$), (5-year DMFS; 90.3% vs. 80.6%, $P = 0.012$), (5-year PFS; 83.9% vs. 71.0%, $P = 0.006$). No significant differences in toxicity.
17	Retrospective	Addition of IC to CCRT with or without nimotuzumab	120 pairs	Nimotuzumab versus no nimotuzumab (5-year DMFS; 95.8% vs. 83.9%; $P = 0.007$); no significant differences in 5-year LRFS, PFS, OS. No significant differences in toxicity.
16	Retrospective	184 patients received nimotuzumab and CCRT with or without IC; 546 patients received CCRT with or without IC	730	Nimotuzumab versus no nimotuzumab (5-year DMFS; 93.09% versus 85.61%; $P = 0.012$), (5-year OS; 88.91% versus 78.30%; $P = 0.006$); no significant differences in 5-year LRFS, PFS. No significant differences in toxicity.

Notes: **Abbreviations:** CCRT, concurrent chemoradiotherapy; IC, induction chemotherapy; ORR, objective response rate; LRFS, local recurrence-free survival; DMFS, distant metastasis-free survival; OS, overall survival; PFS, progression-free survival; LRF, local recurrence-free; DMF, distant metastasis-free; PFF, progression failure-free; LRC, local-regional control.

Table 2. The evidence of addition nimotuzumab to IMRT in locoregionally advanced NPC.

References	Type	Treatment	Cases	Outcomes
22	Retrospective	Nimotuzumab plus IMRT with or without chemotherapy	75	3-year LRFS (95.6%), LRFS (95.5%), DMFS (98.6%), PFS (89.7%), and OS (89.2%). Grade 3/4 mucositis (12.0%); grade 3/4 leukocytopenia (34.7%); no skin rash.
20	Retrospective	IMRT plus nimotuzumab with or without concurrent chemotherapy	50	2-year PFS (83.29%) and OS were (97.67%). Grade 3/4 mucositis (36.0%); nimotuzumab-related anaphylaxis (4.0%); no skin rash.
21	Retrospective	IC followed nimotuzumab plus IMRT	38	3-year LRFS (92.8%), DFS (89.5%), PFFS (78.7%), and OS (87.5%). Grade 3 mucositis (36.8%); no skin rash.
19	Retrospective	231 patients received nimotuzumab plus IMRT with IC; 26 patients received nimotuzumab plus IMRT	257	5-year LRFS (94.3%), RRFS (94.8%), DMFS (91.9%), PFS (83.4%), and OS (86.2%). Grade 3/4 mucositis (10.9%); grade 3/4 leukocytopenia (19.8%); no skin rash and infusion reaction.
18	Retrospective	After IC, 52 patients received nimotuzumab plus IMRT, 52 patients received cisplatin plus IMRT	104	(5-year OS; 63.9% vs. 81.4%; $P = 0.024$); (PFS; 58.0% vs. 80.6%; $P = 0.028$); no significant differences in OS and PFS for patients older than 60 years. Less leukopenia and milder nausea in nimotuzumab group.

Note: IMRT, intensity-modulated radiotherapy; LRFS, local recurrence-free survival; DMFS, distant metastasis-free survival; PFS, progression-free survival; OS, overall survival; PFFS, progression failure-free survival; IC, induction chemotherapy; RRFS, regional recurrence-free survival.

nimotuzumab to CCRT may be a feasible strategy, which had encouraging outcomes and well-tolerated toxicity. Moreover, such a desirable scenario was also corroborated by several investigations which indicated that CCRT in combination with nimotuzumab (200mg/week) improved treatment outcomes without increasing toxicity.[12-15] However, it is of particular note that the number of cases in these trials was relatively small and none of them had more than one hundred patients. Interestingly, a propensity score-matched analysis noted that addition nimotuzumab (200mg/week) to CCRT (184 cases) improved long-term survival of patients compared with CCRT alone group (546 cases).[16] Similarly, a study (120 pairs patients) assessing the efficacy of addition of induction chemotherapy (IC) before the combination of nimotuzumab (200mg/week) and CCRT found that nimotuzumab plus CCRT preceded by IC increased 5-year overall survival (OS) and distant metastases-free survival (DMFS) of patients.[17]

