

## ORIGINAL ARTICLE

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# Targeting EGFR in nasopharyngeal carcinoma

Efthymios Kyrodimos<sup>1</sup>, Aristeidis Chrysovergis<sup>1</sup>, Nicholas Mastronikolis<sup>2</sup>, Evangelos Tsiambas<sup>3</sup>, Vasileios Ragos<sup>4</sup>, Dimitrios Roukas<sup>5</sup>, Panagiotis Fotiades<sup>6</sup>, Vasileios Papanikolaou<sup>1</sup>

<sup>1</sup>1<sup>st</sup> ENT Department, Hippocraton Hospital, University of Athens, Athens, Greece; <sup>2</sup>ENT Department, Medical School, University of Patra, Patra, Greece; <sup>3</sup>Department of Cytology, 417 VAH, Athens, Greece; <sup>4</sup>Department of Maxillofacial, Medical School, University of Ioannina, Greece; <sup>5</sup>Department of Psychiatry, 417 VA Hospital (NIMTS), Athens, Greece; <sup>6</sup>Department of Surgery, 424 GA Hospital, Thessaloniki, Greece

## Summary

*Nasopharyngeal carcinoma (NPC) represents a specific, aggressive pathological entity included in the Head and Neck Carcinoma (HNC) family of malignancies. NPC is derived from the nasopharyngeal epithelia expressing a high invasive and metastatic potential affecting negatively patients' prognosis due to poor survival rates. Concerning pathogenetic factors implicated in its rise and progression, Epstein-Barr virus (EBV) latent but persistent infection is considered the main one. Novel therapeutic strategies are based on targeting specific molecules such as epidermal growth factor receptor (EGFR) by applying anti-EGFR monoclonal antibodies*

*(mABs) that block their natural ligands interrupting also aberrant signal transduction to nucleus. Anti-EGFR therapies combined or not with radiotherapy seem to be a very promising tool in handling the corresponding patients with NPC that demonstrate specific genetic signatures. In the current article, we focused on presenting EGFR expression in NPC combined with novel anti-EGFR agents.*

**Key words:** carcinoma, nasopharyngeal, EGFR, targeted therapies

## Introduction

Head and Neck squamous cell carcinoma (HNSCC) represent a superfamily of malignancies including a variety of anatomical regions on which they rise. In fact, malignant transformation of squamous cells leads to their development and clonal expansion acting as cancerous stem cells for their progression [1]. In contrast to conventional HNSCCs, nasopharyngeal carcinoma (NPC) is a unique, aggressive pathological entity included in the head and neck carcinoma (HNC) family of malignancies that demonstrates specific molecular characteristics including also micro-RNA markers [2,3]. Concerning its geographical distribution, its prevalence is observed in East Asia and Africa with

its highest incidence rate in China. Concerning its histological origin, the malignancy is derived from the nasopharyngeal epithelia demonstrating a high invasive and metastatic potential mainly correlated with poor prognosis. Keratinizing, non-keratinizing and Basaloid carcinoma represent its pathological variants that reflect the corresponding cytogenetic features [4]. Epstein-Barr virus (EBV) latent but persistent infection is predominantly implicated in its development and progression. In fact, EBV's oncogenic activity is mediated by the aberrant expression of specific critical proteins including LMPs and EBNA1 that promote specific genetic signatures even in micro-RNA level [5,6].

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Corresponding author: Evangelos Tsiambas, MD, MSc, PhD. 17 Patriarchou Grigoriou E' Street, Ag. Paraskevi, 153 41 Athens, Greece. Fax: +30 210 6526259; Email: tsiambasecyto@yahoo.gr  
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In the current article, we focused on the alterations of epidermal growth factor receptor (EGFR) gene and protein expression in NPC reporting also novel data for anti-EGFR therapeutic strategies in the corresponding patients.

