Measuring the pons: a non-invasive biomarker for pediatric diffuse intrinsic pontine glioma

Katherine E Warren*

Brain tumors are the most common solid malignancies in children. Although more than 70% of children diagnosed with a brain tumor will survive 5 years or more, brain tumors are one of the most frequent causes of cancer death in children [1]. Those children who do survive frequently have significant adverse effects attributed to the tumor and its treatment. Therefore, the global objective in pediatric neuro-oncology is to improve survival and reduce long-term toxicities. Contemporary approaches being evaluated in current clinical trials include selection of tumor-specific (e.g., molecularly targeted) therapies, and identification of lower risk patients who can be treated with reduced therapeutic intensity. To succeed, we need to understand tumor biology, recognize the effects of therapeutic agents on tumor cells and their microenvironment preferably in real-time, determine predictive factors associated with response, and identify appropriate prognostic factors.

However, brain tumors, particularly in the pediatric population, represent a heterogeneous group of diseases. While meningiomas and supratentorial glioblastomas comprise more than 50% of all primary brain tumors in adults [2], these represent <2% and <3% in children, respectively. The histologic diagnoses in children are

“If our goal remains to improve survival and reduce long-term toxicities, we need to continue to search for biomarkers that will give us a better understanding of tumor biology and reflect the effects of therapy.”

more varied. For example, in children under age 14 years, pilocytic astrocytomas represent 17.5% of CNS tumors, embryonal tumors 15.7%, neuronal and mixed neuronal-glial tumors 6.5%, ependymal tumors 5.6%, nerve sheath tumors 4.8%, craniopharyngiomas 4.0%, and germ cell tumors 3.7% [2]. In addition to the histologic heterogeneity between patients, tumors also exhibit intratumoral heterogeneity with different areas of a given tumor displaying variable biology, genomic and histologic characteristics. Some pediatric brain tumors such as diffuse intrinsic pontine glioma (DIPG) and optic pathway glioma, which together represent a significant number of pediatric brain tumors, are never biopsied during the course of the disease. As a result, little is known about their biology, although recent efforts are attempting to address this for DIPG.

Diffuse intrinsic pontine gliomas are malignant brainstem gliomas that primarily affect children between 3 and 12 years of age. Classic presenting symptoms (cranial neuropathies, ataxia, long tract signs) and typical radiographic findings (hypo- or iso-intense lesion on T1-weighted magnetic resonance imaging, hyperintense lesion on T2-weighted imaging, involvement of more than 2/3 of the pons, tumor epicenter in pons, encasement of basilar

KEYWORDS

- biomarker • brainstem glioma
- DIPG • response • tumor measurement

*National Cancer Institute, Pediatric Oncology Branch, Building 10 CRC, Room 1-5750, Bethesda, MD 20892-1104, USA; Tel.: +1 301 435 4683; Fax: +1 301 480 2308; warrenk@mail.nih.gov

artery) preclude the need for diagnostic biology in most cases. Standard therapy involves radiation therapy, although this is not curative. Most children with DIPG die of their disease within a year of diagnosis, and many enroll on clinical trials in an effort to improve outcome.

The majority of investigational clinical trials in pediatric neuro-oncology are Phase I studies in which the customary design involves administration of a single agent alone or concurrently with radiation therapy, followed by maintenance therapy with the investigational agent alone. Treatment with the investigational agent is continued until disease progression, as long as the child is tolerating it without significant adverse effects. Tumor progression and response are assessed clinically and radiographically using MRI.

