

REVIEW

Targeting EGFR Exon 20 Insertion-mutated Cancers – New Perspectives in Head and Neck Cancers – Lessons to Learn from Non-small Cell Carcinoma (NSCLC)

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Abstract

Mutations in the tyrosine kinase (TKD) domain of the epidermal growth factor receptor (EGFR) are involved in the unfavorable therapeutic response through resistance to targeted molecular therapy. Data from the clinical experience of non-small cell lung carcinoma (NSCLC) treatment demonstrate the benefit of tyrosine kinase inhibitors (TKIs) in cases of EGFR mutation. The next generation sequencing technique (NGS) allows the identification of hot spots involved in mutations, exon 20 insertion being associated with the unfavorable response. Exon 20 insertions are more common in head and neck squamous cell carcinoma (HNSCC) compared to NSCLC, which could explain a resistance to targeted therapy in head and neck cancers. Taking into account the data reported in the NSCLC, Amivantamab, a bi-specific EGFR-MET antibody with potential immune cell modulation of activity, but also other innovative therapies validated in exon20 EGFR mutation could be part of the therapy of sino-nasal cancer, but also of other HNSCC sites exon 20 mutant EGFR.

Keywords: head and neck cancers, TKI, EGFR, HNSCC, lung cancer, NSCLC, Amivantamab, exon 20, sino-nasal cancer.

Rezumat

Mutațiile în domeniul tirozin-kinazei (TKD) ale receptorului factorului de creștere epidermic (EGFR) sunt implicate în răspunsul nefavorabil prin rezistența la terapia moleculară țintită. Datele obținute din experiența clinică a tratamentului carcinomului bronho-pulmonar non-microcelular (NSCLC) demonstrează beneficiul terapiei cu inhibitori ai tirozin-kinazei (TKI) pentru cazurile care prezintă mutația EGFR. Tehnica secvențierii de nouă generație (NGS) permite identificarea "hot spoturilor" implicate în mutații de tip inserție în exonul 20, mutație asociată cu răspunsul nefavorabil la tratamentul prin terapie țintită și cu un prognostic nefavorabil. Inserțiile în exonul 20 sunt mai frecvent întâlnite în carcinomul scuamos de cap și gât (HNSCC) în comparație cu NSCLC, ceea ce ar putea explica o rezistență la terapia țintită în cancerul de cap și gât. Ținând cont de datele raportate în cazul NSCLC, Amivantamab, un nou anticorp bi-specific cu acțiune duală de inhibiție EGFR-MET și potențial de modulare/activare a imunității celulare, dar și alte terapii inovative validate în cazurile cu mutații EGFR tip inserție în exonul 20 ar putea face parte din terapia cancerelor rino-sinusale. O prevalență înaltă a mutațiilor în exonul 20 al EGFR caracteristică carcinomului rino-sinusal ar putea justifica identificarea și evaluarea în trialuri clinice a beneficiului TKI de generație nouă în managementul acestui tip rar de neoplasm al capului și gâtului, dar și a altor HNSCC purtătoare ale acestui tip particular de mutație.

Cuvinte cheie: cancer de cap și gât, TKI, EGFR, HNSCC, cancer bronho-pulmonar, NSCLC, Amivantamab, exon 20, receptori tirozin-kinazici, cancer rino-sinusal.

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INTRODUCTION

Mutations in the tyrosine kinase (TKD) domain of the epidermal growth factor receptor (EGFR) are involved in the unfavorable response through resistance to molecular targeted therapy. Given the data obtained from lung cancer patients proving that cases with mutations in the TKD domain of EGFR respond to small-molecule inhibitors such as, Erlotinib, Gefitinib, Osimertinib and Afatinib, the approach to identify potential therapeutic targets involving this The receptor in head and neck cancers is a topic of interest. The identification of a particular subtype of HNSCC with better response to multimodal treatment and better prognosis, a disease variant linked to Human Papilloma Virus (HPV) infection make it necessary the personalization of the therapy, including identification of new valid biomarkers. Evaluating EGFR mutations in patients with HNSCC, Perisanidis analyzed in a systematic review of the literature the data regarding prevalence of EGFR in HNSCC. A 2.8% percent of the 4,122 patients included in 53 clinical trials expressed a mutation in EGFR. Approximately 90% of HNSCC express EGFR of the transmembrane cell surface receptor in the tyrosine kinase receptor family. The over-expression of EGFR in HNSCC is associated with unfavorable prognosis. EGFR is involved in pathways that modulate carcinogenesis, being a therapeutic target of current interest. Testing in fundamental and clinical research of monoclonal antibodies and tyrosine kinase inhibitors (TKIs) are strategies currently being evaluated, but de novo or acquired resistance to these classes of agents are the causes of therapeutic failures¹.

