Case series

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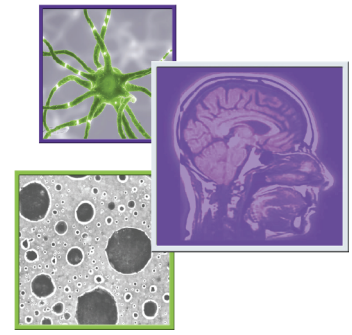

Dabrafenib and trametinib in *BRAFV600E* mutated glioma

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BRAFV600E mutations have been identified in a number of glioma subtypes, most frequently in pleomorphic xanthoastrocytoma, ganglioglioma, pilocytic astrocytoma, and epithelioid glioblastoma. Although the development of BRAF inhibitors has dramatically improved the clinical outcome for patients with *BRAFV600E* mutant tumors, resistance develops in a majority of patients due to reactivation of the MAPK pathway. Addition of MEK inhibition to BRAF inhibition improves survival. Here we report successful treatment of two patients with *BRAFV600E* mutant pleomorphic xanthoastrocytoma using the BRAF inhibitor dabrafenib in combination with the MEK inhibitor trametinib.

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Case one

The first report is of a 48-year-old female with progressive anaplastic pleomorphic xanthoastrocytoma (PXA). She initially presented with a seizure and underwent a craniotomy and resection followed by adjuvant radiotherapy. She remained in remission for 3 years. Subsequent relapses over 2 years were treated with three further debulking surgeries, cyst drainage and chemotherapy. Of note, she developed tumor infiltration in her skin with subsequent postoperative wound dehiscence. There was no clinical evidence of extra-cranial spread. Chemotherapy regimens included six cycles of procarbazine, CCNU (lomustine), vincristine; six cycles of temozolomide and three cycles of carboplatin. MRI after three cycles of carboplatin showed tumor progression of both solid and cystic disease with midline shift, at which point she was referred to our center for ongoing management, 5 years after initial diagnosis.

Analysis of archival tumor tissue from an earlier surgery identified a *BRAFV600E* mutation using DNA sequencing. She underwent a further craniotomy and debulking surgery, which once again resulted in postoperative wound dehiscence. Histopathology showed glial tumor cells with significant nuclear pleomorphism and abundant eosinophilic glassy cytoplasm, multiple giant cells, brisk mitotic activity and necrosis. Immunohistochemistry for *BRAFV600E* was strongly positive, while *IDH1R132H* was negative, and *ATRX* was retained. The Ki67 proliferation index was 15%. Other molecular markers including *CDKN2A* and histone status were not available.

At review, 4 weeks following surgery her symptoms included fatigue and headaches, and her WHO performance status was 2. She commenced treatment with the BRAF inhibitor dabrafenib (150 mg twice daily) in combination with the MEK inhibitor trametinib (2 mg once daily). Following commencement, she developed mild nausea (CTCAE Grade 1), controllable with oral antiemetics and a pruritic rash on her back and shoulders (CTCAE Grade 1) for which she received topical emollients and oral antihistamines. One month later she presented with fever, wound breakdown and infection. She was admitted to hospital for intravenous antibiotics and further surgery to create a skin flap. Aside from the 72-h perioperative period, dabrafenib and trametinib were continued throughout.

MRI of the brain at this time showed a decrease in the bulk of partially enhancing cystic/necrotic mass with reduction of mass effect. Subsequent interval MRI, 4 months following commencement of dabrafenib and trametinib shows continued reduction in the size of both solid and cystic disease, with further resolution of the

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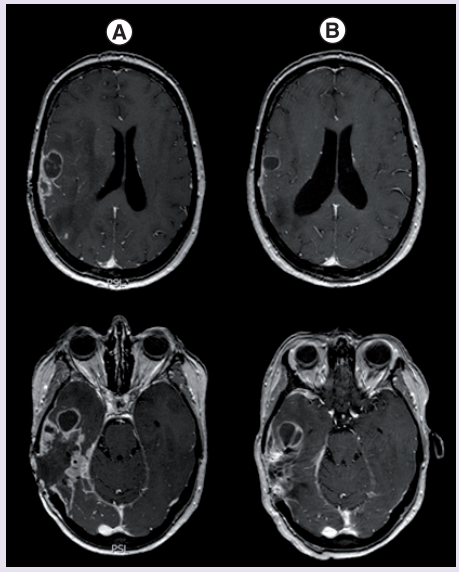

Figure 1. Interval MRI. Above: T1 sequences with Gadolinium, below: T2 sequences at baseline **(A)** and 4 months after commencement of dabrafenib and trametinib **(B)** demonstrating reduction in solid disease, cystic disease and mass effect.

mass effect (partial response by RANO criteria; Figure 1). At last review, 8 months following commencement of treatment, she was well, with a noted improvement in fatigue and resolution of headaches. She continues on dabrafenib and trametinib.