Addition Nimotuzumab to IMRT

To date, there are also some studies evaluating the efficacy and safety of addition nimotuzumab to IMRT in treatment.[18-21] (Table 2) Wang et al[19] demonstrated that 94.3% of 257 patients got 5-year local recurrence-free survival, 86.2% got 5-year overall survival and such regime did not give rise to accumulation of radiation-related toxicities after the treatment of combination nimotuzumab (100 mg or 200mg/week)and IMRT. Moreover, for the elderly patients (aged 60 or older), efficacy of this regime was also encouraging and it may be a better option for these patients who cannot be tolerate chemotherapy.[22] Cisplatin is widely recommended for the use in concurrent chemoradiotherapy for patients with NPC.[1] Therefore, it is crucial to compare efficacy and toxicity of nimotuzumab versus cisplatin concurrent with IMRT in patients. A retrospective study suggested that although cisplatin plus IMRT had better 5-year OS and progression-free survival (PFS) rates, the incidence of toxicity such as nausea and vomiting was higher when comparing to nimotuzumab (200mg/week) plus IMRT.[18] However, in sub-analysis, there was no significant differences in OS and PFS for stage II patients and elderly patients.[18]

Combination With Induction Chemotherapy (IC)

IC followed by CCRT is recommend as level 2A evidence for locoregionally advanced NPC.[23] Whether nimotuzumab plus IC benefit patients draws researchers' attention. In a retrospective study, patients treating nimotuzumab (11% patients: 200mg/week; 89% patients: 200mg/week) plus IC followed by CCRT obtained high 5-year local recurrence-free survival rate (95.6%), distant metastases-free survival rate (91.7%), progression-free survival rate (84.0%), and overall survival rate (88.7%). Importantly, the side effects were tolerable, as evidenced by the fact that 6.2% (13/210) and 5.7% of patients suffered from grade3/4 mucositis and leukocytopenia, respectively.[24] In addition, a multicenter randomized controlled study investigated the difference of safety and efficacy between nimotuzumab (200mg/week), cisplatin plus 5-fluorouracil and docetaxel, cisplatin plus 5-fluorouracil as induction therapy followed by CCRT. The nimotuzumab group had higher lymph node response rate (81% vs 60%) and lower toxicity compared with docetaxel group.[25] Long-term efficacy, however, still requires further follow-up.

Given the encouraging therapeutic effects and tolerated toxicity of nimotuzumab in previous evidence, increasing phase II studies (NCT04223024, NCT03915132, NCT03557112) and

phase III study (NCT03837808) are being carried out to further verify the effectiveness of nimotuzumab in the management of locoregionally advanced NPC.

Nimotuzumab for Recurrent or Metastatic NPC

Nimotuzumab may also conferred benefit for patients with recurrent or metastatic NPC. In a multicenter, phase II clinical trial, patients overall objective response rate was 71.4% (25/35) and median PFS and OS were 7.0 (95% CI 5.8-8.2) months and 16.3 (95% CI 11.4-21.3) months, respectively after treatment with nimotuzumab (200mg/week), cisplatin plus 5-fluorouracil. The only grade 3/4 toxicity was leukopenia (62.9%).[26] Surprisingly, a case experiencing NPC with multiple lung metastases obtained near-complete response and this situation lasted for 1 year after capecitabine plus nimotuzumab treatment.[27] These data led us to draw a conclusion that regimes containing nimotuzumab may be an effective and feasible strategy for recurrent or metastatic NPC. This, however, warrants further prospective evaluation in the future.

Conclusions

To date, radiotherapy and platinum-based chemotherapy are the standard care for NPC. Although major improvement has been made in radiotherapy and chemotherapy modality, about 25% of patients still develop into treatment failure, including recurrence and metastasis. Hence, it is urge need to explore more therapeutic arrows to target NPC. Recently, nimotuzumab, a humanized monoclonal antibody targeting EGFR, has come into our fields of vision. A lot of clinical trials show encouraging advantages for patients with locoregionally advanced NPC as well as recurrent or metastatic NPC treated with nimotuzumab plus chemotherapy, radiotherapy, or concurrent chemoradiotherapy. What's more, the toxicity in terms of grade 3/4 acne-like rash which is common in the use of other monoclonal antibody,[28] is relatively few. However, most of studies discussed above are small sample size retrospective trials. It is noteworthy that many confounding factors existing in retrospective trials could interfere with the results of the researches. This highlights a need to design randomized, controlled, multicenter phase III clinical trials to further verify the clinical benefits and toxicity of nimotuzumab in the treatment of NPC.

Declaration of Conflicting Interests

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