Vismodegib as First-Line Treatment of Mutated Sonic Hedgehog Pathway in Adult Medulloblastoma

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INTRODUCTION

Medulloblastoma (MB) is an aggressive, primitive neuroectodermal tumor mainly affecting pediatric patients and with frequent involvement of the posterior fossa and extraneural metastasis. MB has a low incidence in adults (< 1% of adult brain tumors) and treatment protocols for adult patients have been adapted from pediatric oncology.[1,2]

PTCH1[3] tumor suppressor gene functions as an inhibitor of smoothened (SMO) and downstream sonic hedgehog (SHH) signaling. SHH ligand connects to the receptor on *PTCH1*, which results in SMO suppression (Fig 1). *PTCH1* germline inactivating mutations are associated with Gorlin syndrome, which is associated with a high incidence of basal cell carcinoma (BCC) and predisposition to MB.[4-6] This association is strengthened because somatic mutations that inactivate *PTCH1* are frequently found in the sporadic forms of these types of cancers. Genomic analyses of MB have identified *PTCH1* a mutation incidence of 3%-7% of MB cases. On the basis of gene expression profiling, four molecular subgroups of MB have been identified: WNT, SHH, group 3, and group 4.[7] The prognosis for patients within the SHH subgroup MB differs greatly upon *TP53* mutation status, wherein patients with wild-type *TP53* have a significantly better 5-year overall survival rate (76%) compared with those with *TP53* mutation (41%).[8]

Although several case reports showed promising results for molecular targeted therapy in the population of adults with MB,[9] to our knowledge, this is the second reported case treated with target therapy as first-line treatment.[10] Vismodegib is an SHH pathway inhibitor that acts as an *SMO* development suppressor; it has been approved for BCC treatment[4,6] but not for adult MB.

Here, we present a new approach for the treatment of adult MB based on genomic findings. A young woman without evidence of Gorlin syndrome presented with an unresectable, multifocal, and predominantly spinal form of SHH-type MB and was treated with vismodegib as first-line therapy. She showed positive and sustained response. Although this is a notoriously aggressive neoplasm, this patient is presently alive after 15 months of treatment, presenting leptomeningeal spread of the tumor. This represents a promising treatment and suggests that resistance is slow to develop, which should also spark additional investigation.

CASE REPORT

A 24-year-old woman was admitted to the hospital because of a 6-month history of unsteadiness and worsening lower-limb paresthesia. Neurologic evaluation revealed a fully conscious and oriented patient with normal cranial nerves, lower extremity dysmetria, subxiphoid paresthesia, and grade 3/5 paraparesis. Spinal computed tomography (CT) was normal. Brain and spinal magnetic resonance imaging revealed heterogeneous, nonenhancing right cerebellar and vermis lesions with multiple spinal intramedullary lesions causing significant cord compression (Fig 2). The patient underwent urgent decompressive laminectomy with maximal safe resection.

Histopathology showed a small, round, blue cell tumor infiltrating spinal meninges that was composed of nodular, reticulin-free zones of variable sizes and surrounded by densely packed, highly proliferative cells, occasional nuclear molding, without vascular proliferation or necrotic foci. Pathologic findings indicated metastatic desmoplastic/nodular MB, WHO grade IV. Immunohistochemistry of the internodular hypercellular areas was consistent with SHH-type MB with wild-type *TP53*, as described Figure 3A-3E). In addition, next-generation sequencing–based assay[11] (Foundation Medicine, Cambridge, MA) identified nonsense mutation in *PTCH1* gene R135*. Moreover, microsatellite instability–stable, low tumor mutational burden, and variants of uncertain significance (VUS) were identified as described in Figure 3F. Positron emission tomography (PET)-CT showed postoperative spinal intramedullary hypermetabolic uptake (Fig 4A, blue arrow). Chemoradiotherapy was recommended to

