IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 23, Issue 1 Ser.5 (January. 2024), PP 38-40
www.iosrjournals.org

Epidermal Growth Factor Receptor: Prognostic Marker For Undifferentiated Nasopharynx Carcinomas North-African Patients

Esma Kerboua[1], Chloé Rancoule[2], Nicolas Magné[2], Kamel Bouzid[1],
1.Medical Oncology Department , Centre Pierre &Marie Curie, Algiers, Algeria
2. Radiotherapy Department, Lucien Neuwirth Cancer Institute, St Priest En Jarez, France

Abstract:
Epidermal growth factor receptor (EGFR) is overexpressed in many different cancers and is involved in the regulation of cellular metabolism, growth, migration and differentiation. EGFR expression in UNCT (undifferentiated carcinoma of nasopharyngeal type) has been previously reported for Asian patients, and, as for other head and neck locations, is overexpressed in 80% of cases and is associated with poor prognosis. The nasopharyngeal cancers have an endemic apportionment affecting overwhelmingly East Asia and North Africa, however, at this time, no studies have been conducted in this latter population.
The objective of the present study is to evaluate for the first time at first on a North African population, the correlation between the expression of EGFR and prognosis in UCNT.
The medical records of 70 Algerian UCNT patients who had undergone biopsy prior to chemotherapy and radical radiotherapy between 2003 and 2007 were retrospectively reviewed. Patients were followed-up until death. Immunohistochemistry was used to evaluate the expression of EGFR in UNCT biopsy specimens, and the association between their expression and clinical parameters and survival was analyzed.
In 56 out of 70 (80%) UNTC patients EGFR was overexpressed. EGFR overexpression is significantly correlated to disease-free (p= 0.0008) and overall survival (p= 0.0001).
As in Asian countries and other head and neck cancers, EGFR is a powerful prognostic marker in UCNT Maghreb population. Its therapeutic targeting in UCNT deserves to be assessed in a clinical phase III trial.
Key-words: *UCNT, EGFR, prognosis, targeted therapy*

Date of Submission: 05-01-2024 Date of Acceptance: 15-01-2024

I. Introduction

Nasopharyngeal carcinoma (NPC) is a highly invasive malignancy that rises from the epithelial lining of the nasopharynx. One of its particularities lies in in the predominance of undifferentiated histological forms named UCNT (undifferentiated carcinoma of nasopharyngeal type). If NPC is viewed as a relatively rarer form of cancer worldwide (1), its incidence rate in endemic counties reached 15-50/100000. These particular regions include Maghreb and Southeast Asia. NPC is highly sensitive to radiotherapy and radiotherapy (RT) is the main treatment. However it is closed from progressive cancers showing a highly invasive and metastatic (bone, liver, lungs) nature (2,3). This characteristic mainly leads to a therapeutic failure and the indication of chemotherapy several lines. Thus, the treatment outcome for locally advanced NPC patients remains to be further improved. The research of targeted therapies has considerably grown in the recent few years. Epidermal growth factor receptor (EGFR) is a member of the ErbB family of protein tyrosine kinase receptors and is involved in the regulation of cellular metabolism, growth, migration and differentiation. EGFR overexpression has been observed in many different cancers. EGFR is expressed in 80-100% of head and neck squamous cell carcinomas, and is important in tumor cell growth, repair and survival. Furthermore, its overexpression often indicates a poor prognosis, early metastasis, chemotherapy resistance or a shorter survival (4–6). Therefore, EGFR has become a key target for molecular-based therapies, and several inhibitors of the EGFR, e.g., cetuximab, panitumumab, erlotinib, and gefitinib, have shown favorable results in clinical trials (7–11).

EGFR expression in NPC (including UNCT) has been previously reported (12–15) for Asian patients, and, as for other head and neck locations, is overexpressed in 80% of cases.

It have been recently described, on a Chinese population, that EGFR is overexpressed expression in NPC is associated with unfavorable T stage (16) and poor prognosis (16–18).

Same results are still missing for the North African population. In the present prospective study, lead on Algeria, we proposed to assess EGFR expression in the NPC and especially in UCNT and to evaluate a possible prognostic value of its expression.

II. Patients and methods

This study has been approved by a research ethics committee and all patients received and signed the informed consent. Chemo-radio-naif patients addressed to the Medical Oncology Department of *Pierre et Marie Curie anticancer center* of Algiers between January 2003 and January 2007 with a locally advanced UCNT were systematically prospectively included. Nasopharyngeal biopsies were obtained prior to radiotherapy and chemotherapy. Tumor tissue samples were fixed in 10% formalin, embedded in paraffin and cut into 4-µm-thick sections. EGFR protein expression level was analyzed by immunohistochemestry (ICH) using rabbit monoclonal antibodies that are specifically against EGFR with L858R point mutation in exon 21 (clone 43B2, Cell Signalling Technology) or E746_A750 deletion mutation in exon 19 (clone 6B6, Cell Signalling Technology). The EGFR mutation-specific staining was scored based on membrane staining intensity as previously described: 0= no staining; 1+=faint cytoplasmic staining in >10% of tumor cells; 2+=moderate membranous staining; 3+=strong membranous staining(19,20).