Case two

We have previously reported in this journal, the successful treatment of this 21-year-old female patient with relapsed *BRAFV600E* mutated anaplastic pleomorphic xanthoastrocytoma with dabrafenib, following intolerance to vemurafenib [1]. The patient continued on single-agent dabrafenib for 18 months, at which point she elected to stop therapy and commence radiological surveillance. She had no visible disease on MRI at this time. She subsequently had radiological progression and we now report subsequent treatment and response to combination therapy with dabrafenib and trametinib.

Two months after stopping single-agent dabrafenib, the first surveillance MRI demonstrated a new 8 mm homogeneously enhancing nodular lesion on the posteromedial aspect of the surgical cavity (Figure 2). This was confirmed by subsequent imaging 2 months later with an increase in the size of the recurrence to 20 mm and associated edema (Figure 2). The patient remained clinically stable. Further histology was not obtained at this time and data regarding MEK activation is unknown. The patient was re-commenced on dabrafenib (150 mg twice daily) with the addition of the MEK inhibitor trametinib (2 mg once daily). Serial MRIs demonstrated unequivocal improvement with near complete response of the enhancing nodule on the most recent MRI, 3 months after commencing therapy (partial response by RANO criteria; Figure 2). The patient remains on treatment. At last follow-up, 4 months after starting treatment, she was well with mild treatment related fatigue (CTCAE Grade 1), plantar hyperkeratosis (Grade 1) and an acneiform rash (Grade 1).

Discussion

BRAF mutations have been identified as key drivers of oncogenesis in a number of cancers, most notably melanoma [2]. Over 95% of *BRAF* mutations are missense mutations with substitution of valine to glutamate at amino acid position 600 (*BRAFV600E*) that initiates constitutive activation of the MAPK/ERK signaling pathway [3]. *BRAFV600E* mutations have been identified in a number of glioma subtypes. In the most comprehensive analysis of *BRAF* mutations in glioma to date, direct sequencing of 1320 primary pediatric and adult brain tumors identified 93 with *BRAFV600E* mutations. Mutations were most frequently found in pleomorphic xanthoastrocytoma (42/64, 66%) and pleomorphic xanthoastrocytoma with anaplasia (15/23, 65%); with mutations frequently identified in gangliogliomas (14/77, 18%), anaplastic gangliogliomas (3/6, 50%) and pilocytic astrocytomas (9/97,

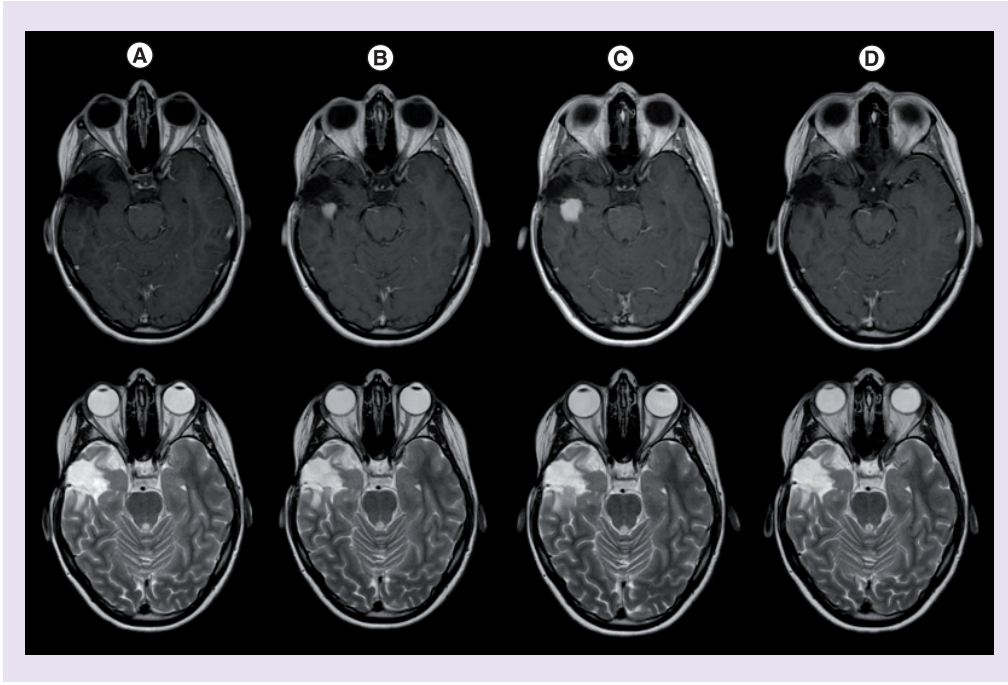

Figure 2. Serial MRI. Above: T1 sequences with Gadolinium, below: T2 sequences. **(A)** Complete radiological response following 18 months of dabrafenib therapy. **(B)** New enhancing nodule after 2 months of stopping dabrafenib. **(C)** Progressing nodule after 2 months. **(D)** Radiological response after 3 months of therapy with dabrafenib and trametinib.

