Functional Genomics Uncover the Biology behind the Responsiveness of Head and Neck Squamous Cell Cancer Patients to Cetuximab

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Abstract

Purpose: To identify the tumor portrait of the minority of head and neck squamous cell carcinoma (HNSCC) patients with recurrent–metastatic (RM) disease who upon treatment with platinum-based chemotherapy plus cetuximab present a long-lasting response.

Experimental Design: The gene expression of pretreatment samples from 40 HNSCC-RM patients, divided in two groups [14 long-progression-free survival (PFS) and 26 short-PFS (median = 19 and 3 months, respectively)], was associated with PFS and was challenged against a dataset from metastatic colon cancer patients treated with cetuximab. For biologic analysis, we performed functional and subtype association using gene set enrichment analysis, associated biology across all currently available HNSCC signatures, and inferred drug sensitivity using data from the Cancer Genomic Project.

Results: The identified genomic profile exhibited a significant predictive value that was essentially confirmed in the single publicly available dataset of cetuximab-treated patients. The main divergence between long- and short-PFS groups was based on developmental/differentiation status. The long-PFS patients are characterized by basal subtype traits such as strong EGFR signaling phenotype and hypoxic differentiation, further validated by the significantly higher association with the hypoxia metagene. The short-PFS patients presented a strong activation of RAS signaling confirmed in an in vitro model of two isogenic HNSCC cell lines sensitive or resistant to cetuximab. The predicted drug sensitivity for all four EGFR inhibitors was higher in long- versus short-PFS patients (P range: <0.0022–1e–07).

Conclusions: Our data uncover the biology behind response to platinum-based chemotherapy plus cetuximab in RM-HNSCC cancer and may have translational implications improving treatment selection. Clin Cancer Res; 22(15): 3961–70. ©2016 AACR.

See related commentary by Chau and Hammerman, p. 3710

Introduction

Approximately 55% of head and neck squamous cell carcinoma (HNSCC) patients presenting with locoregional advanced disease will eventually experience recurrent or metastatic tumor. A study of clinical and pathologic variables, performed before the adoption of cetuximab treatment, showed that weight loss, ECOG performance status, good/moderate tumor cell differentiation, primary tumor in the oral cavity or hypopharynx, and prior radiotherapy (RT) are all associated with an unfavorable outcome (1), and these variables are still valid more than 10 years later.

RM-HNSCC patients who are not candidates for local therapies are usually offered platinum-based chemotherapy (CT) plus a targeted therapy with an anti-EGFR mAb, cetuximab, with the goal of prolonging survival and controlling symptoms. This combination, tested in the Extreme trial versus CT alone, resulted in a significant increase in median overall and progression-free survival (PFS) and increased response rate (2) and entered as first-line standard treatment in RM-HNSCC setting. However, in the Extreme trial, the median PFS obtained with CT plus cetuximab was 5.6 months and the 5-year follow-up showed that only 5% of the patients in both arms were long-term responders (PFS>12 months).
Translational Relevance

The anti-EGFR mAb cetuximab plus a platinum-based chemotherapy is usually offered to head and neck squamous cell carcinoma (HNSCC) patients with recurrent–metastatic (RM) disease. Despite a proven clinical benefit, only a minority of patients present a long-lasting response, and analysis of EGFR or other single markers does not show any correlation with progression-free survival (PFS). By selection of patients with marked opposite outcomes after treatment and a thorough biologic analysis of genomics data, we identify a signature able to predict sensitivity to cetuximab-based therapy. The long-PFS patients are characterized by basal subtype traits, such as strong EGFR signaling phenotype and hypoxic differentiation, while the short-PFS patients presented a strong activation of RAS signaling. This is the first study specifically investigating cetuximab/platinum resistance in RM-HNSCC patients and illustrates the feasibility of gene expression profiling of pretreatment tumor to identify candidate biomarkers of response to anti-EGFR treatment in this subset of patients.

Because after six cycles of CT plus cetuximab, the anti-EGFR antibody is delivered as maintenance, it is likely that long-term effect could be obtained by cetuximab alone. In this context, to increase our understanding of the molecular mechanisms involved in sensitivity to cetuximab treatment, we compared the gene expression of two series of patients with marked opposite outcomes, with the assumption that this selection may enhance sensitivity in discovering relevant molecular pathways associated with response to anti-EGFR antibodies in RM-HNSCC.