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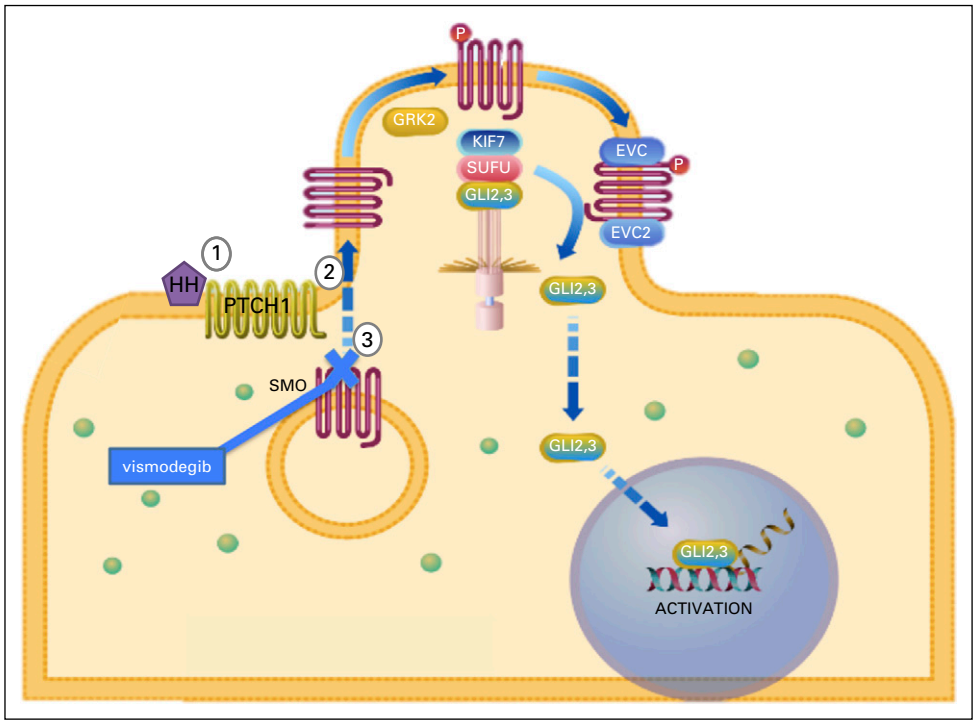


FIG 1. Graphic representation of sonic hedgehog (SHH) pathway. (1) HH ligand binding to *PTCH1*. (2) Binding of HH to *PTCH1* releases *SMO*. (3) Showing the inhibition of *SMO* by vismodegib, which leads to inhibition of the whole pathway.

the patient as standard treatment. However, because of the patient's aversion to chemotherapeutic agents, she was treated only with radiotherapy. Treatment protocol consisted of 36 Gy in 20 fractions to the entire craniospinal axis, followed by a boost of 18 Gy in nine fractions to the posterior fossa and 8 Gy in four fractions to the spinal drop metastases. PET-CT scan after radiation therapy showed extraneural bilateral proximal humorous (Fig 4B, blue