9%) [3]. Epithelioid glioblastoma is a provisional new variant in the 2016 WHO Classification of Tumors of the CNS, of IDH-wildtype glioblastoma that also often harbors a *BRAF* mutation [4].

PXA is an uncommon glioma, with an incidence of fewer than 0.07 cases per 100,000. Children and young adults are most frequently affected, with a median age of diagnosis of 20.5–30.5 years and no significant gender difference [5]. Almost all are supratentorial (97–99%), most frequently in the temporal lobe. Seizures are the most common presenting symptoms, occurring in 64–75% of patients. On MRI, PXA typically appears as a cystic mass with a prominent solid component that is isodense to gray matter on T1, mildly hyperintense on T2, enhances with gadolinium and with variable surrounding edema [6]. Histologically distinct features include pleomorphic giant cells with xanthomatous change, eosinophilic granular bodies and dense deposits [7]. Anaplastic features are found in 20–30% of cases and include a high mitotic index (≥3;5 per 10 high-power fields) with or without necrosis [8]. Anaplasia confers a poorer progression-free and overall survival, and has recently been recognized as a distinct clinical entity, now termed 'Anaplastic PXA' and classified as a Grade III tumor in the 2016 WHO Classification, having previously been categorized as the Grade II 'PXA with anaplasia' [4,9]. Typical treatment is gross total resection if feasible, followed by radiotherapy and cytotoxic chemotherapy at recurrence. Overall survival at 5 years is 76–80% in all patients with PXA, and 57% in those with anaplasia [5].

The development of BRAF inhibitors has dramatically improved the clinical outcomes for patients with *BRAF* mutated tumors. The most robust data of efficacy are from large clinical trials of patients with metastatic melanoma. A pivotal Phase III trial demonstrated superiority of the BRAF inhibitor vemurafenib over dacarbazine in patients with *BRAFV600E* mutated advanced melanoma with significantly superior response rates (48 vs 5%), progression-free survival (5.3 vs 1.6 months) and 6-month survival (84 vs 6%) [10]. The most frequent treatment related adverse events were arthralgia, rash, fatigue, squamous cell carcinoma of the skin and keratoacanthoma. The BRAF inhibitor dabrafenib showed similar superiority over dacarbazine in a subsequent Phase III trial. When comparing the two trials, dabrafenib appears to be better tolerated than vemurafenib with fewer skin toxicities [11]. However, a retrospective cohort review evaluating cutaneous toxicity in 285 patients with advanced melanoma treated with BRAF inhibitors found no significant difference between the frequency of cutaneous toxic effects with vemurafenib or dabrafenib [12]. Encouraging initial evidence of BRAF inhibitor efficacy within the CNS came

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from the treatment of melanoma patients with brain metastases [13]. There is growing evidence to support BRAF inhibitor use in *BRAFV600E* mutated primary brain tumors, although patient numbers are small. A 'basket' study of vemurafenib in nonmelanoma cancers with *BRAFV600E* mutations included four patients with PXA and six patients with other gliomas. A partial response was observed in three out of four patients with PXA and in one out of six patients with glioma (although three out of six had tumor reduction) [14]. A case series of four patients with PXA (one with anaplasia) treated with salvage vemurafenib following surgery, radiation and chemotherapy reported a partial response in one patient, with median overall survival of 8 months (range 4–14) and progression-free survival of 5 months (range 2–10) [15]. There are several case reports of successful treatment with single agent dabrafenib or vemurafenib in *BRAF* mutated gliomas [16–19].