However, response assessment in neuro-oncology has been recognized as problematic [3,4]. Standard response criteria were specifically developed for clinical trials involving patients with brain tumors, in part because of the realization that contrast enhancement reflects disruption of the blood–brain barrier (BBB) and does not necessarily reflect tumor burden, and because the concurrent use of steroids may have an effect on tumor measurements [5]. More recently, with the incorporation of cytostatic agents or immunotherapeutic agents, we have come to the realization that defining efficacy using reduction of tumor size as the key criterion is inadequate. The current paradigm was developed in the era of cytotoxic therapies where a reduction in tumor size was anticipated if a therapeutic agent was efficacious. We now know that clinical benefit and drug efficacy may also be defined by long-term stable disease and improved survival, which can occur in the absence of tumor size reduction on MRI. Clinical and standard radiographic features are non-specific and cannot reliably distinguish tumor response, tumor progression, and treatment effects in the tumor environment. This is particularly pertinent in pediatric brain tumors, particularly DIPG [4].

Diffuse intrinsic pontine gliomas are invasive lesions, and delineating their boundaries accurately and reproducibly on MRI scans is not feasible [6]. Tumor burden is not associated with enhancement; many of these tumors do not significantly enhance at diagnosis, and enhancement after radiation therapy may result from radiation-associated BBB breakdown, tumor progression, or both. Using standard

MRI sequences, DIPG tumor features such as local tumor extension, cystic changes, and enhancement do not reliably predict outcome [7]. Recently, more advanced techniques, including proton spectroscopy and perfusion, have been evaluated; although they do correlate with survival [8, 9], the techniques are not standardized or universally available and post-processing after image acquisition is necessary.

Given this, there is a real need for a marker that can aid in diagnosis, assist with better understanding of tumor biology, predict and monitor response to therapeutics, and detect recurrence. A biomarker is defined by the Biomarkers Task Force of the NCI Investigational Drug Steering Committee [10, 11] as “a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention” [10]. A key word in this definition is ‘objectively’, which implies reproducibility. Biomarkers may be categorized as prognostic, predictive, pharmacodynamic, or surrogate [10]. According to definitions developed by this Biomarkers Task Force, pharmacodynamic biomarkers provide evidence of a direct pharmacological effect of an agent; prognostic biomarkers provide evidence about the patient’s disease outcome independent of a specific intervention; predictive biomarkers provide evidence about the probability of benefit or toxicity from a specific intervention; surrogate biomarkers may serve as a substitute for a clinically meaningful end point [10]. In pediatric neuro-oncology, an ideal tumor biomarker would be one that can be reliably and repeatedly obtained with little if any risk, be objectively measured with minimum inter- and intra-reader variability, and reflect tumor burden. While potential serum, urine, and cerebrospinal fluid biomarkers have been investigated for brain tumors, none are reliable or specific for pediatric brain tumors [12].

Recently, we reported on a relatively simple technique that has potential as a biomarker for children with DIPG [13]. Rather than attempting to define tumor borders or distinguish tumor-associated enhancement from treatment-associated enhancement, we measured the entire pons in 2D on fluid-attenuated inversion-recovery (FLAIR) images. Four readers with widely varying levels of expertise independently performed measurements on 384 images from children with DIPG. Inter-reader variability was low between reader pairs, with coefficients of

variation (CVs) of 3.1 and 4.8%. Increases in 2D measurements of the pons over time correlated with a poorer prognosis, specifically shorter survival. Additionally, pontine size as measured two-dimensionally at baseline was prognostic, with patients with larger measurements doing worse overall [13].

This technique is relatively noninvasive, is widely available, does not add additional burden to the patient or caregiver, and correlates with outcome. It can therefore be considered a surrogate biomarker, serving as a substitute for a clinically meaningful end point such as progression-free survival, and a prognostic biomarker, providing evidence of outcome independent of any specific intervention. It is not, however, an established pharmacodynamic or predictive biomarker.

2D measurement of the pons is not specific for any pathogenic process; whether changes correspond to a direct effect of an investigational agent or therapy remain to be determined. It also does not give us any direct information regarding the biology of the disease. Because most DIPGs are not routinely biopsied at diagnosis and tumor is not routinely obtained to assess response to therapy, correlation of imaging with histologic findings is not feasible. At autopsy, histology varies within and between subjects [14]. Most tumors are WHO Grade IV astrocytic tumors, although Grades II and III are also observed. Tumors can differ significantly in cellularity and mitoses. Some have cysts, calcifications,

or evidence of hemorrhage, and inflammation, edema, infiltration, or scar tissue may be present to various degrees. Both intra- and inter-tumoral heterogeneity limit the applicability of specific imaging findings to the biology of DIPG for the population as a whole.

