Nimotuzumab combined with radiotherapy reduces primary tumor and nodal volume in advanced undifferentiated nasopharyngeal carcinoma

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Nimotuzumab combined with radiotherapy reduces primary tumor and nodal volume in advanced undifferentiated nasopharyngeal carcinoma

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Abstract

Aim: A high expression of epidermal growth factor receptor (EGFR) is found in most human epithelial tumors, including nasopharyngeal carcinomas (NPC). The overexpression of EGFR has been shown to play an influential role in tumorigenesis and the progression of malignant tumors. Therefore, blocking EGFR might be a potential targeted treatment for NPC. Nimotuzumab is an anti-EGFR monoclonal antibody that exhibits remarkable anti-proliferative, anti-angiogenic, and pro-apoptotic effects.

Methods: Here we report five patients with loco-regionally advanced NPC, treated with nimotuzumab 100 mg i.v./week for 8 weeks in combination with radiotherapy in a total dose of 70–74 Gy.

Results: A computed tomography evaluation of all five patients showed that the primary tumor volume was reduced, ranging from 64.1 to 98% and the nodal volume was reduced by 90.7–100%. No severe adverse events related to nimotuzumab were observed.

Conclusion: The use of nimotuzumab in combination with radiotherapy was potentially beneficial and safe for patients with advanced NPC.

Key words: efficacy, nasopharyngeal carcinoma, nimotuzumab, safety.

INTRODUCTION

The high prevalence of nasopharyngeal carcinoma (NPC)1 and its metastasis behavior2 has become a challenging clinical problem in many parts of Asia, including South-East Asia. Treatment of NPC depends on the stage of the disease. The treatment of advanced stages or metastasis of NPC with a combination of radiotherapy and chemotherapy can improve responses, but increases toxicities.3 To improve tumor control, some new strategies have been considered, including a combination of radiotherapy with agents targeting specific molecular pathways.

Overexpression of epidermal growth factor receptor (EGFR) occurs in almost all head and neck squamous cell carcinomas,4,5 and has been correlated with alterations in cell cycle progression,6 increased invasive capacity,7 enhanced angiogenesis8,9 and decreased apoptosis of tumor cells.10 EGFR activation is also associated with larger and advanced stages of tumors and poor prognosis.12 EGFR activation is also associated with resistance to radiation.13 EGFR overexpression is also common in NPC.3,14–16 In undifferentiated NPC, EGFR overexpression was up to 83% and was found to correlate with primary tumor stages of disease and locally aggressive diseases.14 Correlative analysis showed that EGFR extent was a strong, independent prognostic factor that determined locoregional control, relapse-free survival and disease-specific survival in stages III–IV of NPC. Nasopharyngeal cancer patients with strong EGFR staining had poor survival and increased risk of...
locoregional failure after the induction of chemotherapy and radiotherapy compared to patients with weak staining.\textsuperscript{17,18} Nimotuzumab (h-R3), a genetically engineered humanized monoclonal antibody that recognizes an epitope in the extracellular domain of human EGFR,\textsuperscript{19} showed potent antiproliferative, antiangiogenic and proapoptotic activity.\textsuperscript{20} Because ionizing radiation induces a rapid activation of EGFR signaling, which activates MAPK and PI3 kinase pathways to promote cell proliferation and DNA repair, radioresistance is fostered. Therefore, inhibiting EGFR by antiEGFR monoclonal antibody can also enhance radiosensitivity.\textsuperscript{13} Nimotuzumab has been proven by clinical studies to improve response rates with minimal adverse events in epithelial-derived cancers,\textsuperscript{21} and head and neck cancer.\textsuperscript{22} We report five patients with advanced stage NPC who were treated with a combination of nimotuzumab and radiotherapy.

**TREATMENT**

Five NPC patients who refused to receive chemotherapy because of its toxicity were treated with nimotuzumab combined with radiotherapy. Nimotuzumab (TheraCIM; Innogene Kalbiotech, Singapore) at a dose of 100 mg was administered once a week for 8 weeks. Radiation was performed 1 h after the administration of nimotuzumab with locoregional dose \( \sim 56 \) Gy, conformal of the gross tumor and lymph node \( \sim 70 \) Gy, fractionated into 2 Gy/day for 5 days a week.