EGFR exon 20 insertions targeting – lesson to learn from NSCLC

Next-generation sequencing tests (NGS) are used to detect EGFR exon 20 insertions, mutations that may confer special therapeutic features compared to exon 19 deletions, mutations encountered in most cases. The National Comprehensive Cancer Network (NCCN) also supports NGS testing for all cases, taking into account data on differences in disease progression for NSCLC subtypes classified based on EGFR mutation types and the fact that conventional PCR detection methods have a rate of over 50% to omit the correct identification of EGFR mutations. In head and neck cancers, mutations in the TKD tyrosine kinase domain of exon were identified in exon 18, exon 19, exon 20

and exon 21 in percentages of 9.4%, 41.5%, 32.1% and 17%, respectively. A percentage of 5% of EGFR mutations represent insertions in exon 20, a type of mutation that benefits from a new therapy in non-small cell lung carcinoma. The missense T790M mutations in exon 20 are associated with resistance to TKI. It is worth mentioning the higher percentage of insertions in exon 20 in the case of HNSCC compared to NSCLC (5% vs 3%) which justifies the interest for a possible implementation of the innovative target therapy used in lung cancer. Three clinical trials analyzed the results of platinum-based chemotherapy in HNSCC with EGFR mutation in exon 20. With a progression free survival (PFS) between 6.4 and 7.6 months, platinum-based chemotherapy was associated with an overall response. Lower rates of ORR (approximately 19%) compared to Pemetrexed-based treatment (41.6%). In terms of PFS, Pemetrexed based chemotherapy was inferior (5.5 months) to platinum based chemotherapy. Although overall survival (OS) was analyzed only in one clinical trial that included platinum-based chemotherapy, the results were inferior to Pemetrexed (19.9 vs. 25 months). Three generations of TKI were tested in combination with EGFR-mutated NSCLC chemotherapy in exon 20: Gefitinib, Erlotinib and Icotinib, first-generation TKI, Afatinib and Dacomitins, second-generation TKI, and Osimertinib, a third-generation targeted therapy²⁻⁴.

Platinum-based chemotherapy was the treatment of choice for lung cancer before the identification of EGFR mutations and before the implementation of TKI in clinical practice. For this category of patients carrying the EGFR mutation, the use of TKI brings benefits in tumor control being preferred compared to platinum-based chemotherapy. However, for the subgroup of patients with common mutations (EGFR ex19del and EGFR L858R) they have a better prognosis and respond better to TKI. NSLC patients carrying exon 20 insertion have an unfavorable prognosis and, even if TKIs have been approved for this category of patients, they will have minimal benefit to the target therapy, being also patients with an unfavorable prognosis.

A French multicenter study that included rare mutations identified a higher rate of exon 20 mutations in patients who never shared smokers with exon 18 mutations, and metastatic survival was almost double for non-smokers vs. smokers (21 months vs. 14 months). Patients treated with TKI had a median OS of 14 months, but clinical results were more favorable

in cases with exon 18 mutations or complex mutation compared with patients which expresses EGFR exon 20 mutation alone. Clinical data validated the hypothesis from preclinical studies regarding the benefit of high doses of Osimertinib in cases of EGFR T790M resistance time insertion in exon 20. POSITION20 of single arm phase II showed a modest benefit of high doses of Osimertinib, median ORR being 28 % with acceptable toxicity. Piotrowska et al. performed a single-arm phase II study with Osimertinib 160 mg in NSCLC patients with EGFR exon 20 insertion mutations. Of the 20 patients with EGFR mutant insertion in exon 20 tested in a phase II study for high doses of Osimertinib (160 mg), the ORR rate was 25% of which one was fully responsive in term of disease control⁵⁻⁹.

