



THE ROLE OF NIMOTUZUMAB AND AN ANTI-EGFR MAB, IN THE TREATMENT OF LOCALLY ADVANCED SCCHN

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ABSTRACT

SCCHN is a group of neoplasms that develop in the epithelium of the upper gastrointestinal and airway, and it is a diverse disease. Approximately 65,000 individuals were estimated to be affected by SCCHN in the US in 2019, while a significant number of new cancer diagnoses in the oral cavity, pharynx, and lips were reported in South Korea, resulting in 1,170 fatalities from the disease in 2015. In recent decades, significant progress has been made in SCCHN patient treatment outcomes, with a significant increase in the percentage of patients who survived for five years in South Korea. This progress is partly attributed to improvements in surgical and radiation methods, enhanced supportive care, and changes in patient characteristics. In the past, smoking and alcohol consumption have been identified as the predominant etiological factors for SCCHN, while occasional cases have been attributed to chewing betel nut or genetic predisposition, such as in the case of Fanconi anemia.

Keyword: SCCHN, Upper aerodigestive tract, Epithelial neoplasms

Introduction

Approximately 40% of patients with early SCCHN exhibit localized tumors that can be effectively managed with a single type of therapy, typically surgery. However, in certain cases, definitive radiation can yield comparable oncologic outcomes and superior functional outcomes in specific locations. For advanced local SCCHN, a multimodal treatment approach is necessary. If surgery is initially provided, postoperative radiation therapy with or without chemotherapy is recommended. However, definitive radiation treatment with concurrent chemotherapy is not the preferred approach for treating oral cavity SCC due to worse cancer outcomes and higher complication rates. Technological advancements like TORS in minimally invasive surgery allow easier access to specific oropharyngeal areas, such as the root of the tongue, which typically required more extensive operations. TORS is widely used for HPV-positive oropharyngeal SCC, as these patients have a longer lifespan and are more likely to avoid the effects of radiation and/or chemotherapy. Ongoing research is comparing definitive radiation and TORS for early stage oropharyngeal SCC.¹⁻⁵

Chemotherapy administration induces changes in DNA binding and generates highly reactive free radicals that enhance the cytotoxic impact of radiation therapy. Additionally, chemotherapy disrupts the repair and regeneration of both fully

and partially damaged tissues, which can have life-threatening consequences during radiation intervals. Clinical trials have consistently shown that concurrent chemoradiation significantly improves survival rates in cases of locally advanced SCCHN compared to radiotherapy alone or chemotherapy followed by radiotherapy. Concurrent chemoradiation is also more effective in postoperative scenarios for patients with high-risk pathological characteristics, such as involvement of surgical margins and/or extranodal metastasis expansion, compared to radiation therapy alone.⁶

Although induction chemotherapy was previously thought to produce an immediate response and reduce the risk of distant spread, clinical trials comparing neoadjuvant chemotherapy with concurrent chemoradiation have not demonstrated improved overall survival, even in patients with high-risk cancer and large tumors or lymph nodes. Moreover, the toxicity of induction chemotherapy can hinder or delay definitive chemoradiation. A significant Phase III trial was conducted for oral cavity SCC, examining neoadjuvant chemotherapy before definitive surgery, but no benefits in complete or cancer-free survival were observed. The standard approach involves the use of radiation and chemotherapy together, known as chemoradiation. However, in cases where the initiation of chemoradiation is delayed, induction chemotherapy may be considered for patients with a sizable and symptomatic primary or nodal disease.^{7,8}

Discussion

1. Anti-EGFR monoclonal antibody

EGFR, a transmembrane receptor that activates tyrosine kinase activity, plays a crucial role in regulating intracellular signaling pathways in normal and malignant cells. EGFR is overexpressed in various types of human tumors, including breast, colorectal, lung, ovary, brain, head and neck, prostate, kidney, and bladder cancer. Once activated, the receptor is internalized into the

cytoplasm within a few hours and can either be degraded or recycled back to the membrane.⁹⁻¹⁰

