The Role of EGFR and HER2-Activating Mutations in Maxillary Sinus Cancer

Patricia ENE[a]; Radu Cristian POPESCU[b]; Stefan VOICULESCU[c]; Razvan SCAUNASU[c]; Bogdan POPESCU[b]; Raluca GRIGORE[b]; Razvan ENE[d]; Catalin CÎRSTOIU[d]

[a]Emergency University Hospital, Bucharest, E.N.T. Department
[b]Coltea Clinical Hospital, E.N.T. Department
[c]Coltea Clinical Hospital, General Surgery Department
[d]Emergency University Hospital, Bucharest, Department of Orthopedics and Traumathology

ABSTRACT

Head and neck cancers account for less than 5% of all cancers worldwide and for less than 1% of all cancer deaths in Romania. Sinonasal squamous cell carcinomas are malignant tumors with origin in the respiratory mucosa of the paranasal sinuses and the nasal cavity. Because of the proximity to different important structures such as the brain, the eye the relevance of a multimodal therapy is well known. We take into discussion not only the most recent data from novel agents targeting EGF receptor (EGFR), VEGF and p53 pathways for the management of sinonasal cancer, but also further development of multimodal approach, and the use of biomarkers to appreciate the progression of the disease and the prognostic and overall survival rate in clinical practice. EGFR alterations have been implicated in the pathogenesis and progression of many malignancies. EGFR overexpression has been studied extensively regarding its clinical use but the results are yet to be analyzed.

INTRODUCTION

Head and neck cancers account for less than 5% of all cancers worldwide and for less than 1% of all cancer deaths in Romania. Considering risk factors of the population at risk smoking and alcohol are by far the most common etiology taken into consideration. Heavy smokers have an increased rate of developing neoplasia in the head and neck region with a rate of 7 to 25 times greater than the control population. Alcohol by itself can increase the neoplasia risk by as much as 10 times but in association with tobacco consumption the risk elevates to a peak value of 25-fold. These risk factors are responsible for

mutations in the p53 suppressor oncogene with a direct relation to tumor growth (1).

Dietary factors contribute to the increasing risk for oral and pharyngeal tumor occurrence. Sinonasal squamous cell carcinomas are malignant tumors with origin in the respiratory mucosa of the paranasal sinuses and the nasal cavity. Because of the proximity to different important structures such as the brain, the eye the relevance of a multimodal therapy is well known. Patients having this kind of illness have a delayed presentation to the physician, usually in advanced stages.

Considering occupational exposure to different carcinogens metals, different gases, by-products of leather industry and wood working, they have been associated with sinonasal cancers.

Currently, multiple mechanism of action of different agents both external and internal have been identified in the expression and evolution of head and neck squamous cell carcinoma (HNSCC) (2). Therefore, customized patient treatment or individualized patient therapies are the best alternative for the management of these pathological conditions. We take into discussion not only the most recent data from novel agents targeting EGF receptor (EGFR), VEGF and p53 pathways for the management of HNSCC, but also further development of multimodal approach, and the use of biomarkers to appreciate the progression of the disease and the prognostic and overall survival rate in clinical practice. ❑

TUMORIGENESIS

Tumorigenesis in the aerodigestive upper tract is caused by specific genetic modifications caused by continuous or recurrent exposure to different carcinogens. In recent years the research on molecular aspects of tumorigenesis of the head and neck cancers has provided an important field of development for multimodal therapies.

More than 50% of patience that were diagnosed and treated for head and neck neoplasia had an expression of p53 suppressor oncogene mutation. It is now considered that the progression for premalignant stages to invasive disease, as well as survival rates and overall prognostic of the head and neck neoplasia are in direct relation to the expression of p53 and CDKN2A gene (cell cycle regulator). More recently, epi-

dermal growth factor receptors (EGFR) expression was identified in most of the head and neck cancers with an overall rate of as much as 95%. This is associated with a poor prognosis considering the increased resistance to radiotherapy of p53 mutant oncogene expression (3).

