



Anti-epidermal growth factor receptor immunotherapy in combination with cisplatin chemoradiation for patients with advanced head and neck carcinoma – biological and clinical limitations of the triple treatment

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Squamous cell carcinoma of the head and neck region (HNSCC) is the sixth important tumour entity by incidence worldwide associated with more than 300,000 HNSCC related deaths/year (1). Current standard treatment, especially in the advanced situation, comprises definitive cisplatin based chemoradiation therapy (CRT) or adjuvant CRT after surgical resection in patients with high risk tumours (2). Prognosis, however, remains poor for the entire entity with 5-year survival rates around 50% (3).

Due to an increasing understanding of the molecular biology of HNSCC, interest has been prompted in the development of molecularly targeted therapies to improve the efficacy of standard therapeutic regimes while minimizing toxicity. Among these targeted approaches, inhibition of the epidermal growth factor receptor (EGFR) is most advanced in the clinical setting. EGFR is a transmembrane glycoprotein and member of the ErbB receptor tyrosine kinase family. Upon ligand binding [EGF, transforming growth factor (TGF)-alpha, amphiregulin], EGFR phosphorylation induces downstream activation of the Ras/Raf/mitogen-activated protein kinase (MAPK), phospho-inositide 3-kinase (PI3K)/AKT and Janus kinase (JAK)/signal transducer and activator of transcription 3 (STAT3) pathways finally resulting in proliferation, inhibition of apoptosis, neovascularization, and activation of an invasive and metastatic phenotype (4). From a clinical perspective, EGFR is over-expressed in approximately

80–90% of HNSCC and correlates with poor prognosis and resistance to radiation therapy (5). Moreover, preclinical evidences revealed that blocking EGFR by means of antagonistic antibodies restores radiation sensitivity and enhances cytotoxicity (6). Consequently, for more than a decade, EGFR-targeted strategies are evaluated as integral components in the treatment of patients with advanced HNSCC including the use of the chimeric IgG1—human monoclonal antibody cetuximab (Erbix®), the first targeting agent to demonstrate survival advantages if combined with radiation therapy (7).

Following pioneering, euphorically commented results from large randomized studies indicating a superiority of combined cetuximab and radiotherapy (RT) in a primary curative intended situation and improved overall survival in patients with recurrent or metastatic disease in combination with cisplatin-based chemotherapy (CT) (7,8), EGFR inhibition seemed to be a promising approach to further improve efficacy of RT or CT in patients with HNSCC. Based on these evidences, Radiation Therapy Oncology Group investigators launched a phase III trial (RTOG 0522) published in the *Journal of Clinical Oncology* in 2014 (9). In a large cohort (n=891) of eligible patients with stage III or IV HNSCC, the study aimed to test the hypothesis that adding cetuximab to an accelerated RT and cisplatin-platform (experimental arm) improves progression-free survival (PFS) in comparison to standard cisplatin-based

CRT. Results, however, were highly disappointing. Addition of cetuximab did not significantly affect 3-year PFS and overall survival, locoregional tumour control and distant metastases. To the contrary, cetuximab plus CRT resulted in more frequent interruptions in RT despite incomplete cetuximab administration in 26.4% of the patients. Moreover, elevated levels of treatment-related radiation mucositis, rash, fatigue, anorexia, and hypokalaemia were observed. The authors thus concluded that concomitant cetuximab administration does not add clinical benefit to conventional cisplatin CRT. These negative results corroborated findings of other studies that combined anti-EGFR therapy with concurrent CRT in the locally advanced setting and consistently confirmed lack of benefit of a triple modality strategy (10).

The authors discussed their negative results to originate (1) from the toxicity burden of RCT to be at the maximum tolerated level, resulting in RT interruption(s) in 26.9% of patients after adding cetuximab and (2) lack of benefit due to similar mechanisms of radiation sensitization by platinum derivatives and cetuximab such as inhibition of DNA damage repair.

In line with that, they argued that tumours having proficient repair machinery would be resistant to both modalities, while sensitive tumours would gain no additional benefit. Consequently, use of cetuximab with agents displaying different modes of action may improve sensitization. Interestingly, RTOG 0234, a phase II trial published in the same issue (11), investigated the feasibility of an antitubulin drug docetaxel-cetuximab-radiation adjuvant regimen versus cisplatin-cetuximab-radiation triplet strategy in terms of disease-free survival (DFS). The docetaxel regimen indeed showed favourable outcome, with improved 2-year DSF compared to both, the cisplatin-arm of the trial (66% *vs.* 57%, respectively) and relative to a historical cisplatin-based control (RTOG-9501), thus supporting their hypothesis.

