Received Date : 15-Dec-2015

Accepted Date : 12-Feb-2016

Article type : Case Report

TITLE:

Prolonged disease control with MEK inhibitor in neurofibromatosis type I associated glioblastoma

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CONFLICTS OF INTEREST

No conflicts of interest have been declared.

AUTHOR CONTRIBUTIONS

M. Ameratunga – Manuscript writing, study concept or design, analysis of data

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/JCPT.12378](https://doi.org/10.1111/JCPT.12378)

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SUMMARY:

What is known and objective

Neurofibromatosis is associated with overactivation of the *RAS-MAPK* pathway. MEK inhibitors have been shown to be an effective treatment modality in other malignancies.

Case summary

We present a 24 year old male with treatment-refractory neurofibromatosis associated glioblastoma, who experienced clinical and radiological benefit from the MEK inhibitor, trametinib.

What is new and conclusion

This case highlights the therapeutic success of a MEK inhibitor in neurofibromatosis-associated glioblastoma. As a corollary, this should prompt evaluation of MEK inhibitors in tumors associated with neurofibromatosis. It remains to be elucidated if tumors with somatic *NF1* mutations may also benefit from therapy targeting the *RAS-MAPK* pathway.

WHAT IS KNOWN AND OBJECTIVE:

Neurofibromatosis type 1 (NF1), is a common inherited autosomal dominant genetic disorder, and is associated with a wide range of tumours(1). Biallelic mutations have been found in NF1-associated tumours, leading to the classification of NF1 as a tumour-suppressor gene.(2) The protein encoded by the *NF1* gene, neurofibromin, is involved with the downregulation of RAS-MAPK pathway. Loss of *NF1* therefore leads to activation of the RAS signalling pathway and has been associated with the development of multiple tumours.(2)

In a clinical phase I study of selumetinib in NF1-associated inoperable plexiform neurofibromas, promising activity has been observed.(3) To our knowledge, there is no therapeutic data demonstrating activity of molecules targeting the RAS-MAPK pathway in NF1-associated glioblastoma (GBM). We report a case of a patient with NF1-associated GBM who received substantial clinical benefit from the MEK inhibitor trametinib.

CASE REPORT:

A 24 year-old male with a history of NF1-associated optic glioma (age 4), presented with headaches, drowsiness and ataxia and was found to have hydrocephalus secondary to a left cerebellar tumor. An external ventricular drain was inserted and craniotomy and debulking was performed. The initial histology was GBM. On immunohistochemistry, the tumor was negative for the IDH-1 mutation. The patient recovered uneventfully and was treated with chemoradiotherapy utilising temozolomide (TMZ). During adjuvant treatment, the patient developed pseudo-progression,(4) but subsequently had radiological improvement over the course of six cycles of TMZ and was weaned off corticosteroids. The patient was stable clinically and radiologically for two years.

After two years, the patient developed headaches and vomiting and recurred with a large cerebellar cystic lesion extending to the fourth ventricle and cerebellar-pontine angle. Maximal surgical debulking was performed. Histology was recurrent GBM. The post-operative course was complicated by hydrocephalus requiring a ventriculo-peritoneal shunt. The patient was treated with carboplatin, but had rapid and significant clinical and radiological progression after two months, developing brainstem extension. Further debulking was performed with removal of the superficial cerebellar cystic lesion and insertion of an Ommaya reservoir. Histology was unchanged.

Genomic profiling was performed on the recurrent tumour post temozolomide treatment, (FoundationOne©), revealing the following abnormalities: *KDR* amplification, *KIT* amplification, *NF1* splice site 3870+1G>T (predicted to generate a truncated protein), *PDGFRA* amplification, *CDKN2A/B* loss and *ATRX* splice site 4809+1G>A. Due to implication of the mammalian target of rapamycin (mTOR) pathway in *NF1*,⁽²⁾ an mTOR inhibitor, everolimus, was trialled. There was no significant radiological improvement after two months, and given the tolerability of everolimus, TMZ was added (due to clinical benefit previously with TMZ). Two months later, there was clinical and radiological progression. A MEK inhibitor (trametinib) was obtained on a compassionate access scheme, due to possible overactivity of the MEK pathway in *NF1*. Within three weeks of treatment, there was a definite reduction in the degree of enhancement and mass effect. Treatment was well tolerated apart from an acneiform rash, which was managed with oral doxycycline. Further improvement on an MRI performed at 2 months of treatment (Figure 1), was observed and corticosteroids were weaned completely. Given the treatment-refractory disease, the ongoing clinical benefit at four months compares favourably to other standard treatment options.⁽⁴⁾

