Editorial

Positron emission tomography imaging in diffuse intrinsic pontine glioma

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In pediatric patients with brain tumors, both the monitoring of brain tumor therapy and evaluation of treatment response is of paramount importance (1). In particular, the early identification of non-response allows the termination of an ineffective therapy to avoid possible side effects (e.g., bone marrow depression, nausea, fatigue, allergies, and polyneuropathy) and therefore to maintain or even improve life-quality. Furthermore, the early identification of non-response allows an earlier treatment change. For example, in the event of chemotherapy failure, negative side effects can be avoided and an earlier switch to another chemotherapeutic agent is possible before bone marrow reserves are exhausted. Moreover, identification of treatment failure may help reduce costs. To date, this is highly relevant because the expense of newer systemic treatment options (e.g., immunotherapy and targeted therapy options such as tyrosine kinase inhibitors, BRAF inhibitors, and MEK inhibitors) is considerably higher than conventional alkylating chemotherapy.

Brainstem tumors represent approximately 10–20% of pediatric brain tumors and with around 80% the diffuse intrinsic pontine glioma (DIPG) is the most common brainstem tumor of childhood. DIPG grow diffusely and infiltrate critical structures of the brainstem, i.e., predominantly the pons. Usually, DIPG are surgically not resectable and may display histological features ranging from grade II to grade IV of the World Health Organization (WHO) classification for gliomas. They frequently harbor a K27M mutation in one or other histone variant (2), with H3.1 mutant tumors displaying a younger patient age, distinct clinicopathological and radiological features, and a slightly longer survival time (3,4). Generally, DIPG are incurable; no significant therapeutic progress has been made in the past 50 years (4). In clinical trials, numerous experimental therapeutic approaches have been evaluated; however, none of them showed a survival benefit compared to standard external fractionated radiotherapy (5). Patients with DIPG have a two-year survival rate of less than 10% (6), representing the leading cause of brain tumor-related death in children.

Not infrequently, the diagnosis of a DIPG is based on the combination of clinical signs with findings on structural MRI only, without performing tissue biopsies. More recently, due to the steadily growing importance of molecular characterization of tumor tissue, diagnostic biopsies are increasingly being performed (7). On conventional MRI, DIPG appear with a T2/fluid-attenuated inversion recovery hyperintense lesion with non-delineated borders and do not significantly enhance on T1-weighted MRI sequences after application of a gadolinium-based

contrast agent. However, it has been demonstrated that the diagnostic value of this technique is limited regarding tumor delineation and treatment monitoring of DIPG (8,9).

In order to overcome the limitations of conventional MRI for monitoring of tumor growth and treatment monitoring, Kossatz and colleagues targeted the poly(ADP) ribose polymerase 1 (PARP1) in a pediatric DIPG mouse model. This enzyme is overexpressed in DIPG and regulates cell proliferation and DNA damage repair induced by alkylating agents. PARP1 positive cells were imaged with a radiolabeled PARP1-targeted tracer (^{18}F-PARPi) using positron emission tomography (PET) (5). High expression levels of PARP1 in DIPG (10) have attracted considerable interest due to its potential role as a surrogate marker for tumor cell activity, allowing the non-invasive quantification of DIPG burden by advanced neuroimaging methods. Furthermore, due to its properties on regulating cell proliferation and DNA damage repair, PARP1 inhibition may also be a potential treatment target in DIPG (11), as it has been demonstrated for ovarian cancer (12).

In the work by Kossatz and co-workers published 2017 in Cancer Research (5), the authors provided data in a genetically modified mouse model of DIPG which suggest that PARP1-targeted PET imaging allows to quantify higher PARP1 expression levels in DIPG than in the normal appearing, unaffected brain tissue. This may allow a more precise delineation of DIPG, the quantification of tumor burden and tumor growth changes by serial PET imaging, and thus improved treatment monitoring.

PARP1-targeted PET is an interesting new approach in the field of translational research. It is of great interest whether the clinical use of PET with a radiolabeled PARP1-targeted tracer in children with DIPG will confirm these promising and encouraging preclinical observations. A further important question which needs to be answered is whether the PARP1-targeted PET tracer is able to penetrate the intact blood-brain barrier (BBB). It is well known that the uptake of other PET tracers for cell proliferation evaluation such as ^{18}F-3´ deoxy 3´ fluorothymidine (^{18}F-FLT) are dependent on a disruption of the BBB (13,14). Since the majority of DIPG exhibit no contrast enhancement, i.e., no BBB disruption, further research on the influence of BBB permeability on the uptake of the PARP1-targeted PET tracer in animal models would be helpful prior to clinical introduction, e.g., by Evans blue fluorescence, as described previously (15).

In the light of novel treatment options based on molecular features of DIPG in children (16,17), a more reliable diagnostic tool for treatment monitoring than standard MRI would be of substantial interest.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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