Materials and Methods

Patients and study design

Each one of the 15 RM-HNSCC patients treated between 2008 and 2012 with first-line CT and cetuximab-based combination and showing a PFS >12 months (long-PFS) was matched for at least three prognostic factors (1) with two RM-HNSCC patients, similarly treated but with PFS <5.6 months, median PFS reported in the Extreme trial (short-PFS; see Fig. 1 for further details). The study was approved by the Independent Ethics Committee of Fondazione IRCCS Istituto Nazionale dei Tumori (Approval Number 55/12).

Whole genome gene-expression profiling

Formalin-fixed, paraffin-embedded (FFPE) tumor specimens of the recurrence or, if unavailable, of the primary tumor were collected and selected areas were macrodissected. RNA extraction, quality control, and hybridization on a Whole Genome–cDNA-mediated Annealing, Selection, extension, and Ligation (WG-DASL) microarray were performed essentially as previously described (3). Raw data were deposited with accession number GSE65921 on GEO repository (http://www.ncbi.nlm.nih.gov/geo/). The WT-Ovation FFPE System Version 2 (NuGEN) was used for technical validation of the gene expression.

Statistical and bioinformatic analyses

Statistical analysis was performed using R (4), version 2.15, BioConductor (5), release 2.10, and the BrB-ArrayTools developed by Dr. Richard Simon and the BRB-ArrayTools Development Team (v4.2.0; National Cancer Institute, USA). The differentially expressed (DE) genes between long- and short-PFS patients were defined by imposing an FDR of <15% and a list of 509 genes was identified. The probability of finding 509 genes significant by chance at FDR=<15% if there were no real differences between the classes was 0.01, determined by the global test through 1,000 permutations as computed by BRB-tool using default parameters. Principal component analysis (PCA) was performed using the PCA module present in the imDEV graphical interface (6). Because 9 cases derive from recurrence or metastasis, we assessed the influence of tissue origin in our gene signature through Biosigam R package (7). The method allows the visualization using orthogonal projections of a gene expression matrix by vectors quantifying the outcome and the tissue of origin. For comparison purposes, a dataset (ID: GSE5851) containing the Affymetrix gene expression profile of 80 pretreatment biopsies from metastatic colon cancer patients who had undergone cetuximab treatment was analyzed (8). Pathway and oncosignature analysis was performed using Gene Set Enrichment Analysis (GSEA). From the gene ontology terms, a total of 556 gene sets (GS) with FDR < 0.15 were included in the pathway analysis; for oncosignatures, 188 GSs were analyzed. The degree of genes’ enrichment in the long- and short-PFS patients was represented by a normalized enrichment score (NES) and NES with FDR < 0.05 and fold change >1.5 was considered statistically significant. We used single-sample gene set enrichment analysis (ssGSEA) projection (9) through GenePattern (10) to assess gene set activation scores in each sample of our case material. ssGSEA is a variant of GSEA designed for single sample analyses, which both transform gene-level expression data into pathway-level scores. Graphical representation of GSEA findings was provided by GOCircle plot function of GOpilot R package (11), displaying information about the significance of the enrichment (−log10 adjusted P) and the z-score of each gene set. To better disclose the biology underlying long- and short-PFS, we applied the Prediction Analysis for Microarrays (PAM) subtype classifier described in De Cecco and colleagues (12) and the centroid supergroup classification described in Keck and colleagues (13). Subsequently, a score was determined according to the Pearson correlation between the gene expression profile of each sample of our case material and the centroids for C13 and Basal subtypes of De Cecco and Keck classification, respectively. In silico confirmation of molecular pathways was achieved by retrieving the gene expression data of a cetuximab-sensitive cell line (SCC1) and its cetuximab-resistant derivative (1Cc8; GSE21483; refs. 14, 15). The GS, oncosignatures, and subtype classifications as described above were applied to the data to support our findings.