Radiographic biomarkers may be suitable prognostic and surrogate biomarkers in neuro-oncology [10]. However, we must be mindful of their application, interpretation and limitations. For children with DIPG, simple 2D measurements of the pons are informative; the information obtained is a prognostic and a surrogate biomarker of progression. It cannot yet inform us, though, of tumor biology or real-time response to therapy. If our goal remains to improve survival and reduce long-term toxicities, we need to continue to search for biomarkers that will give us a better understanding of tumor biology and reflect the effects of therapy.

Financial & competing interests disclosure

This research was supported in part by the part by the Intramural Research Program of the National Institutes of Health, National Cancer Institute, Center for Cancer Research. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

- Smith M, Seibel N, Altekruse S *et al.* Outcomes for children and adolescents with cancer: challenges for the twenty-first century. *J. Clin. Oncol.* 28(15), 2625–2634 (2010).
- Ostrom Q, Gittleman H, Farah P *et al.* CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2006–2010. *Neuro-oncology* 15(Suppl. 2), ii1–ii56 (2013).
- Van Den Bent M, Vogelbaum M, Wen P *et al.* End point assessment in gliomas: novel treatments limit usefulness of classical Macdonald's criteria. *J. Clin. Oncol.* 27, 2905–2908 (2009).
- Warren K, Poussaint T, Vezina G *et al.* Challenges with defining response to antitumor agents in pediatric neuro-oncology: a report from the response assessment in pediatric neuro-oncology (RAPNO) working group. *Pediatr. Blood Cancer* 60(9), 1397–1401 (2013).
- Macdonald D, Cascino T, Schold S *et al.* Response criteria for Phase II studies of supratentorial malignant glioma. *J. Clin. Oncol.* 8, 1277–1280 (1990).
- Hayward R, Patronas N, Baker E, Vezina G, Albert P, Warren K. Inter-observer variability in the measurement of diffuse intrinsic pontine gliomas. *J. Neurooncol.* 90, 57–61 (2008).
- Hargrave D, Chuang N, Bouffet E. Conventional MRI cannot predict survival in childhood diffuse intrinsic pontine glioma. *J. Neurooncol.* 86, 313–319 (2008).
- Hipp S, Steffen-Smith E, Hammoud D, Shih J, Bent R, Warren K. Predicting outcome of children with diffuse intrinsic pontine gliomas using multiparametric imaging. *Neuro-oncology* 13(8), 904–909 (2011).
- Steffen-Smith E, Shih J, Hipp S, Bent R, Warren K. Proton magnetic resonance spectroscopy predicts survival in children with diffuse intrinsic pontine glioma. *J. Neurooncol.* 105, 365–373 (2011).
- Dancey J, Dobbin K, Groshen S *et al.* Guidelines for the development and incorporation of biomarker studies in early clinical trials of novel agents. *Clin. Cancer Res.* 16(6), 1745–1755 (2010).
- Biomarkers Definition Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. *Clin. Pharmacol. Ther.* 69, 89–95 (2001).
- Russell M, Young A, Karri S. Biomarkers of pediatric brain tumors. *Front. Pediatr.* 1, 7 (2013).
- Steffen-Smith E, Baker E, Venzon D, Shandilya S, Bent R, Warren K. Measurements of the pons as a biomarker of progression for pediatric DIPG. *J. Neurooncol.* 116, 127–133 (2014).
- Ballester L, Wang Z, Shandilya S *et al.* Morphologic characteristics and immunohistochemical profile of diffuse intrinsic pontine gliomas. *Am. J. Surg. Pathol.* 37(9), 1357–1364 (2013).