The normal synthesis of body cells is controlled by different mechanisms. When escaping from normal growth control mechanisms some cells or clonal units develop to be an expanding field displacing and replacing normal mucosal epithelium. This abnormal cell growth turns the subclonal unit into an invasive cancer that has the tendency to metastasis (4). This process follows three critical steps: the conversion of a single mutated stem cell from a patch into a group of stem cells without proper growth control (field); the eventual transforming event, which turns a field into a potential carcinoma with invasive growth and metastasis; and the development of metastasis.

Using some genetic markers combined with TP53 mutations, it was shown that in at least 35% of the nasal and sinonasal tumors analyzed, the carcinoma was surrounded by mucosal epithelium that contains genetic changes. This mucosal epithelium next to the primary tumor characterized by genetic changes has also been termed 'field'. Comparison of the genetic profiles of carcinomas and their surrounding fields often indicates a clonal relationship (5), and this lead to the hypothesis that such a field of contiguous preneoplastic cells precedes the development of an invasive carcinoma. ❑

EGFR BIOLOGY

In 1962, Stanley Cohen work lead to the isolation and description of a salivary gland protein that induced eye-lid opening and tooth eruption in newborn mice (6). After further experimentation he showed that this protein could stimulate the proliferation of epithelial cells. This was the point that converged to the birth of the EGF. The first mentioning of the EGFR activated by mutations was initially in 2004.

EGFR is a member of the EGFR tyrosine kinase family formed by EGFR (ErbB1/HER1), HER2/neu (ErbB2), HER3 (ErbB3) and HER4 (ErbB4). All family members have certain characteristics that explain the association into this class: an extracellular ligand-binding domain (I, II, III, IV), a single membrane-spanning region,

a juxtamembrane nuclear localization signal, and a cytoplasmic tyrosine kinase domain. HER2 has no known ligand. HER3 is the only family member that lacks intrinsic kinase activity (7); however, downstream signaling is readily achieved through heterodimerization (8). Aberrant expression or activity of EGFR has been identified as an important factor in many human epithelial cancers, including head and neck squamous-cell carcinoma (HNSCC), in particular sinonasal neoplasia, non-small cell lung cancer (NSCLC), colorectal cancer (CRC), breast cancer, pancreatic cancer and brain cancer. HER receptors are ubiquitously expressed in various cell types, mainly in epithelial, mesenchymal and neuronal sites.

The EGFR and members of its family play an important role in carcinogenesis through their actions concerning modulation of cell proliferation, apoptosis, cell motility and neovascularization (9,12). EGFR alterations have been implicated in the pathogenesis and progression of many malignancies. Although the exact molecular models by which the mutant receptors lead to carcinogenesis are not completely understood, there are certain data than indicates that EGFR have enhanced tyrosine kinase (TK) activity.

A novel nuclear localization sequence for EGFR and its family members has been reported. Furthermore, mechanisms of transport of EGFR to the nucleus have been reported (10, 14,15). These mechanisms involve interactions with dynamin, importins, Sec61, and exportin-1. More importantly, reports have indicated a mechanism of EGFR-mediated kinase-independent gene regulation in the nucleus, which involves direct interaction with the transcription factors STAT3, STAT5 and E2F1 (11,16,17).

EGFR overexpression has been studied extensively regarding its clinical use but the results are yet to be analyzed. The phosphor-specific antibody used for determining the correlation between phosphorylation and EGFR mutation status brought new leads of examination for the effects EGFR has on normal cells. Activation mutations identified within the kinase domain of the EGFR opened several opportunities for the study of pharmaceutical agents to inhibit the receptors for EGFR TK. These mutations in the researched domain lead to the development of two classes of anti-EGFR agents: monoclonal anti-EGFR antibodies (e.g., cetuximab, panitumumab) and small-molecule TKIs of EGFR (e.g., gefitinib, erlotinib).

According to large-cohort Phase III clinical trials, the response rates range from 15 to 37.5%. Clinical trials were initiated that employed novel agents targeting the EGFR TK. The results of these clinical trials indicated that many of the tumors harboring mutant EGFR are highly sensitive to EGFR TKIs, with 10–30% demonstrating a significant overall clinical response and more specifically 15% in sinonasal cancers (4,18,19).