Patients’ data from regular physical examinations, laboratory examination and computed tomography (CT) evaluation were recorded. Physical examination (vital signs, Karnofsky score and lymph node examination), routine hematological examination, and recording of adverse events and concomitant medications were conducted during the patient’s first visit and every visit thereafter. Efficacy assessment was based on gross tumor volume (GTV) reduction of the primary tumor and diseased lymph nodes. Gross tumor volume calculations were based on the contouring of the area of visible disease on cross-sectional CT scans, which were performed three times: pre-treatment (2–4 weeks before the treatment), on the 5th week of the treatment, and post-treatment (4 weeks after completion of the treatment). Pre- and post-treatment CT scans were used to evaluate primary tumor volume reduction (\( \% \text{vol}_{\text{red}} \sim 100 \times (1 - \frac{\text{vol}_{\text{post}}}{\text{vol}_{\text{pre}}}) \)).\textsuperscript{23}

Diseased lymph node volume reduction was evaluated from pre- and post-treatment measurements (\( \text{vol}_{\text{pre}} - \text{vol}_{\text{post}} \)). Nodal tumor volume (NTV) is defined as the sum of the volumes of all metastatic lymph nodes. Diseased lymph node volumes were estimated by the ellipsoid approximation with which the method volume is approximated as half the product of the maximum dimension in each axis (\( \text{vol} \sim \frac{1}{2} \times X \times Y \times Z \)). The percentage of volume reduction (\( \% \text{vol}_{\text{red}} \)) was calculated as \( 100 \times (1 - \frac{\text{vol}_{\text{post}}}{\text{vol}_{\text{pre}}}) \), such that a 100\% vol\(_{\text{red}}\) corresponds to complete resolution of the lymph node and a 0\% vol\(_{\text{red}}\) corresponds to no change in lymph node volume.\textsuperscript{24}

**RESULTS**

Five patients confirmed with advanced stage NPC were enrolled for treatment. Four of the five patients had undifferentiated NPC (World Health Organization type A) (Table 1). Pre-treatment tumor volumes varied from 15.6 to 320.32 cm\(^3\), and lymph node volumes were between 14.125 and 1098.25 cm\(^3\) (Table 2).

Pre- and post-treatment CT evaluations of all patients are shown in Figure 1, with primary tumor volume reduction ranging from 64.1 to 98\%. Nodal volume was reduced between 90.7 and 100\%. All patients experienced improvement of performance status as assessed by the Karnofsky (Table 2).

**Table 1** Demographic of patients treated with nimotuzumab combined with radiotherapy for advanced undifferentiated nasopharyngeal carcinoma

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (years)</th>
<th>Gender</th>
<th>TNM/staging</th>
<th>WHO classification/classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40</td>
<td>Male</td>
<td>T4N2M0/IVA</td>
<td>WHO type A, undifferentiated</td>
</tr>
<tr>
<td>2</td>
<td>32</td>
<td>Female</td>
<td>T2N3M0/IVB</td>
<td>WHO type A, undifferentiated</td>
</tr>
<tr>
<td>3</td>
<td>35</td>
<td>Male</td>
<td>T4N3M0/IVB</td>
<td>WHO type A, undifferentated</td>
</tr>
<tr>
<td>4</td>
<td>31</td>
<td>Male</td>
<td>T4N3M0/IVB</td>
<td>WHO type A, undifferentated and moderately well-differentiated</td>
</tr>
<tr>
<td>5</td>
<td>45</td>
<td>Female</td>
<td>T2bN3M0/IVB</td>
<td>Squamous cell-carcinoma, non-keratinizing, poorly differentiated</td>
</tr>
</tbody>
</table>

\(\text{TNM, tumor node metastasis; WHO, World Health Organization.}\)
Patient 1 complained of nasal obstruction, difficulty in swallowing, tinnitus, headache, left eye ptosis, stridor, solid neck mass for the past 1.5 years and 5 kg body-weight loss within 6 months. The patient’s first physical examination revealed paresis of left cranial nerves III, IV, VI, VII, and XII; tongue deviation to the left; a mass in the soft palate with a volume of 16 cm³, and one in the neck (diseased lymph node) with a volume of 14.125 cm³. After 4 weeks of treatment, the patient could open his left eye by 10 mm. By the 7th week of treatment, all symptoms had disappeared; the mass in the soft palate and the diseased lymph node were not palpable (100% volume reduction) and the primary tumor had reduced by 90.35%.

The second patient had bloody nasal discharge, headaches and palpable solid masses in both sides of the neck with a total volume of 108.5 cm³ for 3 years. After treatment, all signs and symptoms disappeared. The primary tumor was reduced by 64.1% and lymph node volume was reduced by 93.4%.

The third patient had headaches, bloody nasal discharge, nasal obstruction and solid masses on both sides of the neck which had a total volume of 1098.25 cm³. All symptoms disappeared after 4 weeks of treatment. The lymph node volume was reduced by 98.7% and the tumor was reduced by 88.4%.

The fourth patient had headaches, progressive weight loss, no appetite, left eye ptosis and a mass in the neck. One month after treatment all symptoms disappeared. The patient could open his left eye by approximately 5 mm. The tumor and nodal volume reductions were 91.1 and 91.09%, respectively.

The fifth patient had headaches and a mass in the neck. Physical examination revealed mild conductive deafness and a mass with a volume of 172.5 cm³ in the neck. One month after treatment no symptoms were observed and hearing function had improved. CT evaluation showed tumor and nodal volume reductions of 98% and 90.7%, respectively.

