Prolonged response to vismodegib in a patient with systemic medulloblastoma metastases

Seth A Climans ,[1] David R Macdonald,[2] Duncan EK Sutherland,[3] Warren P Mason[1]

[1]Department of Medicine, Princess Margaret Cancer Centre, Toronto, Ontario, Canada
[2]Department of Medical Oncology, London Regional Cancer Program, London, Ontario, Canada
[3]Department of Medical Imaging, London Health Sciences Centre, London, Ontario, Canada

Correspondence to
Dr Seth A Climans;
seth.climans@gmail.com

Accepted 20 September 2020

SUMMARY

Some patients with metastatic medulloblastoma can be successfully treated with targeted therapy. We report the case of a 42-year-old woman who was diagnosed with sonic hedgehog (SHH)-subgroup medulloblastoma. She was treated with surgery, radiation and chemotherapy. She then developed bone pain. A positron emission tomography (PET) scan confirmed widespread bone metastases from her medulloblastoma. She was started on vismodegib, an oral smoothened inhibitor that targets her tumour type. Her bone pain resolved. A repeat PET scan showed resolution of almost all metastases. Fourteen months after starting vismodegib, her disease recurred and she was transitioned to temozolomide chemotherapy. We document an important case of prolonged response to vismodegib in a patient with systemic SHH-subgroup medulloblastoma metastases.

BACKGROUND

Medulloblastomas are malignant embryonal tumours of the cerebellum. They are more common in children than adults. Since 2016, they have been classified into both histological and genetic subgroups. The main genetic markers are sonic hedgehog (SHH), p53 and WNT. The three genetically defined subgroups are SHH-activated and TP53-mutant, SHH-activated and TP53-wildtype, and non-WNT/non-SHH.[1]

Initial treatment of medulloblastoma includes surgery followed by radiation therapy and, depending on certain clinical factors, chemotherapy. Patients who develop disease recurrence after initial therapy have a 2-year survival of approximately 9%.[2] By comparison, the 2-year survival of all adult Americans with medulloblastoma is 80%.[3] Thus, new therapies for recurrent medulloblastoma are urgently needed.

Unlike most brain tumours, medulloblastomas can metastasise outside of the central nervous system. When they do, they tend to invade bones and lymph nodes.[1]

Constitutive activation of hedgehog signalling is a hallmark of SHH-activated medulloblastomas. Oral small molecule inhibitors of smoothened can target the hedgehog pathway. Vismodegib is one such molecule. In Canada, it is approved for the treatment of metastatic or locally advanced basal cell carcinoma. Vismodegib can also lead to regression of medulloblastoma tumours.[2] Common side effects of vismodegib include nausea, vomiting, diarrhoea, muscle cramps, fatigue, alopecia and dysgeusia.[4]

CASE PRESENTATION

A 42-year-old woman presented to her family physician in January 2017 with headache and gait instability. She was previously healthy. She did not have any relevant family history.

Brain imaging revealed a cerebellar mass. Staging CT body scan and MRI of the spine showed no systemic or spinal metastases. She had surgery and was diagnosed with SHH subgroup, p53-negative medulloblastoma with desmoplastic/nodular features. She was treated with surgery, then craniospinal radiotherapy (February–April 2017) and vincristine. Her clinical course was complicated by pulmonary toxicity, pulmonary emboli, possible pneumocystosis and myelosuppression. She did not receive planned adjuvant chemotherapy due to slow recovery of myelosuppression. She was diagnosed with a basal cell carcinoma on her right shoulder October 2018, which was surgically resected.

INVESTIGATIONS

In October 2018, she developed bone pain. She was found to have bone metastases. She never had a bone biopsy, but based on the clinical situation, they were presumed to be from her medulloblastoma. She had focal radiotherapy to her right hip and left humerus (January 2019). Baseline MRI of the head and spine in February 2019 showed no intracranial tumour recurrence, but there were extensive enhancing bone metastases with no intradural drop metastases. She had a baseline ^{18}F-fluorodeoxyglucose (FDG) whole body positron emission tomography (PET) scan March 2019 (figure 1A–C).

TREATMENT

Vismodegib, an oral competitive antagonist of the smoothened receptor, was started in April 2019 at the standard dose of 150 mg orally daily.