Five microarray-based signatures are described as associated with outcome in HNSCC: (i) the hypoxia metagene (16); (ii) the 13-gene OSCC signature (17); (iii) the radio-sensitivity index (RSI) (18); (iv) the 42-gene Chung’s high-risk signature (19); (v) the 172-gene signature (20). We applied the procedures developed in the respective papers by the authors, and a value for all the samples entering into our dataset was assessed.

For external validation of drug sensitivity, the cetuximab sensitivity signature was assessed on the public data from the Cancer Genomic Project (CGP; ref.21) through pRRophetic R package (22). The analysis was performed by selecting 46 HNSCC cell lines. ROC curves were estimated by pROC R package (23).
Results

Case material

After the retrieval of matched tumor specimens from RM-HNSCC patients, 1 and 4 samples from the long-PFS (15 patients) and the short-PFS (30 patients) groups, respectively, were excluded (see consort diagram, Fig. 1A). Thirty-one samples were from primary tumor and 9 from recurrence or metastasis. The two groups were well balanced for prognostic factors, and no statistical
difference was present for gender; primary tumor stage, site, grade and HPV status (only oropharynx); age; prior radiotherapy; performance status; weight loss; origin of tissue analyzed for gene expression; types of drugs associated with cetuximab treatment (Fig. 1B). The group achieving a long PFS had a median PFS of 19 months (range, 12–36), with 7 patients maintaining response at the time of data analysis; the median PFS in the short-PFS group was 3 months (range, 1–5).

Identification and technical validation of a gene expression profile differentiating long- from short-PFS patients
After profiling by the WG-DASL assay, a supervised class comparison analysis identified 509 differentially expressed (DE) genes imposing an FDR of <15% (336 and 173 upregulated in long- and short-PFS samples, respectively; Supplementary Fig. S1 and Supplementary Table S1) and PCA distributed patients in two main clusters, matching with the long- and short-PFS groups (Fig. 2A). The whole transcriptome observed by WG-DASL profiling was essentially confirmed by NuGEN methodology (Supplementary Fig. S2). In order to ascertain the degree of influence of the tissue origin on the identified gene signature, we applied an orthogonal projection through two vectors quantifying the outcome (long vs. short PFS; Y axes) and the tissue origin (primary vs. recurrence/metastatic; B axes). Because the B vector lied orthogonal to the Y vector and all 509 genes fall along the Y vector (Supplementary Fig. S3), the expression of our gene signature is associated with outcome and not to the tissue origin.

Challenging the identified signature in a dataset of cetuximab-treated patients
To explore whether the DE genes from our selected RM-HNSCC patients has a predictive value in other studies, we searched for publicly available datasets of cetuximab-treated patients. We found a single available dataset (GSE5051) that is composed of a metastatic colorectal population after several lines of treatment (1–4), treated with cetuximab monotherapy and not dichotomized into long and short responders. When we applied our signature to these 80 metastatic colorectal cancer patients, we classified them in 28 and 52 cases expected with a long- and short-PFS, respectively. Kaplan–Meier survival analysis confirmed our prediction (Fig. 2B). The differences between the two studies may account for the lower PFS of colorectal cancer patients with a signature similar to long-PFS HNSCC patients; in spite of that, the signature of the long-PFS group is able to identify some metastatic colorectal cancer cases having a durable response in this confirmation group.

Pathway analyses
To gain further insight into the biologic pathways involved in response to CT plus cetuximab treatment, we applied GSEA analysis, and due to the limited number of cases we used very stringent thresholds. Starting analysis from 556 GSs, we found 11 (from GS-01 to GS-11) and 7 (from GS-12 to GS-18) of them significantly enriched in long- and short-PFS groups, respectively (Supplementary Table S2, ordered for each group according to NES significance); considering the redundancy in GS terms with NES significance); considering the redundancy in GS terms with overlapping genes, 7 GSs were selected as representative and graphical representation is displayed by the heatmap of Fig. 3A. The main divergence between the tumors was associated with their developmental/differentiation status, being those from long-PFS patients characterized by genes of "Ectoderm/Epidermis" (GS-01, -02, and -03) and those from short-PFS patients by genes of "Muscle" (GS-12, -13, -14, -15, and -18). Furthermore, in the long-PFS group, GS-06, -07, -08, and -09 were associated with "Defense response," GS-10 and GS-11 characterized the "EGFR Signaling Pathway" and the "Protein catabolism," respectively; in the short-PFS group, GS-16 and -17 were associated with "Cation-transport."
Ability of existing gene expression signatures to predict outcome following cetuximab treatment