Despite impressive initial response rates, acquired resistance to BRAF inhibitors occurs in majority of patients. One of the most frequently implicated causes of acquired resistance is reactivation of the MAPK pathway [20]. Furthermore, paradoxical activation of the MAPK pathway within *BRAF*-wildtype cells has been implicated in the development of secondary skin tumors in patients treated with BRAF inhibitors [21]. MEK is an essential kinase within the MAPK pathway [20]. The addition of MEK inhibitors to BRAF inhibitors has demonstrated superiority over BRAF inhibition alone in two Phase III trials in patients with *BRAF* mutant metastatic melanoma [22,23]. A Phase III trial of dabrafenib in combination with the MEK inhibitor trametinib versus vemurafenib monotherapy demonstrated significantly better response rates (64 vs 51%), progression-free survival (11.4 vs 7.3 months) and 12-month survival (74 vs 65%) with combination therapy [22]. Adverse events were similar in both arms. While pyrexia was more common in the combination arm (53 vs 1%), skin toxicity was higher in the vemurafenib arm (rash 43 vs 22%, photosensitivity 22 vs 4%, palmar-plantar erythema 25 vs 4%, papilloma 32 vs 2%, SCC & keratoacanthoma 18 vs 1%, and hyperkeratosis 25 vs 4%). Results from a further Phase III trial evaluating dabrafenib with trametinib versus dabrafenib with placebo confirmed the superiority of combination BRAF and MEK inhibition [23].

Combination dabrafenib and trametinib has also been shown to be superior to dabrafenib monotherapy in a *BRAFV600E* mutant and *CDKN2A* deficient intracranial murine glioma model [24]. Clinical experience of combination BRAF and MEK inhibition in primary CNS tumors is reported in case reports in patients with meningioma, craniopharyngioma and primary brain melanoma [25–27]. Our two cases add to a recent case report of combination BRAF and MEK inhibitor use in anaplastic pleomorphic xanthoastrocytoma following prior progression with vemurafenib monotherapy in which the addition of an MEK inhibitor appears to overcome previous BRAF inhibitor resistance [28]. However, superiority of combination BRAF and MEK inhibition over BRAF monotherapy has not yet been established within the CNS. Given trametinib is a p-glycoprotein substrate, it is unclear whether it penetrates the blood–brain barrier sufficiently to be clinically active [29]. While successful use within case reports (such as the two patients we describe in this report) supports tolerability of combination therapy in patients with CNS tumors, it is not possible to determine whether the same clinical efficacy would have been observed with dabrafenib alone. Clinical trials of dabrafenib plus trametinib in patients with brain metastases from melanoma are ongoing (NCT02039947, NCT01978236). While the CNS efficacy of trametinib is being formally evaluated, given the clinical superiority in extra-CNS disease in clinical trials without increased toxicity, we believe it is reasonable to treat CNS disease in the same fashion as extra-CNS disease.

We report in Case 2 a patient with radiological relapse after 2 months of stopping dabrafenib but having a subsequent response to dabrafenib when it was re-introduced in combination with trametinib. Whilst with cytotoxic chemotherapy it would not be typical to re-challenge with the same therapy if a patient had progressed shortly after stopping it, this approach may not be applicable with BRAF inhibitor therapies where a re-challenge may be appropriate. We again note that the addition of trametinib in this patient makes it difficult to make definitive conclusions. Furthermore, this case highlights the importance of close radiological surveillance if BRAF therapies are stopped for reasons other than progression and the potential for successful re-challenge.

While the authors recognize that longer follow-up would be ideal, we believe the radiologic and clinical improvement is significant. We had difficulty obtaining funding for targeted therapies for *BRAFV600* mutated glioma due to limited published evidence of benefit, thus we feel it is important to highlight these specific cases.

Conclusion

In patients with glioma, the *BRAFV600E* status should be determined in those with PXA, ganglioglioma, pilocytic astrocytoma and epithelioid glioblastoma. If a *BRAFV600E* mutation is identified, treatment with combination BRAF and MEK inhibition should be considered.

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No writing assistance was utilized in the production of this manuscript.

Informed consent disclosure

The authors state that they have obtained verbal and written informed consent from the patient/patients for the inclusion of their medical and treatment history within this case report.

Executive summary

- *BRAFV600E* mutations are drivers of oncogenesis in a variety of tumors and can be successfully targeted with small molecule inhibitors.
- In primary CNS tumors, *BRAFV600E* mutations are most frequently found in pleomorphic xanthoastrocytoma, ganglioglioma, pilocytic astrocytoma and epithelioid glioblastoma. The *BRAFV600E* status should be established for all patients with these tumors.
- Dabrafenib and vemurafenib have demonstrated clinical activity in patients with primary brain tumors.
- Resistance to BRAF inhibitors frequently occurs through reactivation of the MAPK pathway. Combining BRAF and MEK inhibitors can overcome this resistance and has been established as superior to BRAF inhibition alone in patients with metastatic melanoma outside of the CNS.
- It has not yet been established whether the addition of MEK inhibitors is superior to BRAF inhibition alone for tumors within the CNS.

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