No severe adverse events were observed in these patients treated with nimotuzumab combined with radiotherapy. Common adverse events were mild anemia, nausea/vomiting, dermatitis/itching and stomatitis. Mild hypotension was observed in the fourth patient.

**DISCUSSION**

All patients had undifferentiated to moderately well-differentiated NPC with advanced stage (IVA and IVB). The recommended treatment for IVA–IVB stages of NPC was a combination of chemotherapy and radiotherapy. Radiotherapy combined with platinum-based chemotherapy could increase the local control rate of tumor from 54 to 78%. Response to treatment in the present case report was based on GTV reduction and nodal volume reduction. Several studies have demonstrated that GTV is an important prognostic factor for NPC patients treated with definitive radiotherapy or combined chemotherapy and radiotherapy. In the present report, a combination of nimotuzumab and radiation showed impressive results and achieved a highest tumor volume reduction of 98%. Nodal volume showed drastic reduction of more than 90%, and one patient even achieved complete nodal volume reduction (100%). Symptom and performance status improvement were observed as early as week 4 of treatment.

The efficacy of antiEGFR monoclonal antibody in combination with radiotherapy has been shown in several studies. A phase III trial evaluating an antiEGFR monoclonal antibody, cetuximab, combined with radiation in local-regionally advanced squamous cell carcinoma of the head and neck showed that the median
<table>
<thead>
<tr>
<th>Patient</th>
<th>Physical Appearance</th>
<th>CT Scan</th>
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<tbody>
<tr>
<td>1</td>
<td>Pre-treatment</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Post-treatment</td>
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<tr>
<td>2</td>
<td>Pre-treatment</td>
<td></td>
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<tr>
<td></td>
<td>Post-treatment</td>
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<tr>
<td>3</td>
<td>Pre-treatment</td>
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<td></td>
<td>Post-treatment</td>
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<tr>
<td>4</td>
<td>Pre-treatment</td>
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<td></td>
<td>Post-treatment</td>
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<tr>
<td>5</td>
<td>Pre-treatment</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Post-treatment</td>
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</tbody>
</table>

Figure 1. Treatment response of five nasopharyngeal carcinoma patients. Improvement after combination therapy of nimotuzumab and radiotherapy can be observed from the physical appearance of the patients and their computed tomography (CT) scan results.
duration of local regional control was higher in the combined treatment arm, compared to the control group (24.4 months vs 14.9 months, \( P = 0.005 \)). The survival rate was also higher in the combined treatment arm (49 months vs 29.3 months). Grades 3–4 toxicity occurred in the cetuximab arm in the form of acneiform rash and infusion reactions (17 and 3% of patients, respectively).26

The combination of nimotuzumab and radiotherapy in head and neck cancer is well-tolerated and can enhance tumor radio curability. The addition of nimotuzumab to standard modalities might increase the response and survival rates without significantly potentiating toxicity.22 Nimotuzumab has been shown to recognize the epitope located in the extracellular domain of human EGFR with high specificity and blocking ligand binding and receptor activation.27 The in vitro and in vivo study also showed that this monoclonal antibody exerted an antiproliferative, antiangiogenic and proapoptotic activity upon tumor cells overexpressing EGFR.20 Immunohistochemistry assay of tumor tissues from 24 patients with locally advanced head and neck cancer showed decrease of proliferative activity and vascularity after nimotuzumab treatment in combination with radiotherapy.21

Despite the improving response of chemo-radiotherapy combination, chemotherapy increased the severity of radiation’s adverse events. The acute toxicities observed in the chemo-radiotherapy arm were more severe compared to radiotherapy alone.28,29 In contrast, all adverse events observed in the combination of nimotuzumab and radiotherapy were mild. Thus, nimotuzumab administration did not add acute toxicity to radiotherapy. This therapy modality offered an advantage to patients who could not tolerate cytotoxic agents. While severe skin rash is a common and severe side-effect of EGFR-targeted therapy,22,30 no skin rash occurred during nimotuzumab combination treatment. Studies of nimotuzumab in various tumors also demonstrated remarkable dermatological safety.12,21,22 This favorable toxicity profile can be explained by a kinetic binding model of antiEGFR antibodies, where intermediate affinity of nimotuzumab \((K_D = 10^{-9} \text{ M})\) results in a high tumor uptake and low uptake into normal tissues.21,22

**CONCLUSION**

Nimotuzumab combined with radiotherapy showed clinical benefits in our five locoregionally advanced stage NPC patients. In all five NPC cases, we found effective EGFR blockade in tumors without deleterious skin toxicity (skin rash) commonly found in treatment with other EGFR inhibitors. This finding was in accordance with several previous trials of nimotuzumab in other cancers.

**ACKNOWLEDGMENT**

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**REFERENCES**