Given the dissatisfying outcome of the RTOG-0522 trial, however, additional determinants should be taken into consideration. Besides modulation of oncogenic intracellular mechanisms, cetuximab exerts its therapeutic activity by means of induction of an antibody dependent cell-mediated cytotoxicity. In line with that, there is growing evidence on a prognostic relevance of elevated levels of tumour infiltrating immune cells for RCT response in HNSCC (12). Thus, a role of both innate and adaptive immune responses (13) should be considered as relevant for cetuximab response in

future preclinical and clinical investigations.

From a radiobiological point of view, lack of benefit might further arise from modulation of tumour cell cycle distribution after anti-EGFR treatment. Cetuximab is reported to induce a G1 arrest by upregulating the cyclin-dependent kinase inhibitors p27^{CIP1/WAF1} and p27^{KIP1} (14). This may augment the efficacy of RT in situations in which rapid repopulation of surviving tumour cells during fractionated schedules might counteract the radiation-induced cell eradication—a phenomenon that could well apply to the successful combination of sole RT and cetuximab for patients with HNSCC (7). The same, however, does not hold true for the triple combination of RT, chemotherapeutic drugs and cetuximab. Platinum based drugs exert their maximal radiosensitizing and cytotoxic potential when cells proliferate into the S/G2/M phases of the cell cycle. This effect might be impaired if the cells are arrested by cetuximab in the G1 phase before and during CRT resulting in diminished cytotoxicity and radiation efficacy. Furthermore, data suggested a sequence dependency of a cetuximab and platinum drug combination (15). In these studies, maximal synergy was observed when oxaliplatin was followed by cetuximab, but antagonistic effects were detected when cetuximab preceded oxaliplatin (15). Importantly, no study has yet clinically defined the best sequence of cytotoxic agents and cetuximab application for triple modality treatment.

Although a smoking history is considered to display a major risk factor for HNSCC, human papilloma virus (HPV) infection is increasingly associated with development of the disease with 36% of patients being virus-positive in a global statistical analysis in 2013 (16). HPV- or surrogate marker p16-positive patients represent a subset with better prognosis, treatment outcome and elevated average 5-year survival rates (17). Notably, HPV positivity is associated with a lower EGFR expression and lack of copy number events for EGFR ligands (18), suggesting that EGFR expression may display a negative prognostic marker in HNSCC.

In the RTOG 0522 trial, trends were evident for worse PFS (HR, 1.57; P for interaction =0.12) and OS (HR, 1.42; P for interaction =0.13) for patients with p16-positive oropharyngeal carcinomas receiving cetuximab slightly supporting this consumption. Histochemical detection of EGFR expression, on the contrary, could not support this thesis in the RTOG 0522 trial, probably due to a restricted availability of specimens from only 43% of patients.

Patients enrolled in the RTOG 0522 trial were not selected before treatment nor did the authors define subsets of patients likely to respond to cetuximab treatment. A multitude of biomarkers, including tumour EGFR expression, copy numbers and mutations in downstream signalling pathways (e.g., KRAS) have been suggested as predictive for cetuximab resistance in HNSCC (19). However, none of these markers is yet validated in prospective trials and a single marker is not expected to be sufficient for the prediction of a complex cetuximab resistance. Against this background, Lupini *et al.* very recently reported on a multigene next-generation sequencing approach in patients with colorectal cancer (20). In their analyses, mutation in coding sequences of 21 genes (e.g., KRAS, BRAF, PI3KCA, SMAD4), predicted unfavourable response to anti-EGFR antibody cetuximab and panitumumab treatment that may also be relevant in the head and neck situation.

In conclusion, treatment of patients with locally advanced HNSCC remains challenging. A combination of the EGFR antagonists' cetuximab and panitumumab with CRT, however, not only failed to show benefit over standard therapy but was associated with elevated toxicity and thus, is not a therapeutic revolution. Reasons for this failure are multifaceted and may include burden of toxicity, impaired DNA damage response, cell cycle effects, not fully understood immunologic effects and lack of selection of patients likely to benefit from EGFR inhibition. Although there are a number of ongoing randomized trials comparing the effect of cetuximab or alternative inhibitors plus RT or cisplatin based CRT in patients with HNSCC [for an overview see (19)], research activities should further focus on establishing an predictive EGFR sensitivity signature and optimizing sequences of application in a multimodal setting (21).