In the last decade, a number of gene expression–based signatures have been proposed as prognostic factors in HNSCC, but no data exist on their capability to predict sensitivity/resistance to anti-EGFR/platinum regimens. In order to assess whether and to what extent five signatures (16–20) are associated with response to cetuximab/platinum, we applied to our cohort the algorithms developed by the authors in the respective papers. A score for all the samples entering into our dataset was assessed and it was compared between long- and short-PFS cases. The hypoxia signature, the 13-gene OSCC, and the RSI signatures displayed a significant difference in relationship to outcome with the long-PFS cases having higher scores (Supplementary Fig. S4).

Then, we extended our analysis on determining to which molecular subtype our cases belong. For this aim, two recent molecular classifications were considered (12, 13). We stratified our case material determining to which of the three subtypes (BA, basal; CL, classical; IMS, inflamed/mesenchymal) reported by Keck and colleagues (13) and to which of the EGFR-expressing HNSCC subtypes (Cl2-Mesenchymal and Cl3-Hypoxia) described in De Cecco and colleagues (12) the cases are classified. As reported at the bottom of the heatmap of Fig. 3A, 11 of 14 long-PFS patients could be attributed to the BA (P = 0.0005) and the Cl3-Hypoxia (P = 0.0017) subtypes. The centroid scores for BA
and Cl3-Hypoxia were able to reflect cetuximab outcome; long-PFS compared with short-PFS cases showed higher correlation score to BA and Cl3 subtypes (Fig. 3B and C, respectively), reaching a significant accuracy as demonstrated by ROC analysis with AUC = 0.876 for BA and 0.885 for Cl3 (Fig. 3D and E, respectively).

**Oncosignature analyses**

To further analyze the correspondence of the expression data of the long-PFS group and our Cl3-hypoxia subtype, starting from 188 oncosignatures, we selected those reported enriched by De Cecco and colleagues (12). The pathways related to TGFβ, RAS, Cyclin D1, βCAT, p53, WNT, and E2F3 were tested for their association in our cohort of patients. The most significant association was recorded with signatures related to cell lines transfected with oncogenic forms of KRAS, and the genes upregulated upon oncogenic transformation are enriched in short-PFS; furthermore, gene sets related to βCAT, E2F3, MYC, and p53 oncopathways were significantly enriched in long-PFS (Fig. 4A). To support our findings on the molecular pathways involved in outcome following cetuximab treatment, we took into consideration an isogenic model of two sensitive and resistant cell lines (15) for whom the gene expression data are publicly available. 1CC8 cetuximab-resistant cells confirmed a significant upregulation of RAS oncogenic pathway compared with SCC1-sensitive cells along with GS-15, while SCC1 cells showed significant upregulation of GS-1 (Fig. 4B); furthermore, when compared with gene expression subtype classification, SCC1 cells have higher Cl3 scores than 1CC8 (Fig. 4B).

**Drug-sensitivity analysis**

We searched for a potential link between the expression profiles of the patients entered in this study with those of CGP cell lines for which sensitivity data to 130 drugs are available. Cetuximab was not screened against the cell lines, but data on other four EGFR pathway inhibitors are available and selected; in addition, we selected other drugs of interest for HNSCC treatment (chemotherapeutics and targeted agents in clinical development). The association of drug sensitivity for 11 of the 18 compounds selected retaining a significance threshold is depicted in Fig. 5A and B. Among the four EGFR inhibitors, the long-PFS patients showed the significantly greater sensitivity to afatinib (Fig. 5C and D). Seven other compounds showed a significance difference in predicted activity between long- and short-PFS patients, and the drug to which short-PFS patients showed the greater sensitivity was gemcitabine (Fig. 5E and F).

**Discussion**

Cetuximab, an anti-EGFR monoclonal antibody, has been the first targeted therapy approved for HNSCC patients, representing the major systemic treatment improvement in the last decade (24); however, about 40% of patients are responsive, and the median PFS is limited (2).