Amivantamab – a dual EGFR and MET inhibitor with promising potential

Amivantamab, a double-acting antibody on both EGFR mutation and mesenchymal epithelial transition factor receptor (MET) activity and on immune cells was evaluated in the clinic in the phase I study of CHRYSALIS including EGFR NSCLC cases with exon20 insertion. The study established the recommended dose for phase II trials in order to keep toxicities within normal limits. Administration of Amivantamab at a dose of 1050 mg (1400 mg ≥80 kg) given once a week for the first 4 weeks and then every 2 weeks from week 5, after platinum-based chemotherapy. The 40% response rate including 3 complete responses from 40 patients and a median response time of 11.1 months recommends treatment as effective after progression of NSCLC cases with exon 20 EGFR insertion. Rash, infusion reactions, paronychia, hypokalemia, pulmonary embolism, neutropenia and diarrhea have been reported as toxicities, with dose reductions and treatment discontinuations reported in 13% and 4% of cases, respectively. Vyse et al. hypothesizes that Amivantamab, being a large molecule, will not cross the brain blood barrier and will have reduced activity on brain metastases, but through its extracellular action will help delay the onset of resistance to other therapies. Amivantamab also demonstrates benefit in patients with NSCLC MET exon 14 skipping mutation (METex14) previously treated with MET inhibitors. Thus ORR was 33% 46 and 21% for naïve treatment cases, with no previous MET inhibitors, respectively for the patient previously treated with MET inhibitors¹⁰⁻¹³.

Pozitinib, a next-generation TKI for targeting exon20 aberration in EGFR

Pozitinib, a next-generation TKI demonstrated efficacy in the treatment of NSCLC with aberrations in EGFR exon 20. A case of a 62-year-old patient who progressed after surgery and adjuvant chemotherapy showed a favorable, long-term response after pozitinib therapy, the patient being in the metastatic stage of disease at the moment of TKI treatment initiation. Data from the ZENITH20 trial mention alopecia, skin rash, conjunctivitis as well as diarrhea and xerostomia associated with Pozitinib as toxicities¹⁴.

Amivantamab and chemotherapy – a successful partnership?

By now, the safety profile of Amivantamab has been evaluated in 250 cases and the PAPILLON phase III trial aims to identify a possible benefit of the combination of Amivantamab and Carboplatin-Pemetrexed versus Carboplatin-Pemetrexed. The trial includes patients with EGFR mutants with exon 20 insertion in advanced or metastatic NSCLC. The results of this trial will determine the value of an association between EGFR-MET therapy and chemotherapy in this subgroup of patients¹⁵⁻¹⁶.

EGFR exon 20 insertion – a surprising predominance in sino-nasal cancers

Recurrent mutations involved in EGFR activation have been reported in squamous cell carcinoma, a rarer form of head and neck cancer but with a mortality of over 40% at 5 years. Although in most HNSCC mutations other than NSCLC associated with exon 19 deletion and L858R mutation predominate, in the case of sino-nasal carcinoma it is noted by the predominance of exon 20 insertion. By analogy with data obtained from lung cancers we can assume that this mutation is associated with pathogenesis as well as with treatment resistance and testing the strategies validated in NSCLC would open new therapeutic perspectives for this subtype of cancers. Pacini and colleagues also mention the possible involvement of mutated EGFR by inserting exon 20 into the conversion of inverted sino-nasal papilloma, a locally aggressive benign tumor, into sino-nasal carcinoma¹⁷.

Perisanidis also mentions the major difference between EGFR mutations in NSCLC and HNSCC, noting an association of lung cancer with hot spots in exons 18 and 21. Head and neck cancers also involve

hot spot regions in exons 19 and 21. Given that some studies have reported only mutations in exons 19 and 21 it is possible that there is an under-reported prevalence of EGFR mutations in HNSCC. In the systematic review, the author identifies a 2.8% prevalence of EGFR mutations in HNSCC with a minor variation between geographic regions¹.

