J Neurooncol. 2023 Jun 24. doi: 10.1007/s11060-023-04372-w. Online ahead of print.

An effective kinase inhibition strategy for metastatic recurrent childhood medulloblastoma

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PMID: 37354357 DOI: 10.1007/s11060-023-04372-w

Abstract

Purpose: Medulloblastomas (MBs) constitute the most common malignant brain tumor in children and adolescents. MYC-amplified Group 3 MBs are characterized by disease recurrence, specifically in the leptomeninges, whereby patients with these metastatic tumors have a mortality rate nearing 100%. Despite limited research on such tumors, studies on MB metastases at diagnosis suggest targeting kinases to be beneficial.

Methods: To identify kinase inhibitors that eradicate cells driving therapy evasion and tumor dissemination, we utilized our established patient-derived xenograft (PDX) mouse-adapted therapy platform that models human MB metastatic recurrences following standard chemoradiotherapy. High-throughput screens of 640 kinase inhibitors were conducted against cells isolated from mouse spines in the PDX model and human fetal neural stem cells to reveal compounds that targeted these treatment-refractory, metastatic cells, whilst sparing healthy cells. Blood-brain barrier permeability assays and additional in vitro experimentation helped select top candidates for in vivo studies.

Results: Recurrent Group 3 MB PDX spine cells were therapeutically vulnerable to a selective checkpoint kinase 1 (CHK1) inhibitor and small molecular inhibitor of platelet-derived growth factor receptor beta (PDGFRβ). Inhibitor-treated cells showed a significant reduction in MB stem cell properties associated with treatment failure. Mice also demonstrated survival advantage when treated with a CHK1 inhibitor ex vivo.

Conclusion: We identified CHK1 and PDGFRβ inhibitors that effectively target MB cells fueling treatment-refractory metastases. With limited research on effective therapies for Group 3 MB metastatic recurrences, this work highlights promising therapeutic options to treat these aggressive tumors. Additional studies are warranted to investigate these inhibitors' mechanisms and recommended in vivo administration.

Keywords: High-throughput screening; Kinase inhibitors; Recurrent medulloblastoma; Spinal metastases.