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Footnote

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References

1. Jemal A, Bray F, Center MM, et al. Global cancer statistics. *CA Cancer J Clin* 2011;61:69-90.
2. Grégoire V, Lefebvre JL, Licitra L, et al. Squamous cell carcinoma of the head and neck: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010;21 Suppl 5:v184-6.
3. Cognetti DM, Weber RS, Lai SY. Head and neck cancer: an evolving treatment paradigm. *Cancer* 2008;113:1911-32.
4. Ceresa BP, Peterson JL. Cell and molecular biology of epidermal growth factor receptor. *Int Rev Cell Mol Biol* 2014;313:145-78.
5. Burtness B. The role of cetuximab in the treatment of squamous cell cancer of the head and neck. *Expert Opin Biol Ther* 2005;5:1085-93.
6. Milas L, Mason K, Hunter N, et al. In vivo enhancement of tumor radioresponse by C225 antiepidermal growth factor receptor antibody. *Clin Cancer Res* 2000;6:701-8.
7. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med* 2006;354:567-78.
8. Vermorken JB, Mesia R, Rivera F, et al. Platinum-based

- chemotherapy plus cetuximab in head and neck cancer. *N Engl J Med* 2008;359:1116-27.
9. Ang KK, Zhang Q, Rosenthal DI, et al. Randomized phase III trial of concurrent accelerated radiation plus cisplatin with or without cetuximab for stage III to IV head and neck carcinoma: RTOG 0522. *J Clin Oncol* 2014;32:2940-50.
 10. Mesía R, Henke M, Fortin A, et al. Chemoradiotherapy with or without panitumumab in patients with unresected, locally advanced squamous-cell carcinoma of the head and neck (CONCERT-1): a randomised, controlled, open-label phase 2 trial. *Lancet Oncol* 2015;16:208-20.
 11. Harari PM, Harris J, Kies MS, et al. Postoperative chemoradiotherapy and cetuximab for high-risk squamous cell carcinoma of the head and neck: Radiation Therapy Oncology Group RTOG-0234. *J Clin Oncol* 2014;32:2486-95.
 12. Balermipas P, Michel Y, Wagenblast J, et al. Tumour-infiltrating lymphocytes predict response to definitive chemoradiotherapy in head and neck cancer. *Br J Cancer* 2014;110:501-9.
 13. Yang X, Zhang X, Mortenson ED, et al. Cetuximab-mediated tumor regression depends on innate and adaptive immune responses. *Mol Ther* 2013;21:91-100.
 14. Peng D, Fan Z, Lu Y, et al. Anti-epidermal growth factor receptor monoclonal antibody 225 up-regulates p27KIP1 and induces G1 arrest in prostatic cancer cell line DU145. *Cancer Res* 1996;56:3666-9.
 15. Morelli MP, Cascone T, Troiani T, et al. Sequence-dependent antiproliferative effects of cytotoxic drugs and epidermal growth factor receptor inhibitors. *Ann Oncol* 2005;16 Suppl 4:iv61-68.
 16. Liu H, Li J, Diao M, et al. Statistical analysis of human papillomavirus in a subset of upper aerodigestive tract tumors. *J Med Virol* 2013;85:1775-85.
 17. Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med* 2010;363:24-35.
 18. Keck MK, Zuo Z, Khattri A, et al. Integrative analysis of head and neck cancer identifies two biologically distinct HPV and three non-HPV subtypes. *Clin Cancer Res* 2015;21:870-81.
 19. Alorabi M, Shonka NA, Ganti AK. EGFR monoclonal antibodies in locally advanced head and neck squamous cell carcinoma: What is their current role? *Crit Rev Oncol Hematol* 2016;99:170-9.
 20. Lupini L, Bassi C, Mlcochova J, et al. Prediction of response to anti-EGFR antibody-based therapies by multigene sequencing in colorectal cancer patients. *BMC Cancer* 2015;15:808.
 21. Nyati MK, Morgan MA, Feng FY, et al. Integration of EGFR inhibitors with radiochemotherapy. *Nat Rev Cancer* 2006;6:876-85.

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