CONCLUSIONS

The NGS technique will play an essential role in accurately detecting the type of mutation and the exon involved in the detailed characterization of the EGFR mutation in HNSCC. Taking into account the data reported in HSCLC, Amivantamab, a bispecific EGFR-MET antibody with potential immune cell

modulation of activity but also other innovative therapies validated in exon20 and other types of HNSCC.

Compliance with ethics requirements: The authors declare no conflict of interest regarding this article. The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

References

1. Perisanidis C. Prevalence of EGFR Tyrosine Kinase Domain Mutations in Head and Neck Squamous Cell Carcinoma: Cohort Study and Systematic Review. *In Vivo*. 2017 Jan 2;31(1):23-34. doi: 10.21873/in vivo.11020.
2. Wang Y, Li J, Zhou Y, Cao S, Ling X, Zhang Y, Nie W, Zhong H. Tumor genomics and response to chemotherapy in advanced non-small cell lung cancer with exon 20 insertion epidermal growth factor receptor mutations. *Ann Transl Med*. 2020 Oct;8(20):1297. doi: 10.21037/atm-20-6172.
3. Shi J, Yang H, Jiang T, Li X, Zhao C, Zhang L, Zhao S, Liu X, Jia Y, Wang Y, Xi L, Zhang S, Su C, Ren S, Zhou C. Uncommon EGFR mutations in a cohort of Chinese NSCLC patients and outcomes of first-line EGFR-TKIs and platinum-based chemotherapy. *Chin J Cancer Res*. 2017 Dec;29(6):543-552. doi: 10.21147/j.issn.1000-9604.2017.06.09.
4. Xu CW, Wang WX, Wang D, Wang QM, Pu XX, Zhu YC, Huang JH, Yu ZY, Cui ZL, Chen XH, Li JL, Fang Y, Wang H, Zhuang W, Lan SJ, Cai X, Zhang YB, Gao WB, Wang LP, She KL, Rao CZ, Zhou YF, Fang MY, Miao LY, Lei L, Lv TF, Song Y. Pemetrexed-based chemotherapy for non-small-cell lung cancer patients with EGFR exon 20 insertion mutation: a multicenter study. *Transl Lung Cancer Res*. 2020 Oct;9(5):1853-1861. doi: 10.21037/tlcr-20-382.
5. Hou J, Li H, Ma S, He Z, Yang S, Hao L, Zhou H, Zhang Z, Han J, Wang L, Wang Q. EGFR exon 20 insertion mutations in advanced non-small-cell lung cancer: current status and perspectives. *Biomark Res*. 2022 Apr 13;10(1):21. doi: 10.1186/s40364-022-00372-6.
6. Beau-Faller M, Prim N, Ruppert AM, Nanni-Metellus I, Lacave R, Lacroix L, Escande F, Lizard S, Pretet JL, Rouquette I, de Crémoux P, Solassol J, de Fraipont F, Bièche I, Cayre A, Favre-Guillevin E, Tomasini P, Wislez M, Besse B, Legrain M, Voegeli AC, Baudrin L, Morin F, Zalzman G, Quoix E, Blons H, Cadranet J. Rare EGFR exon 18 and exon 20 mutations in non-small-cell lung cancer on 10 117 patients: a multicentre observational study by the French ERMETIC-IFCT network. *Ann Oncol*. 2014 Jan;25(1):126-31. doi: 10.1093/annonc/mdt418.
7. Rebegea, L.; Anghel, R.; Nechita, A.; Firescu, D.; Bacinski, X.; Dumitru, M.; Craescu, M. Radiotherapy delivering in covid-19 pandemic context. galati radiotherapy center's experience and recommendations of professional societies. *Medicina Moderna* ; 27(2):97-101, 2020.
8. Cocolos A-M, Poiana C. Differentiated Thyroid Cancer Genetic Mechanisms - Focus on Vitamin D Receptor and Methylenetetrahydrofolate Reductase Gene Polymorphisms. *Medicina Moderna* ; 29 (1); 7-13, 2022
9. Piotrowska Z, Fintelmann FJ, Sequist LV, Jahagirdar B. Response to Osimertinib in an EGFR Exon 20 Insertion-Positive Lung Adenocarcinoma. *J Thorac Oncol*. 2018 Oct;13(10):e204-e206. doi: 10.1016/j.jtho.2018.05.017.
10. Park K, Haura EB, Leighl NB, Mitchell P, Shu CA, Girard N, Viteri S, Han JY, Kim SW, Lee CK, Sabari JK, Spira AI, Yang TY, Kim DW, Lee KH, Sanborn RE, Trigo J, Goto K, Lee JS, Yang JC, Govindan R, Bauml JM, Garrido P, Krebs MG, Reckamp KL, Xie J, Curtin JC, Haddish-Berhane N, Roshak A, Millington D, Lorenzini P, Thayu M, Knoblauch RE, Cho BC. Amivantamab in EGFR Exon 20 Insertion-Mutated Non-Small-Cell Lung Cancer Progressing on Platinum Chemotherapy: Initial Results From the CHRYSALIS Phase I Study. *J Clin Oncol*. 2021 Oct 20;39(30):3391-3402. doi: 10.1200/JCO.21.00662.