Standard treatment for GBM consists of maximal surgical debulking, followed by chemoradiotherapy and adjuvant temozolomide.⁽⁴⁾ There is no standard therapy at recurrence, with anti-angiogenic therapies and chemotherapy often considered, and prognosis is poor.⁽⁴⁾ Germline *NF1* mutated GBM is rare,⁽¹⁾ and little is understood regarding its natural history and whether this differs from sporadic GBM. There is,

however, evidence that germline NF1 mutations confer resistance to chemotherapy and radiotherapy in other tumor types,(2) consistent with the aggressive clinical behaviour of the patient's malignancy. Additionally, somatic mutations in NF1 are common, potentially occurring in up to one third of GBMs, and have also been implicated in other malignancies, where mutations are associated with sensitivity to MEK-inhibition(5). There is limited data regarding targeting this pathway in somatic disease, although NF1 may represent a resistance mechanism for many molecularly-driven cancers including those driven by activation of the MEK pathway.(2, 6) Moreover, even in preclinical models, despite strong evidence for activity of MEK inhibition, resistance invariably emerges.(2) In non B-RAF associated malignancies, there is data to suggest that trametinib may be more effective than other MEK inhibitors due to prevention of resistance via upregulated C-RAF.(7)

WHAT IS NEW AND CONCLUSION:

There is a good preclinical rationale for the use of MEK inhibitors in NF1 associated tumors. The case described, is to our knowledge, the first to describe the clinical benefit of a MEK inhibitor in neurofibromatosis associated glioblastoma. These findings warrant further investigation into MEK inhibitors for germline NF1 associated malignancies. It remains to be elucidated whether MEK inhibitors have a therapeutic role in somatic NF1 associated tumours.

REFERENCES

1. Brems H, Beert E, de Ravel T, Legius E. Mechanisms in the pathogenesis of malignant tumours in neurofibromatosis type 1. *The lancet oncology*. 2009;10(5):508-15.
2. Ratner N, Miller SJ. A RASopathy gene commonly mutated in cancer: the neurofibromatosis type 1 tumour suppressor. *Nature Reviews Cancer*. 2015.
3. Widemann BC, Marcus LJ, Fisher MJ, Weiss BD, Kim A, Dombi E, et al., editors. Phase I study of the MEK1/2 inhibitor selumetinib (AZD6244) hydrogen sulfate in children and young adults with neurofibromatosis type 1 (NF1) and inoperable plexiform neurofibromas (PNs). *ASCO Annual Meeting Proceedings*; 2014.
4. Khasraw M, Ameratunga M, Grommes C. Bevacizumab for the treatment of high-grade glioma: an update after Phase III trials. *Expert opinion on biological therapy*. 2014;14(5):729-40.

5. Nissan MH, Pratilas CA, Jones AM, Ramirez R, Won H, Liu C, et al. Loss of NF1 in cutaneous melanoma is associated with RAS activation and MEK dependence. *Cancer research*. 2014;74(8):2340-50.
6. Whittaker SR, Theurillat J-P, Van Allen E, Wagle N, Hsiao J, Cowley GS, et al. A genome-scale RNA interference screen implicates NF1 loss in resistance to RAF inhibition. *Cancer discovery*. 2013;3(3):350-62.
7. Lito P, Saborowski A, Yue J, Solomon M, Joseph E, Gadgil S, et al. Disruption of CRAF-mediated MEK activation is required for effective MEK inhibition in KRAS mutant tumors. *Cancer Cell*. 2014;25(5):697-710.

FIGURE LEGEND**Figure 1:** MRI pre and post treatment

- A** T1 weighted post-contrast MRI pre-treatment
B T1 weighted post-contrast MRI post-treatment
C FLAIR MRI pre-treatment
D FLAIR MRI post-treatment

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Title:

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Date:

2016-06-01

Citation:

Ameratunga, M., McArthur, G., Gan, H. & Cher, L. (2016). Prolonged disease control with MEK inhibitor in neurofibromatosis type I-associated glioblastoma. JOURNAL OF CLINICAL PHARMACY AND THERAPEUTICS, 41 (3), pp.357-359. <https://doi.org/10.1111/jcpt.12378>.

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