EGFR dimers undergo degradation, while EGFR-HER2 heterodimers enhance mitogenic signaling by promoting recycling through endocytosis. Heterodimers, particularly EGFR-HER2, have a stronger effect compared to homodimers. The combination of HER2:3 with neuregulin is the most potent, and HER2 inhibits the internalization of HER1. Ligand binding is necessary for HER1 dimerization, while HER2 can form dimers without ligand binding and is often present at much higher concentrations than HER1.¹

2. Nimotuzumab

Nimotuzumab, also referred to as the h-R3 code, is an IgG1 isotype humanized monoclonal antibody. Its development involved a process of transferring the complementarity-determining region (CDR) of the murine *ior egf/r3* monoclonal antibody, which belongs to the IgG2a class, into a human framework. This transformation was facilitated through the use of computer modeling techniques. The primary function of nimotuzumab has been demonstrated to be the inhibition of tumor proliferation, survival, and angiogenesis. In vitro studies using A431 squamous cell carcinoma cultures demonstrated dose-dependent anti-proliferative activity of nimotuzumab and inhibition of VEGF expression. In A431 subcutaneous xenograft tumors, nimotuzumab inhibited VEGF expression, reduced microvascular density, and decreased vascular channel diameter. Tumors treated with nimotuzumab also exhibited a higher apoptosis index, indicating increased cellular death. Nimotuzumab exerts its impact on tumor growth by effectively binding to the extracellular domain of EGFR. Through this binding, it successfully obstructs the interaction between EGFR and its specific ligands, thereby impeding the process of receptor autophosphorylation. By preventing receptor mechanisms underlying the immune response against cancer.¹

Nimotuzumab is an antibody that specifically targets EGFR. It has been found to enhance the sensitivity of radiotherapy and stimulate the immune response against cancer cells in glioma models. Nimotuzumab accomplishes these effects by diminishing the population of cancer stem cells, which are believed to play a crucial role in tumor growth and resistance to therapy. By promoting the function of these immune cells, nimotuzumab aids in recognizing and eliminating cancer cells more effectively. Some cancer cells can downregulate or evade MHC-I expression as a strategy to evade immune recognition. Nimotuzumab counteracts this evasion mechanism by restoring MHC-I expression, thereby facilitating the recognition and targeting of cancer cells by the immune system.

By preventing EGFR from evading the immune system, nimotuzumab enhances the immune response against cancer cells. EGFR is known to employ various mechanisms to escape immune surveillance, including downregulating MHC-I expression. However, nimotuzumab disrupts this evasion tactic by inhibiting EGFR and restoring MHC-I expression, rendering cancer cells more vulnerable to immune attack. The antigenic determinant of

autophosphorylation, nimotuzumab plays a crucial role in inhibiting the growth of tumors. This mechanism of action demonstrates the ability of nimotuzumab to disrupt the signaling pathways associated with EGFR, leading to the suppression of tumor growth and proliferation. Consequently, nimotuzumab emerges as a promising therapeutic agent in the field of cancer treatment by specifically targeting EGFR and disrupting its downstream signaling events crucial for tumor progression. The antibody acts by targeting EGFR on tumor cells, blocking ligand binding, and inhibiting receptor phosphorylation, thereby impeding tumor cell growth. This particular technique is highly effective in detecting and visualizing the process of DNA fragmentation that occurs during apoptosis, the programmed cell death. By employing the TUNEL staining technique, researchers have been able to observe and verify the occurrence of ADCC and CDC, which are significant processes in the immune response against cancer cells. The detection of DNA fragmentation serves as a reliable indicator of cellular demise and provides valuable evidence supporting the involvement of ADCC and CDC mechanisms in the destruction of targeted cancer cells. Through the utilization of this technique, a deeper understanding of the cytotoxic effects induced by antibodies has been achieved, shedding light on the intricate