All the patients received the following treatment:

- neo-adjuvant chemotherapy including 3 cycles (28 days each) of 5 fluorucil (1000 mg/m^2 Day 1 to Day 3) and cisplatyl (100 mg/m^2 Day 1),
- and 4 to 6 weeks after chemotherapy, exclusive locoregional radiothreapy (conventional radiotherapy 70 Gys)

Clinical and imaging (RECIST1.1 criteria) responses to treatment are evaluated. Patients are then followed-up 2 years after end of treatment ,every 3 months the first year and every 06 months , and progression free survival and overall survival assessed.

All statistical analyses were performed using SPSS software (SPSS, Inc., Chicago, IL, USA). Differences of survival time were analyzed using the chi 2 test. The Kaplan-Meier estimator was used to calculate survival rates. $P<0.05$ was considered to indicate a statistically significant difference.

III. Results

Patients' characteristics

The present study has included 70 patients, 45 men and 25 women. Mean age was 37.7 years old, range 18 to 75 years. Patients presented good general status (performance status <2 or Karnofsky index> 60%). These patients had locally advanced tumors, classified stages IVB for 40 patients (57.1%), III for 2 patients (2.8%), IVA for 14 patients (20%), IIB for 12 patients (17,1%), according to the UICC1997 system. They all underwent a neo-adjuvant chemotherapy followed by locoregional radiotherapy and complete the schedule treatment. These figures are summarized Table 1.

EGFR expression classes

EGFR expression has been assessed by IHC. Among the 70 UCNT pre-treatment biopsies, 14 (20%) do not overexpress EGFR. Conversely, 56 biopsies (80%) overexpressed the receptor.

We proposed arbitrary to dived tumor in 4 classes based on EGFR expression: negative (0), positive low level (1), positive medium level (2) and positive high level (3) . Regarding this ranking, we counted 10 biopsies (17.8%) with a level 1, 24 (42.8%) with a level 2 and 22 (39.2%) with a level 3. These results are presented Table 2.

EGFR expression and patient survival

Overexpression of EGFR, whatever the score (1, 2 and 3), is associated with a shorter progression-free survival ($p = 0,0008$) and a shorter overall survival ($p = 0,0001$). These data are summarized Figure 1.

Kaplan Meier survival analysis for both progression-free and overall survivals, confirm that EGFR is a pejorative bio-markers. Indeed, logrank analysis confirms that EGFR expression is a prognostic value, with a significant difference between 0 and 1 for progression free and overall survivals ($p=0.0001$ and 0.0001 respectively), 0 and 2 ($p=0.0001$ and 0.0001 respectively), 0 and 3 ($p=0.0001$ and 0.0001 respectively?). EGFR expression level 2 has a poorer prognosis than expression level 1 ($p=0.0001$ and 0.0001 respectively), however, there are no differences between when we compare prognosis for level 2 and level 3 tumor EGFR expression. These results are presented Figure 1.

IV. Discussion

The present study is the first trial conducted on a North African population evaluating the prognosis value of tumor EGFR expression in UNTC. If, because of their low incidence in the world, the NPC are unwell studied, a more stringent focus on UNTC is scattered. In 56 out of 70 (80%) UNTC patients EGFR was overexpressed. These data are fully in agreement with those published from Asian population (12–16). Moreover, EGFR-positive expression was found to be associated with the clinical stage and with a poor

prognosis. Indeed, a worse survival was observed in patients with positive EGFR expression when compared with patients with negative EGFR expression. Then, EGFR seems to be an interesting prognosis bio-marker. These data too, are coherent with the 3 studies led on Asian population (17,16,18).

EGFR overexpression in UCNT is a prognostic factor which could be considered as other conventional prognostic factors such as tumor size and lymph node infiltration, and its detection standardized by anatomopathology laboratories. Thus, monoclonal antibody blocking epidermal growth factor receptor (EGFR) sounds a promising therapeutic in the treatment of locally advanced nasopharyngeal carcinoma. A recent retrospective study investigated nimotuzumab combined with concurrent chemoradiotherapy and presented encouraging outcomes, without accumulation of toxicity andwell-tolerated(21).

References

[1]. Torre La, Bray F, Siegel Rl, Ferlay J, Lortet-Tieulent J And Jemal A: Global Cancer Statistics, 2012. Ca Cancer J Clin 65: 87–108, 2015.

[2]. Zhang Z-C, Fu S, Wang F, Wang H-Y, Zeng Y-X And Shao J-Y: Oncogene Mutational Profile In Nasopharyngeal Carcinoma. Onco Targets Ther 7: 457–467, 2014.