OUTCOME AND FOLLOW-UP

She had almost immediate resolution of her bone pain. A follow-up PET scan 7.9 months after starting the drug showed resolution of the remainder of the FDG-avid axial and proximal appendicular skeletal lesions, though a humerus and a femur lesion were still visible (figure 1D–F). Follow-up MRI of the head and spine in January 2020 showed no intracranial recurrence and a significant improvement of her spine bone metastases. The vismodegib caused dysgeusia, muscle cramps and alopecia. In May 2020 a staging MRI of the spine showed growth of her presumed medulloblastoma bony metastases. Her bone pain recurred. The vismodegib was stopped in June 2020. A July 2020 bone

To cite: Climans SA, Macdonald DR, Sutherland DEK, *et al*. *BMJ Case Rep* 2020;**13**:e236406. doi:10.1136/bcr-2020-236406

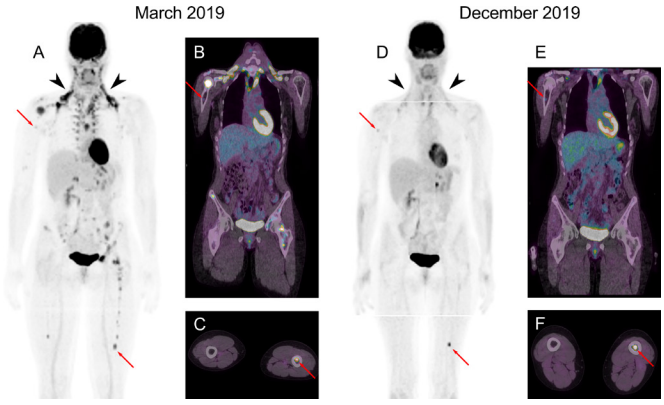

Figure 1 Tumour response to vismodegib on ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT imaging: (A) maximum intensity projection (MIP) pretreatment imaging (March 2019) shows metabolically active osseous, marrow-based axial and appendicular skeletal lesions. Correlative hybrid PET/CT images (B and C) show multiple foci of activity in the right humerus, bilateral hemipelvis and left femur. (D) MIP follow-up imaging (December 2019) after 7.9 months of vismodegib therapy. A complete metabolic response is seen in almost all lesions with associated sclerotic osseous healing. These findings are concordant with the resolution of bone pain. Correlative hybrid PET/CT images (E and F) show persistent FDG uptake in the right humerus and left femur (red arrows) consistent with residual disease. Metabolic activity in the supraclavicular, paraspinal and suprarenal regions is consistent with brown-fat activation and is a variant of normal (black arrowheads).

scan confirmed progression of her multiple bone metastases. She started temozolomide chemotherapy. She received focal radiotherapy to painful bone metastases. In total she had a 14-month duration of response to vismodegib monotherapy.

DISCUSSION

Smoothened inhibitors, including vismodegib, can be used in SHH-subgroup medulloblastoma, and vismodegib has shown efficacy in recurrent disease.[4] To our knowledge there have been four documented cases of systemic medulloblastoma metastases treated with vismodegib. The first was a 26-year-old man who had 3 months of response to vismodegib and died 5 months after starting the drug.[2] The second was a 38-year-old man who had 6 months of response to vismodegib and died 10 months after starting the drug (personal communication with Katrine Riklund).[5] The third was a 16-year-old man who had 8 months of response to vismodegib and died 27 months after starting the drug.[6] The fourth was a 24-year-old woman with metastases at the time of diagnoses who had at least 15 months of response to first-line vismodegib.[7]

We document an important case of prolonged response to vismodegib in a patient with systemic SHH-subgroup medulloblastoma metastases. She had one of the longest responses to vismodegib of any reported patient with medulloblastoma metastases.

Learning points

- Sonic hedgehog subgroup medulloblastomas are sensitive to inhibition with smoothened inhibitors.
- Vismodegib is an oral targeted therapy that can treat metastatic sonic hedgehog subgroup medulloblastoma.
- In select patients, vismodegib can probably improve quality of life and prolong survival.

Acknowledgements We would like to thank Katrine Riklund who gave permission for us to cite our personal communication.

Contributors SAC consulted with the research patient, collected and analysed data, drafted and edited the text, and approved the final version of the manuscript. DRM consulted with the research patient, edited the text and approved the final version of the manuscript. DS assisted with scintigraphic investigations, revised the manuscript for intellectual content and approved the final version of the manuscript. WPM consulted with the research patient, edited the text and approved the final version of the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD
Seth A Climans http://orcid.org/0000-0002-4961-237X

REFERENCES

1 Louis DN, Perry A, Reifenberger G, *et al*. The 2016 World Health organization classification of tumors of the central nervous system: a summary. *Acta Neuropathol* 2016;131:803–20.
2 Rudin CM, Hann CL, Laterra J, *et al*. Treatment of medulloblastoma with hedgehog pathway inhibitor GDC-0449. *N Engl J Med* 2009;361:1173–8.
3 Ostrom QT, Gittleman H, Truitt G, *et al*. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2011-2015. *Neuro Oncol* 2018;20:iv1–86.
4 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* 2015;33:2646–54.
5 Asklund T, Henriksson R, Axelsson J, *et al*. Early and persisting response to vismodegib in a patient with bone metastasizing medulloblastoma. *Acta Oncol* 2013;52:862–5.
6 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* 2018;9:10175–83.
7 Kian W, Roisman LC, Goldstein IM, *et al*. Vismodegib as first-line treatment of mutated sonic hedgehog pathway in adult medulloblsatoma. *JCO Precis Oncol* 2020;4:437–41.