## EGFR in NPC

Among oncogenes that have already been identified and cloned, EGFR remains one of the most significant [7]. Understanding its deregulation mechanisms improves critically patients' selection for isolated therapies based on modern molecular biology and oncology guidelines. The EGFR (other names include: ERBB ERBB1 HER1) gene is located on the short (p) arm of chromosome 7 at position 12 (cytogenetic chr band 7p12.1). The protein encoded by the corresponding gene acts as a transmembrane glycoprotein. It is a member of the v-erb-b2 erythroblastic leukemia viral oncogene (ErbB)/human epidermal receptor (HER) family of receptor tyrosine kinases, that includes also other three cell membrane receptor tyrosine kinases: HER2/c-neu (ERBB2), HER3 (ERBB3) and HER4 (ERBB4) [8]. All of those members share mainly a common domain structure consisting of a large extra cellular ligand-binding region, a single hydrophobic transmembrane bridge adjusting to an intracellular juxtamembrane (JM) region, a tyrosine kinase domain and finally a C terminal tail with multiple tyrosine residues acting as a regulatory region (with the exception of HER3 that lacks direct kinase activity) [9]. Three main EGFR depended pathways have been already identified including the PI3K-AKT-PTEN-mTOR, the RAS-(B) RAF-MEK-ERK/MAPK and also the IL6-JAK1/2-STAT3 [10]. Anti-EGFR targeted therapeutic strategies have been developed based on specific genetic profiles and applied in sub groups of patients suffering from solid cancers of different histo-genetic origin. Detection of specific EGFR somatic mutations leads to tyrosine kinase inhibitors (TKIs) application in subsets of them. Concerning EGFR gene numerical imbalances, identification of pure gene amplification is critical for targeting the molecule via monoclonal antibodies (mAbs) [11].

Approaching the influence of EGFR aberrant expression -due to gene deregulation-in NPC, there are some very interesting recently reported molecular data. A study based on a multiple protein analysis -including EGFR, p53, MDM2, and eIF4E molecules detected very high EGFR expression lev-

els correlated with advanced stage, predominantly with increased metastatic potential (lymph node metastasis) [12]. Interestingly, they also observed that EGFR overexpression was strongly associated to poor survival rates in a three-year survival analysis. Similarly, another study showed that EGFR overexpression affected negatively overall survival and locoregional control in the corresponding NPC patients [13]. Increased oncogenic activity of the EGFR gene is implicated also in specific signaling transduction pathways such as EGFR-PKM2 axis. Another study group reported almost recently that increased protein levels of the two molecules motivate F3, FOSL1, EPHA2, ANTXR2, and AKR1C2 metastatic factors leading to NPC aggressive phenotype (advanced stage) [14]. In these patients, cetuximab-based targeted therapeutic strategy is an optimal aspect of oncological management. Similarly, other studies focused on the efficacy of mAbs in subgroups of NPC patients showed that not only cetuximab but also other anti-EGFR agents including nimotuzumab and antivascular endothelial growth factor (VEGF) combined or not with conventional cisplatin-based chemoradiotherapy improve the biological and clinical behavior of the malignancy [15-19]. Referring to multiple-molecule targeted therapeutic protocols in NPCs, another study group analyzed the efficacy of the combined nimotuzumab and celecoxib - an anti-COX-2 selective inhibitor- application on the cytoplasmic and nuclear EGFR signaling pathways in cell cultures [20]. They concluded that interaction of these agents leads to enhanced NPC cytotoxicity and radiosensitivity, especially in poorly differentiated ones.

## Conclusions

NPC is a unique histogenetic entity which requires specific oncological management due to its aggressive phenotype (increased metastatic potential) and limited response rates to conventional chemo-radiotherapy. Introduction of anti-EGFR targeted therapeutic agents -predominantly mAbs- such as cetuximab and/or nimotuzumab- affects positively the prognosis of subgroups of patients that overexpress the marker.

## Conflict of interests

The authors declare no conflict of interests.