11. Vyse S, Huang PH. Amivantamab for the treatment of EGFR exon 20 insertion mutant non-small cell lung cancer. *Expert Rev Anticancer Ther.* 2022 Jan;22(1):3-16. doi: 10.1080/14737140.2022.2016397.
12. Zwierenga F, van Veggel B, Hendriks LEL, Hiltermann TJN, Hiddinga BI, HijmeringKappelle LBM, TerElst A, Hashemi SMS, Dingemans AC, van der Leest C, de Langen AJ, van den Heuvel MM, van der Wekken AJ. High dose osimertinib in patients with advanced stage EGFR exon 20 mutation-positive NSCLC: Results from the phase 2 multicenter POSITION20 trial. *Lung Cancer.* 2022 Jun 23;170:133-140. doi: 10.1016/j.lungcan.2022.06.012.
13. Matthew Krebs, Alexander I. Spira, ByoungChul Cho, Benjamin Besse, Jonathan W. Goldman, Pasi A. Janne, Zhiyong Ma, Aaron Scott Mansfield, Anna Rachel Minchom, Sai-Hong Ignatius Ou, Ravi Salgia, Zhijie Wang, CasildaLlacer Perez, Grace Gao, Joshua C Curtin, Amy Roshak, Robert W. Schnepf, MeenaThayu, Roland Knoblauch, and Chee Khoon Lee. *Journal of Clinical Oncology* 2022 40:16_suppl, 9008-9008
14. Prelaj A, Bottiglieri A, Bhat G, Washington R, Calareso G, Greco GF, Ferrara R, Brambilla M, De Toma A, Occhipinti M, Manglaviti S, Soro A, Ganzinelli M, Lo Russo G, Proto C. Case Report: Exceptional Response to Poziotinib in Patient with Metastatic Non-Small Cell Lung Cancer With EGFR Exon 20 Insertion Mutation. *Front Oncol.* 2022 Jun 8;12:902967. doi: 10.3389/fonc.2022.902967.
15. <https://trials.cancervic.org.au/details.aspx?ID=feed-cta-trial159>
16. Minchom A, Viteri S, Bazhenova L, Gadgeel SM, Ou SI, Trigo J, Bauml JM, Backenroth D, Bhattacharya A, Li T, Mahadevia P, Girard N. Amivantamab compared with real-world therapies in patients with advanced non-small cell lung cancer harboring EGFR exon 20 insertion mutations who progressed after platinum-based chemotherapy. *Lung Cancer.* 2022 Jun;168:74-82. doi: 10.1016/j.lungcan.2022.03.005.
17. Pacini L, Cabal VN, Hermesen MA, Huang PH. EGFR Exon 20 Insertion Mutations in Sinonasal Squamous Cell Carcinoma. *Cancers (Basel).* 2022 Jan 13;14(2):394. doi: 10.3390/cancers14020394.