EBioMedicine 58 (2020) 102901

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.elsevier.com/locate/ebiom

Commentary

A new prognostic hypoxia biomarker consisting of imaging and gene-based data

Elisa Thomas[d,e], Mechthild Krause[a,b,c,d,e,*]

[a] German Cancer Consortium (DKTK) partner site Dresden, Dresden and German Cancer Research Center (DKFZ), Heidelberg, Germany
[b] OncoRay-National Center for Radiation Research in Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Helmholtz-Zentrum Dresden-Rossendorf, Dresden, Germany
[c] Helmholtz-Zentrum Dresden-Rossendorf, Institute of Radiooncology-OncoRay, Dresden, Germany
[d] Department of Radiotherapy and Radiation Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany
[e] National Center for Tumor Diseases (NCT), Partner Site Dresden, Germany: German Cancer Research Center (DKFZ), Germany

ARTICLE INFO

Article History:
Received 2 July 2020
Accepted 2 July 2020

In the research article of EBioMedicine [1], Fjeldbo and colleagues developed a combined biomarker based on hypoxic fraction from dynamic contrast enhanced (DCE)-MRI imaging and genetic data of cervical cancer. They were able to predict the response to radiochemotherapy of these patients. The patients were divided into groups less or more hypoxic, based on a previously defines cut-off for the gene-based biomarkers (6 hypoxia-related genes) [2]. In the same group of 41 patients, a cut-off for the imaging biomarker was newly assessed by analyzing DCE-MRI data and using A_{Brix}-images as parameter for the hypoxic fraction. In the next step these cut-offs were validated in 77 patients and subsequently a combined hypoxic biomarker was generated. The combination of the biomarkers revealed the same hypoxic status in 75% of the 118 patients. Therefore, besides the more and less hypoxic group, a third group with different hypoxia status was constituted.

The authors suspected at a first glance these contradictory results of both measurements to be based on the fact that only a small part of the tumor (biopsy of the distal part of the cervical carcinoma) can be examined in a biopsy, while the MRI technique shows the whole picture of intratumour heterogeneity. However, the variance analysis could not confirm this hypothesis, both biomarkers were robust against intratumoural heterogeneity. It is interesting to note that in the case of expected heterogeneity of a tumor, the hypoxia status in the biopsy was representative for the entire tumor. A possible explanation could be that the gene-based biomarker detects persistent changes in the genome and thus even a small sample can be representative for that.

The clinical endpoint of the trial was progression-free survival (PFS). Fjeldbo et al. show that higher tumor hypoxia is associated with a worse PFS. Both biomarkers alone could predict PFS, but the combination of both enabled a better prediction than one biomarker alone. The multivariate analysis identified the combined hypoxic biomarker and the tumor stage independently as prognostic factors for patients with cervical carcinoma.

These data show the potential for clinical use of the combined image- and genetic biomarker as a prognostic parameter for patients with cervical carcinoma, even though both markers are enough to measure the same resistance factor. While the gene array biomarker has already been validated [2], the DCE-MRI biomarker still needs proof of transferability to another patient cohort [3]. In order to apply the biomarker combination in clinical routine, the following step would then be an interventional trial with a treatment modification based on the prognosis given by the biomarkers. In the long term, an establishment in other tumor entities would also be desirable.

From a biological and clinical point of view, it is known from previous studies that tumor hypoxia significantly influences tumor progression and resistance to chemo- and radiotherapy and is associated with a worse outcome of the patients [4–6]. Hypoxia changes the tumor microenvironment and influences a variety of signaling pathways in tumor cells. As a result, hypoxia targeted therapy is an interesting approach for an individualised cancer treatment and could also be an intervention for the above-mentioned trial. Several studies have already investigated hypoxic-cell sensitizers like nimorazole in head-and neck cancers [7] or molecular targeting using small molecules, the modulation of hypoxia-dependent signaling pathways, e.g. VEGF inhibition or gene targeting (HIF-1alpha) [8, 9]. In a prospective randomized study, Di Silvestro and colleagues investigated the additional administration of tirapazamine, a drug that is activated under hypoxic conditions, in addition to standard radiochemotherapy with cisplatin in locally advanced cervical carcinomas. However, no advantage for local control, progression-free and overall survival could be determined by a combination treatment [10]. Therefore, further investigations, possibly the identification of new hypoxia targets are desirable to improve the prognosis of these patients.

E-mail address: Mechthild.Krause@uniklinikum-dresden.de (M. Krause).

https://doi.org/10.1016/j.ebiom.2020.102901

Declaration of Competing Interests

In the past 5 years, Dr. Krause received funding for her research projects by IBA (2016), Merck KGaA (2014–2018 for preclinical study; 2018–2020 for clinical study), Medipan GmbH (2014–2018). She is involved in an ongoing publicly funded (German Federal Ministry of Education and Research) project with the companies Medipan, Attomol GmbH, GA Generic Assays GmbH, Gesellschaft für medizinische und wissenschaftliche genetische Analysen, Lipotype GmbH and PolyAn GmbH (2019–2021). For the present article none of the above mentioned funding sources were involved. Both authors declare no conflict of interest.

References

[1] Fjeldbo CS, Hompland T, Hillestad T, et al. Combining imaging- and gene-based hypoxia biomarkers in cervical cancer improves prediction of chemoradiotherapy failure independent of intratumor heterogeneity. EBioMedicine 2020 https://doi.org/10.1016/j.ebiom.2020.102841.

[2] Fjeldbo CS, Julin CH, Lando M, et al. Integrative Analysis of DCE-MRI and gene expression profiles in construction of a gene classifier for assessment of hypoxia-related risk of chemoradiotherapy failure in cervical cancer. Clin Cancer Res 2016;22(16):4067–76.

[3] O'Connor JPB, Aboagye EO, Adams JE. Imaging biomarker roadmap for cancer studies. Nat Rev Clin Oncol 2017;14(3):169–86.

[4] Yaromina A, Krause M, Baumann M. Individualization of cancer treatment from radiotherapy perspective. Mol Oncol 2012;6(2):211–21.

[5] Vaupel P, Mayer A. Hypoxia in Cancer: significance and Impact on Clinical Outcome. Cancer Metastasis Rev 2007;26(2):225–39.

[6] Wilson WR, Hay MP. Targeting Hypoxia in Cancer Therapy. Nat Rev Cancer 2011;11(6):393–410.

[7] Overgaard, et al., et al. A randomized double-blind Phase III study of nimorazole as a hypoxic radiosensitizer of primary radiotherapy in supraglottic larynx and pharynx carcinoma. Results of the danish head and neck cancer study (DAHANCA) protocol 5-85. Radiother Oncol 1998;46(2):135–46.

[8] Jing X, Yang F, Shao C, et al. Role of hypoxia in cancer therapy by regulating the tumor microenvironment. Mol Cancer 2019;18(1):157.

[9] Casazza A, Gonza GD, Wenes M, et al. Tumor stroma: a complexity dictated by the hypoxic tumor microenvironment. Oncogene 2014;33(14):1743–54.

[10] DiSilvestro PA, Ali S, Craighead PS, et al. Phase III randomized trial of weekly cisplatin and irradiation versus cisplatin and tirapazamine and irradiation in stages IB2, IIA, IIB, IIIB, and IVA cervical carcinoma limited to the pelvis: a gynecologic oncology group study. J Clin Oncol 2014;32(5):458–64.