[3]. Chua Dtt, Ma J, Sham Jst, Et Al.: Long-Term Survival After Cisplatin-Based Induction Chemotherapy And Radiotherapy For Nasopharyngeal Carcinoma: A Pooled Data Analysis Of Two Phase Iii Trials. J Clin Oncol 23: 1118–1124, 2005.

[4]. Berg M And Soreide K: Egfr And Downstream Genetic Alterations In Kras/Braf And Pi3k/Akt Pathways In Colorectal Cancer: Implications For Targeted Therapy. Discov Med 14: 207–214, 2012.

[5]. Baselga J: The Egfr As A Target For Anticancer Therapy--Focus On Cetuximab. Eur J Cancer 37 Suppl 4: S16-22, 2001.

[6]. Nicholson Ri, Gee Jm And Harper Me: Egfr And Cancer Prognosis. Eur J Cancer 37 Suppl 4: S9-15, 2001.

[7]. Reddy Bkm, Lokesh V, Vidyasagar Ms, Et Al.: Nimotuzumab Provides Survival Benefit To Patients With Inoperable Advanced Squamous Cell Carcinoma Of The Head And Neck: A Randomized, Open-Label, Phase Iib, 5-Year Study In Indian Patients. Oral Oncol 50: 498–505, 2014.

[8]. Dorsey K And Agulnik M: Promising New Molecular Targeted Therapies In Head And Neck Cancer. Drugs 73: 315–325, 2013.

[9]. Köhler J And Schuler M: Afatinib, Erlotinib And Gefitinib In The First-Line Therapy Of Egfr Mutation-Positive Lung Adenocarcinoma: A Review. Onkologie 36: 510–518, 2013.

[10]. Prenen H, Vecchione L And Van Cutsem E: Role Of Targeted Agents In Metastatic Colorectal Cancer. Target Oncol 8: 83–96, 2013.

[11]. Yewale C, Baradia D, Vhora I, Patil S And Misra A: Epidermal Growth Factor Receptor Targeting In Cancer: A Review Of Trends And Strategies. Biomaterials 34: 8690–8707, 2013.

[12]. Zheng X, Hu L, Chen F And Christensson B: Expression Of Ki67 Antigen, Epidermal Growth Factor Receptor And Epstein-Barr Virus-Encoded Latent Membrane Protein (Lmp1) In Nasopharyngeal Carcinoma. Eur J Cancer, B, Oral Oncol 30b: 290–295, 1994.

[13]. Fujii M, Yamashita T, Ishiguro R, Tashiro M And Kameyama K: Significance Of Epidermal Growth Factor Receptor And Tumor Associated Tissue Eosinophilia In The Prognosis Of Patients With Nasopharyngeal Carcinoma. Auris Nasus Larynx 29: 175–181, 2002.

[14]. Leong J-L, Loh Ks, Putti Tc, Goh Bc And Tan Lks: Epidermal Growth Factor Receptor In Undifferentiated Carcinoma Of The Nasopharynx. Laryngoscope 114: 153–157, 2004.

[15]. Putti Tc, To Kf, Hsu Hc, Et Al.: Expression Of Epidermal Growth Factor Receptor In Head And Neck Cancers Correlates With Clinical Progression: A Multicentre Immunohistochemical Study In The Asia-Pacific Region. Histopathology 41: 144–151, 2002.

[16]. Zhang P, Wu S-K, 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 9: 113–118, 2015.

[17]. Chua Dtt, Nicholls Jm, Sham Jst And Au Gkh: Prognostic Value Of Epidermal Growth Factor Receptor Expression In Patients With Advanced Stage Nasopharyngeal Carcinoma Treated With Induction Chemotherapy And Radiotherapy. Int J Radiat Oncol Biol Phys 59: 11–20, 2004.

[18]. Ma Bby, Poon Tcw, To Kf, Et Al.: Prognostic Significance Of Tumor Angiogenesis, Ki 67, P53 Oncoprotein, Epidermal Growth Factor Receptor And Her2 Receptor Protein Expression In Undifferentiated Nasopharyngeal Carcinoma--A Prospective Study. Head Neck 25: 864–872, 2003.

[19]. Brevet M, Arcila M And Ladanyi M: Assessment Of Egfr Mutation Status In Lung Adenocarcinoma By Immunohistochemistry Using Antibodies Specific To The Two Major Forms Of Mutant Egfr. J Mol Diagn 12: 169–176, 2010.

[20]. Hasanovic A, Ang D, Moreira Al And Zakowski Mf: Use Of Mutation Specific Antibodies To Detect Egfr Status In Small Biopsy And Cytology Specimens Of Lung Adenocarcinoma. Lung Cancer 77: 299–305, 2012.

[21]. Liu Z-G, Zhao Y, Tang J, Zhou Y-J, Yang W-J, Qiu Y-F And Wang H: Nimotuzumab Combined With Concurrent Chemoradiotherapy In Locally Advanced Nasopharyngeal Carcinoma: A Retrospective Analysis. Oncotarget, 2016.