nimotuzumab was identified using phage display methodology and extensive mutagenesis of EGFR, along with Fab fragments of the antibody. The active antigenic determinant of nimotuzumab encompasses adjacent amino acid residues (S356-H359) along with a distal residue (R353). To gain insights into the binding characteristics of nimotuzumab, a comparison was made with cetuximab, an antibody that has been approved for the treatment of advanced head and neck cancer. Interestingly, the presence of the R353 residue, situated within the conformational epitope of cetuximab, indicates a degree of similarity between the binding sites of the two antibodies. This observation provides an explanation for the competition that can occur between nimotuzumab and cetuximab when targeting EGFR. The contrasting binding sites of nimotuzumab and cetuximab on domain II of the EGFR molecule. This comparative analysis sheds light on the structural similarities and differences between these antibodies, contributing to our understanding of their unique binding properties and potential implications for therapeutic interventions.⁵

Ramos et al. developed a mathematical model suggesting that nimotuzumab, an antibody with moderate affinity, specifically accumulates in tumors with increased EGFR expression compared to normal tissue. The model consists of four equations representing the behavior of antibodies in different sections (skin, liver, plasma, and tumor). By solving these equations numerically over time,

concentration profiles are obtained for each tissue, and the area under the curve (AUC) represents the pharmacodynamic impact of the antibody on the tissue. Patients with high EGFR expression or gene amplification may potentially benefit more from nimotuzumab. However, this prognostic biomarker requires further validation in future clinical trials⁴

3. Anti-EGFR monoclonal antibody as SCCHN management

A crucial diagnostic biomarker that can predict therapeutic effectiveness should be able to identify patients who would benefit the most from such treatments.

However, EGFR overexpression is not a predictive biomarker for the effectiveness of cetuximab or panitumumab. Immunohistochemistry analysis in a large SCCHN clinical trial failed to show any association between EGFR status and the effectiveness of cetuximab. Similarly, EGFR gene copies were not correlated with cetuximab response in SCCHN or colorectal cancer (CRC). Additionally, EGFR expression and amplification do not affect the effectiveness of monoclonal antibodies (MAbs) targeting EGFR in advanced CRC. The tumor mutation profile has not been specifically linked to the effectiveness of cetuximab or panitumumab in SCCHN patients.⁹

An effective CD8+ T cell response is crucial for an immune reaction to cancer. Despite the rarity of detecting tumor antigen-specific T-cell responses to monoclonal antibodies, patients who did not receive cetuximab were found to have T cells that specifically recognize tumor-associated antigens (TAAs). These EGFR-specific T cells were able to kill EGFR-expressing tumor cells and produce cytokines, indicating their potential as a therapeutic strategy for cancer treatment. This observation suggests that cetuximab can induce a specific and effective CD8+ T cell response against cancer. In contrast, panitumumab failed to provoke detectable T cell responses in SCCHN patients, which

might explain why panitumumab exhibits less clinical activity than cetuximab. Hence, it is essential to investigate the capacity of MAbs to elicit T cell responses in cancer patients.¹¹

Nimotuzumab has been shown to generate more significant cytotoxic CD8+ T lymphocytes specific to the epidermal growth factor receptor (EGFR) in patients who received nimotuzumab for at least twelve months compared to those who did not undergo nimotuzumab treatment. This finding suggests that nimotuzumab may induce a more specific and effective CD8+ T cell response against cancer.

In addition to EGFR specificity, additional tumor-associated antigen (TA)-specific T cells can be stimulated through the cross-presentation of antigens by dendritic cells (DCs). Therefore, it is important to assess the specificity of TA-induced T cells in addition to EGFR specificity. In vitro studies using cetuximab have demonstrated the cross-presentation of non-EGFR antigens (MAGE-3) to MAGE-specific cytotoxic T lymphocytes (CTLs). This discovery implies that MAbs may stimulate a broader T cell response against cancer by inducing the cross-presentation of non-EGFR antigens

Table 1. Features of monoclonal antibodies (MAbs)