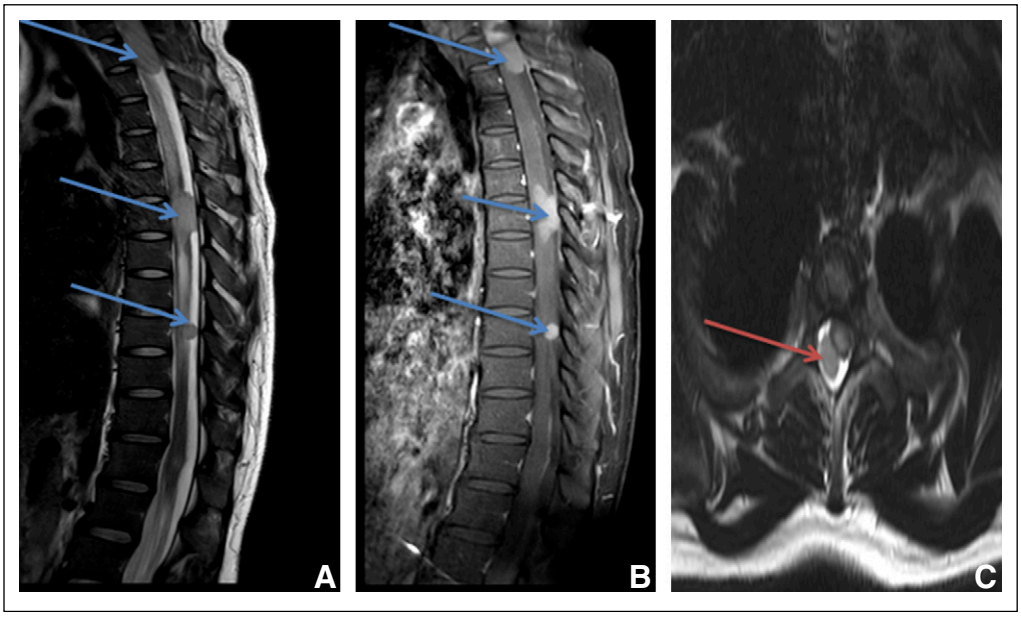
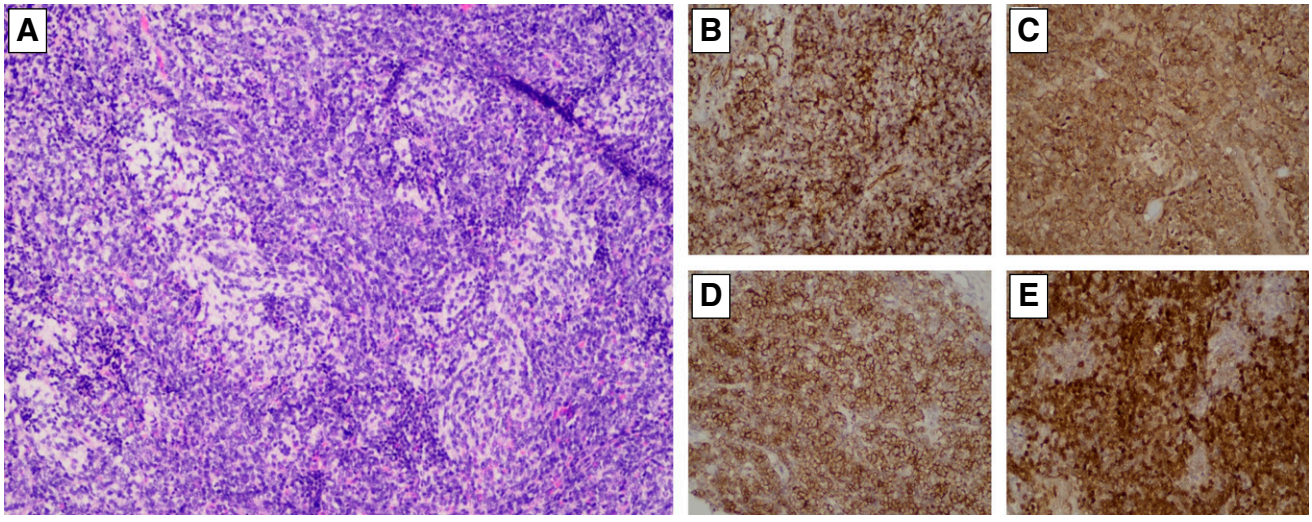


FIG 2. Spinal magnetic resonance images. (A) Preoperative magnetic resonance imaging (MRI) scan: sagittal T2. (B) Sagittal T1 with gadolinium MRI. (C) Cross-section MRI. Blue arrows point to multiple spinal intramedullary, homogenously enhancing lesions. Orange arrow points to substantial spinal cord compression.