The data presented here indicate that tumors with marked opposite treatment outcomes have different molecular patterns, with separate specific deregulated pathways. To our knowledge, this is the first study of RM-HNSCC that specifically investigates sensitivity to cetuximab/platinum-based therapy by gene expression and biology behind. After many years of unsuccessful research for biomarker identification and in-depth analysis of EGFR (25, 26), our data suggest that a whole-transcriptome approach followed by in silico validation, a thorough functional genomics and drug-sensitivity estimate could uncover the biology behind responsiveness to cetuximab/platinum in RM-HNSCC patients, opening the way to the definition of a cetuximab-based treatment-sensitivity predictor.

Our selection of RM-HNSCC cases potentially sensitive to cetuximab/platinum treatment was based on their PFS...
extraordinarily long, as already done with some success on another cancer type by others (27).

We should note that cetuximab exhibits two distinct mechanisms of action: (i) a competitive inhibition of ligand binding to EGFR, thereby inhibiting activation of EGFR tyrosine kinase activity and subsequent signaling; and (ii) an antibody-dependent cellular cytotoxicity mediated by host immune cells. Our functional annotation analysis of the

Figure 5.
Prediction of drug sensitivity in RM-HNSCC. A, the heatmap depicts predicted sensitivity in each sample of our study. Colors range from blue (sensitive) to yellow (resistant). B, the table summarizes relative $P$ values and differences between IC$_{50}$ values for long- and short-PFS (selection criteria $P < 0.05$ and a $|$log(IC$_{50}$)| difference between long- and short-PFS cases $> 0.15$). C and D, boxplot of predicted sensitivity to afatinib for long- and short-PFS patients ($P = 3.47E-09$) and ROC curve (AUC = 0.992; 95% CI, 0.897-1.000; $P < 0.0001$). E and F, boxplot of predicted sensitivity to gemcitabine for long- and short-PFS patients ($P = 0.00228$) and ROC curve (AUC = 0.788; 95% CI, 0.631-0.901; $P = 0.0003$).
identified molecular profile may suggest that the long-PFS patients are sensitive to the competitive inhibition of cetuximab. In fact, long-PFS cases showed significant enrichment in (i) genes belonging to EGFR signaling, including molecules whose regulation is related to EGFR activation due to its physiologic ligands; (ii) processes related to tissue development, with significant upregulation of genes located in a region on human chromosome 1q21 known as the "epidermal differentiation complex" (28) and in many genes of the kallikrein family, directly involved in many steps in cancer development, such as regulation of tumor proliferation and invasion (29); (iii) genes involved in intracellular catabolic processes. Altogether, these deregulated pathways can partially explain the success of a therapy based on EGFR signaling blocking and degradation following cetuximab binding.

Several studies, including our recent ones, have indicated the relevance of analysis of whole transcriptome in identifying potentially useful prognostic or predictive signatures (16–20) and patient subtypes (12, 13). These signatures have never been tested in the context of cetuximab treatment. The hypoxia metagene, the 13-gene OSCC signature, and RSI display a significant association with long-PFS cases having higher scores with aggressive prognosis compared with short-PFS cases. When our cases were classified according to the EGFR-expressing subtypes identified in De Cecco and colleagues (12) and the three supergroups reported by Keck and colleagues (13), long-PFS cases were stratified as C33-hypoxia and Basal subtypes, respectively, characterized by poor prognosis. Noteworthy, the scores associated with C33-hypoxia and BA, indicating similarity to those subtypes, might foresee long-PFS cases with poor accuracy. In addition, a previous work by Chung and colleagues (30) identified a G1 cluster that subsequently proved to be associated with basal subtype (12, 31) with detrimental outcome. Taken together, the signatures and the molecular subtype stratification highlight that long-PFS cases are a defined molecular subgroup with poor prognosis that can be rescued by cetuximab/platinum treatment.

The oncosignature analysis emphasizes the importance of considering all the signaling pathways linked to the activation of EGFR when evaluating a model for determining outcome. In fact, short-PFS tumors were characterized by strong RAS signaling activation. Our data suggest the relevance of the integrity of RAS downstream signaling in conferring sensitivity to cetuximab/platinum, while overactivation of RAS pathway leads to resistance.