## References

1. Graziano A, d'Aquino R, Tirino V, Desiderio V, Rossi A, Pirozzi G. The stem cell hypothesis in head and neck cancer. *J Cell Biochem* 2008;103:408-12.
2. Tsiambas E, Mastronikolis NS, Fotiades PP et al. Epstein-Barr Virus MicroRNAs in Nasopharyngeal Carcinoma. *Pathol Oncol Res* 2019;1-2.
3. Zhao L, Fong AHW, Liu N, Cho WCS. Molecular subtyping of nasopharyngeal carcinoma (NPC) and a microRNA-based prognostic model for distant metastasis. *J Biomed Sci* 2018;25:16-28.
4. Lo KW, Chung GT, To KF. Deciphering the molecular genetic basis of NPC through molecular, cytogenetic, and epigenetic approaches. *Semin Cancer Biol* 2012;22:79-86.
5. Lung RW, Hau PM, Yu KH et al. EBV-encoded miRNAs target ATM-mediated response in nasopharyngeal carcinoma. *J Pathol* 2018;244:394-407.
6. Hiromu S, Maruyama R, Yamamoto E, Masahiro K. DNA methylation and microRNA dysregulation in cancer. *Mol Oncol* 2012;6:567-78.
7. Albertson DG, Collins C, McCormick F, Gray JW. Chromosome aberrations in solid tumours. *Nat Genet* 2003;34:369-76.
8. Mendrola JM, Berger MB, King MC, Lemmon MA. The single transmembrane domains of ErbB receptors self-associate in cell membranes. *J Biol Chem* 2002;277:4704-12.
9. Yarden Y, Sliwkowski MX. Untangling the ErbB signalling network. *Nat Rev Mol Cell Biol* 2001;2:127-37.
10. Schlessinger J. Cell Signaling by Receptor Tyrosine Kinases. *Cell* 2000;103:211-25.
11. Harari PM. Epidermal growth factor receptor inhibition strategies in oncology. *Endocr Relat Cancer* 2004;11:689-708.
12. Zhang P, Wu SK, Wang Y et al. p53, MDM2, eIF4E and EGFR expression in nasopharyngeal carcinoma and their correlation with clinicopathological characteristics and prognosis: A retrospective study. *Oncol Lett* 2015;9:113-8.
13. Sun W, Long G, Wang J, Mei Q, Liu D, Hu G. Prognostic role of epidermal growth factor receptor in nasopharyngeal carcinoma: a meta-analysis. *Head Neck* 2014;36:1508-16.
14. Chen S, Youhong T, Tan Y et al. EGFR-PKM2 signaling promotes the metastatic potential of nasopharyngeal carcinoma through induction of FOSL1 and ANTXR2. *Carcinogenesis* 2019;41:723-33.
15. Zhao C, Miao J, Shen G et al. Anti-epidermal growth factor receptor (EGFR) monoclonal antibody combined with cisplatin and 5-fluorouracil in patients with metastatic nasopharyngeal carcinoma after radical radiotherapy: a multicentre, open-label, phase II clinical trial. *Ann Oncol* 2019;30:637-43.
16. Lin M, You R, Liu YP et al. Beneficial effects of anti-EGFR agents, Cetuximab or Nimotuzumab, in combination with concurrent chemoradiotherapy in advanced nasopharyngeal carcinoma. *Oral Oncol* 2018;80:1-8.
17. Peng L, Liu ZL, Xu C et al. The Efficacy and Safety of Anti-epidermal Growth Factor Receptor Monoclonal Antibodies in Nasopharyngeal Carcinoma: Literature-based Meta-analyses. *J Cancer* 2018;9:4510-20.
18. Mao L, Tan J, Wang F et al. Retrospective study comparing anti-EGFR monoclonal antibody plus cisplatin-based chemoradiotherapy versus chemoradiotherapy alone for stage II-IVb nasopharyngeal carcinoma and prognostic value of EGFR and VEGF expression. *Clin Otolaryngol* 2019;44:572-80.
19. Almobarak AA, Jebreel AB, Abu-Zaid A. Molecular Targeted Therapy in the Management of Recurrent and Metastatic Nasopharyngeal Carcinoma: A Comprehensive Literature Review. *Cureus* 2019;11:e4210.
20. Huang J, Yuan X, Pang Q et al. Radiosensitivity enhancement by combined treatment of nimotuzumab and celecoxib on nasopharyngeal carcinoma cells. *Drug Des Devel Ther* 2018;12:2223-31.