F

Variants of Unknown Significance					
TERT promoter-92C>A	**BCL6** R122Q	**FANCD2** K770R	**FAT1** R881C	**IRS2** D1068N	**AURKB** R328Q
MED12 Q2119_Q2120insHQQQ	**PRKDC** T1924I	**SOX9** P307R	**SPTA1** L1565Q	**LRP1B** T4298S	**TNFAIP3** R697K

FIG 3. (A) Histopathologic examination of the tumor shows a biphasic, small, round, blue cell tumor with hypocellular nodules with a hypercellular internodular area. The pattern was confirmed with a reticulin stain. (hematoxylin and eosin; original magnification, ×10). (B-E) On immunostaining, the tumor cells showed strong cytoplasmic immunoreactivity, but, more importantly, negative nuclear staining with (B) β-catenin, (C) cytoplasmic staining with filamin A and (D) *GAB1*, and (E) cytoplasmic and nuclear staining with YAP-1. This particular combination of immunostaining patterns is consistent with SHH-type medulloblastoma, and additional immunostains with *TP53* showed a wild-type immunoreactivity pattern. (F) Variants of unknown significance analyzed by next-generation sequencing.

arrow) and a new, small, lung opacification (Fig 4B, green arrow), most probably due to radiation pneumonitis. On the basis of the patient mutational profile, vismodegib was initiated as compassionate treatment at 150 mg orally daily after local institutional review board approval. Six months later, there was no clinical or radiologic evidence of MB lesions, including complete response of extraneural lesions (Fig 4C). Currently, 15 months since starting treatment, the patient shows significant clinical symptoms improvement and is under rehabilitation treatment.

DISCUSSION

We describe here a case of adult MB with mutation in the *PTCH1* gene that achieved a remarkable and prolonged clinical and radiologic response to the SHH pathway inhibitor vismodegib as first-line therapy following craniospinal irradiation. Although vismodegib is not approved by the US Food and Drug Administration for this indication, the treatment was given as compassionate therapy after the molecular findings.

The identification of molecular drivers involved in MB tumorigenesis, including WNT, SHH, and groups 3 and 4, has enabled the identification of additional prognostic markers to the established histopathologic typing.[12] MB with SHH subtype is associated with desmoplastic histology in the vast majority of reported cases, including pediatric and most adult patients, and has been associated with better prognostic outcomes.[13] Moreover, loss of heterozygosity (LOH) of *PTCH1* has been associated with prolonged progression-free survival in a setting of second-line therapy with vismodegib, whereas in the same setting, mutations in the SHH pathway downstream to *SMO* did not respond to the treatment.[14] The patient presented in this case has a nonsense mutation in position R135* of *PTCH1* and mutation allele frequency of 97%, which could be an indication of LOH. Moreover, the patient has a mutation in the promoter of *TERT*, which has significant co-occurrence with small nuclear RNA mutations and subsequently could be indicative of *PTCH1* inactivation; Figure 3F presents details about VUS mutations.[15] The promising findings in this case demonstrate that vismodegib may be considered a first-line treatment in adult patients with MB with SHH-type MB with mutations upstream to *SMO* in the SHH pathway.