RAS mutations were not analyzed in our case material, but they are very rare in HNSCC (3% as reported in tumourportal) compared with other cancer types (32). We investigated the activation of the RAS pathway in an isogenic cetuximab-sensitive versus -resistant cellular model having wild-type RAS and confirmed an aberrant overactivation of RAS signaling in the resistant cell line compared with the sensitive one along with consistent activation of G5-15 (ectoderm development) and downregulation of G5-1 (regulation of muscle contraction) and low C33-hypoxia score. Our findings support the idea that the activation of the RAS pathway even in absence of constitutive gene mutations could lead to cetuximab/platinum resistance. Indeed, we also showed the validity of our predictive signature in a colon cancer setting (8). Notably, the proteomic profile predicting for cetuximab efficacy in colon cancer was valid only in subjects with RAS WT tumors (33). These observations, if confirmed more widely in HNSCC case materials, could open the way to the selection of the genes most relevant in strong RAS signaling activation as companion diagnostics for anti-EGFR therapy of RM-HNSCC.

Finally, the association of long-PFS with C33-hypoxia (12) is in line with the predicted high sensitivity to afatinib of this subgroup of patients. Because C33-hypoxia patients are characterized by an altered hypoxia pathway, the use of EGFR-targeted therapies combined with antioxidant agents and/or additional strategies exploiting hypoxia, as already suggested (13, 34), deserves to be tested in preclinical models recapitulating the gene expression profile of long-PFS patients.

The analysis of the link between the expression profiles of patients entered in this study with that of cell lines that exhibited a particular sensitivity to a drug (21) confirmed dependence on the EGFR pathway signal for the long-PFS tumors. In this group of patients, cisplatin and docetaxel gave some hints of activity, although to a far lower extent than EGFR pathway inhibitors. On the other hand, it is worth noting how the short-PFS group segregates with the activity of other chemotherapeutic drugs, namely, gemcitabine and doxorubicin.

We should accept a limit in defining the predictive value of the identified gene expression profile because it was not possible to compare our results using profiles of similar RM-HNSCC patients not receiving cetuximab but only CT. However, the importance of maintenance cetuximab in the long-PFS group should be emphasized; in fact, CT was stopped after six cycles (about 5 months), whereas cetuximab administration was continued till progression (range in long-PFS, 7–31 months), suggesting that the predictive value of our signature and underlying molecular mechanisms could be related to anti-EGFR treatment.

Our genomic analysis did not take into consideration the cetuximab’s second mechanism of action, i.e., ADCC. Thus, the prospective validation of our signature is currently ongoing on two phase II trials based on (i) cetuximab combination with cisplatin with/without paclitaxel in a multicentric phase II trial to further define the role of the altered pathways in determining sensitivity to cetuximab independently on the mechanism of action of the associated chemotherapeutic agent (2011-002564-24 on www.clinicaltrialsregister.eu); (ii) treatment with an anti-EGFR-Mab, panitumumab, showing less ADCC activity than cetuximab (35) to identify the potential contribution of the host immune system in conferring sensitivity/resistance to an anti-EGFR antibody treatment (36). Because in this study we selected patients with marked opposite outcomes after treatment, these prospective validations in the entire spectrum of patient’s outcome could also help in transposing our predictor of response into a useful clinical grade assay.

Finally, because in other cancer settings restricting the use of targeted therapy to a molecularly selected group of patients has been proven to be cost-effective (37), we believe that the identification of a gene-expression profile able to potentially identify patients benefiting from anti-EGFR treatment could reduce the incremental cost-effectiveness ratio and favor a more tailored use of this targeted therapy approach.

Disclosure of Potential Conflicts of Interest

P. Bossi is a consultant/advisory board member for Merck Serono. L. Licita is a consultant/advisory board member for AstraZeneca, Bayer, Boehringer, Bristol-Myers Squibb, Debiopharm, Eisai, Merck-Serono, MSD, Novartis, Roche and Sobi; reports receiving research funds, through her
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institution, from AstraZeneca, Boehringer, Eisai, Merck-Serono, MSD, Novartis and Roche; and reports receiving travel reimbursement from Bayer, Debiopharm, Merck-Serono, and Sobi. No potential conflicts of interest were disclosed by the other authors.

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