EGFR has been reported to function in the nucleus as a transcription factor as well as a tyrosine kinase that enhances cell proliferation. (20-22). Detection of EGFR in nuclei of cancer cells from primary tumor biopsies and premalignant stage cells was consistent. The nuclear localization of EGFR correlates with poor prognostic and poor clinical outcome for the patients with sinonasal cancers, and other primary sites in the head and neck region. Nuclear localization of EGFR is associated with increased expression of cyclin D1; B-Myb, inducible nitric oxide synthase and COX-2, all of which increase G1/S progression of the cell cycle and proliferation of cancer cells (23-25). ❑

PREDICTION FOR CLINICAL RESPONSE

Because of the high specificity of anti-EGFR monoclonal antibodies for the extracellular domain it was believed that these molecules (i.e. cetuximab) would be effective in vigorous overexpression of EGFR. However, early clinical studies did not confirm a correlation between EGFR expression level by immunohistochemistry and likelihood of response to EGFR inhibitor therapy (10). Collectively, some studies suggest that immunohistochemistry-based assays measuring EGFR expression do not serve as a robust predictor for response to cetuximab therapy (9). This is considered to be the phenomenon of resistance to EGFR antibodies. Taking into consideration the suppressive effects of EGFR inhibitors on VEGF production some researchers implied that EGFR antibodies inhibit EGFR-mediated VEGF production, thereby decreasing angiogenesis and leading to decreased sinonasal tumor growth. ❑

TREATMENT

Because the first intention therapy for sinonasal cancers is surgery it is important for physicians to know that such operations have a great complexity for both the surgeon and the

patient. Scars and mutilation are the outcome of surgery and have to be accepted by the patient. Advanced stages at the moment of diagnosis means that frequent relapse is probable thus the need for an alternate solution for sinonasal multimodal therapy. The biological therapy is an important lead in the upcoming assessment of management for sinonasal cancers.

For the 60% of patients who present with locally advanced sinonasal cancer at diagnosis, combined-modality therapy is generally recommended. In case of unresectable disease, the current standard treatment is chemotherapy with cisplatin. Despite such an approach, the majority of these patients develop local and/or regional recurrences, and distant metastases occur in more than 25% of the patients. In addition, approximately 10% of patients present with distant metastases at diagnosis.

Cetuximab is a monoclonal antibody of the IgG1 class that is directed against the human EGF receptor (EGFR). It binds with high affinity to the extracellular domain of the human EGFR. Cetuximab binds to the EGFR with an affinity that is approximately 10 times greater than that of endogenous ligands. Cetuximab blocks binding of endogenous EGFR ligands, resulting in inhibition of the function of the receptor by substrate competition. It induces the internalization of EGFR, which can lead to downregulation of receptors. Cetuximab also targets cytotoxic immune effect on tumor cells that express EGFR receptors, almost 90% of the sinonasal cancers. Although this expression should lead to clinical response and a decrease in relapse such data are not yet available and thus such conclusion can not be drawn (12,17). ❑

CONCLUSIONS

The advancement of EGFR inhibitors for cancer therapy is of outmost interest for oncology therapeutics. The fact that four new EGFR inhibitors (gefitinib, cetuximab, erlotinib, and panitumumab) are now in use after being approved in a short period of time shows the interest and the utility of this therapy in patients with head and neck neoplasia and moreover with sinonasal cancers. These new agents will enable the systematic evaluation of multitarget inhibition strategies, which include EGFR blockade, to affect tumor response in human cancers, and to assess the need for biological additional therapy along the more conservative attitude (10,14,27).

Although rapid and important discoveries have been made in the field of EGFR research in the past 10 years there is still room for progress in this direction with special attention to patients that do not respond to therapy accordingly (intrinsic resistance) and with disease progression after well conducted medication administration. Some agents are yet to be tested for the high likelihood of response to anti-EGFR TKIs.

Certain reverse TK (RTK) pathways are activated by the inhibition of the EGFR and this is yet another area for research. These pathways can escape the influence of EGFR thus we need to consider alternative molecular targets for multimodal therapy. The capacity of cancer cells to adapt to different classes of drugs suggests that additional mechanisms of resistance to EGFR inhibitors may play a key role in regulating tumor response, such as the induction of angiogenesis process, translocation of surface receptors to the nucleus, altered DNA damage response, and all other undiscovered mutations.

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