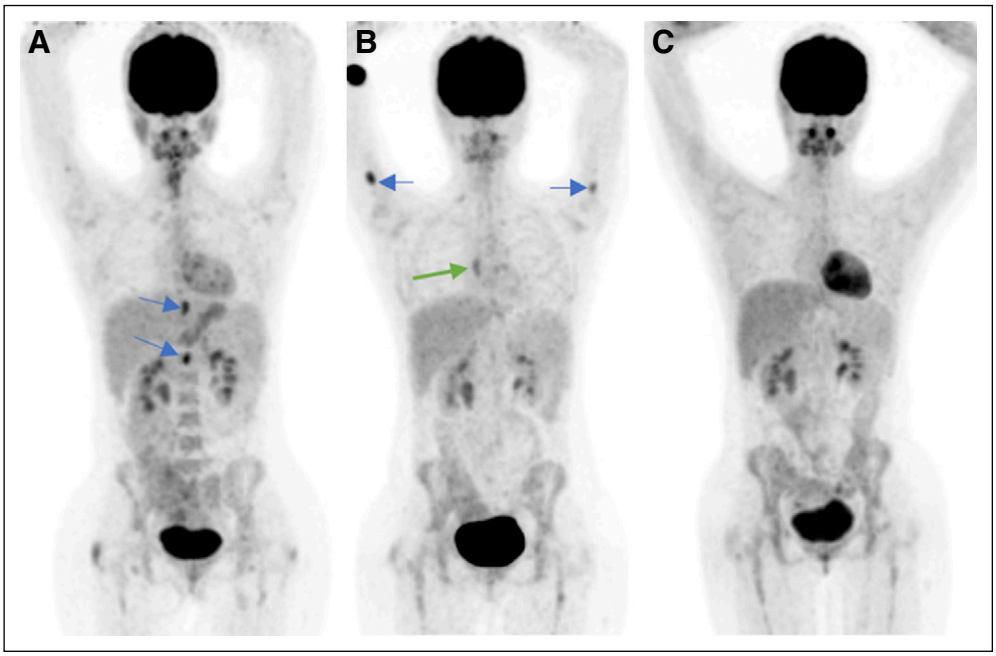


Fig 4. Whole-body imaging ^{18}F-fluorodeoxyglucose positron-emission tomography–computed tomography showing (A) examination postsurgical intervention, (B) postradiation therapy (blue arrows point to extraneural metastasis; green arrow points to postradiation pneumonitis. (C) Six months after vismodegib treatment, imaging shows no evidence of metastatic disease.

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REFERENCES

1. Kumar LP, Deepa SFAJ, Moinca I, et al: Medulloblastoma: A common pediatric tumor: Prognostic factors and predictors of outcome. Asian J Neurosurg 10:50, 2015
2. Parkes J, Hendricks M, Ssenyonga P, et al: SIOP PODC adapted treatment recommendations for standard-risk medulloblastoma in low and middle income settings. Pediatr Blood Cancer 62:553-564, 2015
3. Forbes SA, Beare D, Boutselakis H, et al: COSMIC: Somatic cancer genetics at high-resolution. Nucleic Acids Res 45:D777-D783, 2017
4. Fellner C: Vismodegib (Erivedge) for advanced basal cell carcinoma. Pharm Ther 37:670-682, 2012
5. Lo Muzio L, Pastorino L, Levanat S, et al: Clinical utility gene card for: Gorlin syndrome. Eur J Hum Genet 19:3, 2011
6. Fecher LA, Sharfman WH: Advanced basal cell carcinoma, the hedgehog pathway, and treatment options - role of smoothened inhibitors. Biologics 9:129-140, 2015
7. Northcott PA, Dubuc AM, Pfister S, et al: Molecular subgroups of medulloblastoma. Expert Rev Neurother 12:871-884, 2012
8. Zhukova N, Ramaswamy V, Remke M, et al: Subgroup-specific prognostic implications of TP53 mutation in medulloblastoma. J Clin Oncol 31:2927-2935, 2013
9. Petrirena GJ, Masliah-Planchon J, Sala Q, et al: Recurrent extraneural sonic hedgehog medulloblastoma exhibiting sustained response to vismodegib and temozolomide monotherapies and inter-metastatic molecular heterogeneity at progression. Oncotarget 9:10175-10183, 2018
10. Lou E, Schomaker M, Wilson JD, et al: Complete and sustained response of adult medulloblastoma to first-line sonic hedgehog inhibition with vismodegib. Cancer Biol Ther 17:1010-1016, 2016
11. Alekseyev YO, Fazeli R, Yang S, et al: A next-generation sequencing primer-how does it work and what can it do? Acad Pathol 5:2374289518766521, 2018
12. Louis DN, Ohgaki H, Wiestler OD, et al: The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol 114:97-109, 2007
13. Hadi I, Roengvoraphoj O, Niyazi M, et al: Medulloblastoma in adults. Strahlenther Onkol 194:225-234, 2018
14. Robinson GW, Orr BA, Wu G, et al: Vismodegib exerts targeted efficacy against recurrent sonic hedgehog - Subgroup medulloblastoma: Results from phase II Pediatric Brain Tumor Consortium studies PBTC-025B and PBTC-032. J Clin Oncol 33:2646-2654, 2015
15. Suzuki H, Kumar SA, Shuai S, et al: Recurrent noncoding U1 snRNA mutations drive cryptic splicing in SHH medulloblastoma. Nature 574:707-711, 2019