Complete and sustained response of adult medulloblastoma to first-line sonic hedgehog inhibition with vismodegib.

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Abstract
Medulloblastoma is an aggressive primitive neuroectodermal tumor of the cerebellum that is rare in adults. Medulloblastomas fall into 4 prognostically significant molecular subgroups that are best defined by experimental gene expression profiles: the WNT pathway, sonic hedgehog (SHH) pathway, and subgroups 3 and 4 (non-SHH/WNT). Medulloblastoma of adults belong primarily to the SHH category. Vismodegib, an SHH-pathway inhibitor FDA-approved in 2012 for treatment of basal cell carcinoma, has been used successfully in the setting of chemorefractory medulloblastoma, but not as a first-line therapy. In this report, we describe a sustained response of an unresectable multifocal form of adult medulloblastoma to vismodegib. Molecular analysis in this case revealed mutations in TP53 and a cytogenetic abnormality, i17q, that is prevalent and most often associated with subgroup 4 rather than the SHH-activated form of medulloblastoma. Our findings indicate that vismodegib may also block alternate, non-canonical forms of downstream SHH pathway activation. These findings provide strong impetus for further investigation of vismodegib in clinical trials in the first-line setting for pediatric and adult forms of medulloblastoma.

KEYWORDS: Medulloblastoma; sonic hedgehog; targeted therapy; vismodegib


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