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Commentary

CDK4/6 and diffuse intrinsic pontine glioma - Evaluate at diagnosis?

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Diffuse intrinsic pontine glioma, or DIPG, is an incurable childhood brain cancer. As its name implies, DIPG arises and infiltrates throughout the pons, a part of the brainstem that controls basic functions such as breathing and sleeping, making surgical resection impossible. The diagnosis of DIPG is made by characteristic clinical symptoms together with an abnormality localized to the pons on magnetic resonance imaging or MRI. A biopsy of the lesion to confirm diagnosis or for molecular analysis has been demonstrated to be safe but is still not considered standard of care. The standard of care for DIPG is focal radiation, which provides temporary relief for most patients but is not curative. Clinical trials over the past 50 years have failed to identify a single drug that prolongs survival in this disease [1]. One major reason for the lack of progress is the limited availability of DIPG models that accurately recapitulate the genetic alterations and microenvironment of the human disease. A major advance in the field was the identification of recurrent somatic lysine-to-methionine mutations in histone 3 (H3K27M), in approximately 85% of patients [2,3]. While the mechanism by which H3K27M promotes gliomagenesis is still being investigated, current evidence suggests at least partial interference with the activity of Polycomb Repressive Complex 2, a complex that methylates H3K27 to H3K27me3, a histone mark known to correlate with gene repression [4,5]. In addition to the H3K27M mutation, 30% of DIPGs are known to harbor alterations in genes involved in cell cycle regulation such as amplification of cyclin-dependent kinase 4 (CDK4), cyclin-dependent kinase 6 (CDK6), cyclin D genes, as well as reduced levels of p16, an endogenous inhibitor of CDK4/6 [6,7]. While the development of patient-derived models from autopsy tissue and its application for *in vivo* testing have increased over the past several years, the use of patient-derived models from a diagnostic biopsy for *in vivo* testing has lagged behind. In this issue of Ebiomedicine, Qiaoran Xi and colleagues [8] report that treatment naïve H3.3K27M-mutant DIPG cell-lines are sensitive to treatment with palbociclib, a CDK4/6 inhibitor *in vitro* and *in vivo*. Remarkably, the authors evaluated eight independent human H3.3K27M-mutant DIPG lines *in vitro* and three independent human DIPG models *in vivo*, setting a higher bar for preclinical testing in DIPG.

The authors first confirmed prior observations by others noting elevated CDK4 and CDK6 transcripts and reduced p16 transcript levels in their cohort of treatment naïve H3.3K27M human DIPG lines. Of note is the large variability in sensitivity to palbociclib across the eight cell-lines despite the presence of H3.3K27M in all of them. The heterogeneity in response strongly suggests that other genetic factors influence the response to palbociclib and would be worthy of further study. For example, do genetic alterations in TP53 or PIK3CA correlate with response to palbociclib?

As CDK4/6 inhibitors have already received FDA approval for an adult indication, four clinical trials have already been initiated in the United States for children with brain tumors including children with DIPG. One of these was recently completed - a phase I study of palbociclib to treat children with recurrent brain and spinal cord tumors, including DIPG (NCT02255461). Results of this study have not been published, but with a recurrent patient population, negative results should be interpreted with caution. There are also two ongoing studies with ribociclib, another CDK4/6 inhibitor, in combination with everolimus, initiated either at recurrence or after completion of focal radiation (NCT03355794, NCT03387020). Administration of a CDK4/6 inhibitor after completion of radiation but before recurrence is better than at recurrence but as the effects of radiation on DIPG have not been carefully studied, it may still be too late. Lastly, there is an ongoing study for children with DIPG with abemaciclib, a third CDK4/6 inhibitor (NCT02644460). Based on the observations from Qiaoran Xi and colleagues, this latest study is the most promising with abemaciclib administered at diagnosis.

If all four clinical trials do not demonstrate a 'signal' for efficacy in the DIPG patients, enthusiasm for this class of drugs for DIPG will be significantly diminished. But a lack of 'signal' for efficacy would be difficult to learn from as pharmacodynamics analysis on tumor tissue is not being performed on DIPG patients. Is the lack of efficacy due to inadequate penetration of the drug across the blood-brain-barrier or due to a yet-to-be described resistance mechanism? As the blood-brain-barrier in DIPG is known to be relatively intact, this is an important concern. Regardless of the results of the ongoing studies, the search for a combination therapy with CDK4/6 inhibitors should continue as single agents are unlikely to have durable effects on a complex disease like

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DIPG. As the authors observe elevated expression of PDGFRA in their treatment naïve models, perhaps the combination of a PDGFRA inhibitor and a CDK4/6 inhibitor may be worthy of future investigation?

In summary, this study strengthens the scientific rationale that CDK4/6 is a worthy target in DIPG. In addition, the use of three independent treatment naïve models for *in vivo* testing sets a nice example for other DIPG researchers to follow. This study brings up an important point for future consideration in the design of clinical trials for DIPG. While it is natural to first evaluate novel therapies at recurrence- for a tumor like DIPG which is incurable with a median survival of 11 months- evaluating novel therapies at diagnosis, particularly when there is preclinical evidence to support it may accelerate progress against this deadly cancer.

Declaration of competing interests

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