MAbs	notes
Cetuximab	Cetuximab is a monoclonal antibody (MAb) with an IgG1 isotype and an affinity of 10-9, capable of inducing ADCC through both NK and neutrophil effector cell.
Panitumumab	Panitumumab is a monoclonal antibody (MAb) with an IgG2 isotype and an affinity of 10-11, unable to induce ADCC through any effector cells and there is no evidence of its effect on adaptive immune response. It is approved only for the treatment of colorectal cancer (CRC)
Nimotuzumab	Nimotuzumab is a monoclonal antibody (MAb) with an IgG1 isotype and an affinity of 10-8, capable of inducing ADCC through NK effector cells. It also has the ability to induce EGFR-specific T cells, and is approved for the treatment of glioma, esophageal cancer, pancreatic cancer, and SCCHN

4. The use of Nimotuzumab in treating advanced local Squamous Cell Carcinoma of the Head and Neck (SCCHN)

EGFR is frequently overexpressed in head and neck tumors and is associated with an unfavorable prognosis. Inhibiting the EGFR pathway can impede the proliferation, infiltration, and dissemination of malignant cells, making targeted anti-EGFR therapy a promising approach. Nimotuzumab is a novel monoclonal antibody that specifically targets EGFR and effectively blocks downstream signaling pathways while increasing radiation sensitivity, with fewer adverse reactions compared to other monoclonal antibodies targeting EGFR. Trials conducted on patients with advanced SCCHN have demonstrated that combining nimotuzumab with CRT or RT improves tumor response and long-term survival rates. It is a safe and clinically valuable intervention for patients with locally advanced and unresectable tumors.¹³

In a retrospective analysis, Srinivas and colleagues discovered that incorporating nimotuzumab into intensity-modulated radiation therapy (IMRT) resulted in an elevated tumor response in patients who were not suitable for surgical intervention and

cisplatin-based chemotherapy. A multicenter investigation conducted on the Indian population revealed that simultaneous chemoradiation with cisplatin and BIOMAb had a 64% lower risk of mortality, with a 39% 5-year survival rate in the nimotuzumab plus radiation therapy (RT) group, as opposed to 26% in the RT group. Furthermore, the research team did not observe any long-term adverse reactions linked to the drug. The trial concluded that the inclusion of nimotuzumab in concurrent chemoradiotherapy (CRT) or RT improved locoregional control and treatment outcomes for patients with unresectable advanced local SCCHN.⁹

In a clinical trial conducted by Rodríguez et al., where patients were randomly assigned, 106 participants with advanced SCCHN were evaluated to determine the effectiveness of nimotuzumab in combination with radiotherapy. The results demonstrated that patients who received nimotuzumab plus RT had a significantly higher complete response (CR) rate (59.5%) compared to those who received placebo plus a placebo (34.2%). Additionally, the drug was well-tolerated when used in conjunction with radiation therapy.⁵

The study performed by Talapatra et al. showed that the addition of nimotuzumab in IMRT therapy was both safe and

effective for patients with advanced local SCCHN who were not eligible for cisplatin chemotherapy. Srinivas et al. also conducted a study on nimotuzumab and IMRT, demonstrating favorable outcomes and a safe drug profile without any additional toxicity. The most commonly observed adverse events were Grade 1/2,

Conclusion

The EGFR is a receptor for growth factors present on cell surfaces and is frequently upregulated in diverse human tumors, including SCCHN. Monoclonal antibodies targeting EGFR can attach to its

such as leukocytosis and mucositis, which were consistent with previous studies, and there were no typical anti-EGFR-related toxicities. Nimotuzumab binds to high levels of EGFR in a stable manner, providing a safer profile than other anti-EGFR antibodies.⁶

inactive form, thereby impeding the growth of cancer cells. Nimotuzumab and Cetuximab are two monoclonal antibodies that have demonstrated efficacy against SCCHN; however, Nimotuzumab has exhibited superior effectiveness when compared to Cetuxima.

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