Dabrafenib in BRAFV600-mutated anaplastic pleomorphic xanthoastrocytoma

Nicholas F Brown^{1,2}, Thomas Carter² & Paul Mulholland^{*1,2}

Practice points

- Pleomorphic xanthoastrocytoma (PXA) is an uncommon brain tumor.
- Anaplastic PXA (20–30%) has recently been reclassified as a WHO grade III tumor (previously grade II).
- Typical treatment is with gross total resection, radiotherapy and cytotoxic chemotherapy.
- BRAFV600 mutation status should be determined for all patients with PXA.
- BRAF inhibitors such as dabrafenib and vemurafenib may be effective in the treatment of BRAFV600-mutated PXA.
- Due to well-recognized acquired resistance mechanisms, combining BRAF and MEK inhibitors may be more effective.

Pleomorphic xanthoastrocytoma (PXA) is a rare brain tumor. Anaplastic features are found in 20–30% of cases of PXA and are associated with poor outcomes. Typical treatment is with gross total resection, followed by radiation therapy and cytotoxic chemotherapy at relapse. BRAFV600 mutations have been identified in 38–60% of patients with PXA. Several case reports and small case series have identified clinical benefit with BRAF inhibition in patients with BRAFV600-mutated PXA. We report the second published case of successful treatment with the BRAF inhibitor dabrafenib in a female patient with relapsed anaplastic PXA with a BRAFV600 mutation, and the first published case of dabrafenib treatment following intolerance to vemurafenib.

First draft submitted: 12 July 2016; Accepted for publication: 23 August 2016; Published online: 26 October 2016

Background

• Pleomorphic xanthoastrocytoma

Pleomorphic xanthoastrocytoma (PXA) is a rare brain tumor, with an incidence of fewer than 0.07 cases per 100,000. It most commonly affects children and young adults, with a median age of diagnosis of 20.5–30.5 years. There is no significant gender difference [1–4]. A total of 97–99% of tumors are supratentorial, most frequently occurring in the temporal lobe. The most common initial symptom is seizures, occurring in 64–75% at presentation [1–3]. Other frequent clinical features include focal neurological deficits, visual disturbance, raised intracranial pressure and rarely, intracerebral hemorrhage [5].

PXA have a typical MRI appearance of a cystic mass with a prominent solid component that is isointense to gray matter on T1-weighted views, mildly hyperintense in T2-weighted views,

KEYWORDS

- anaplastic • BRAF inhibitor
- BRAFV600 mutation
- dabrafenib • pleomorphic xanthoastrocytoma • PXA
- vemurafenib

¹Department of Oncology, University College London Hospitals, 235 Euston Road, London NW1 2BU, UK

²UCL Cancer Institute, University College London, 72 Huntley Street, London WC1E 6DD, UK

*Author for correspondence: paul.mulholland@nhs.net

enhancing with gadolinium and with variable surrounding edema [6]. Purely solid and cystic forms also exist. PXAs are histologically distinct with pleomorphic giant cells with xanthomatous change, presence of eosinophilic granular bodies and dense deposition of intracellular reticulin [7].

Anaplastic features are found in 20–30% of cases and include a high mitotic index ($\geq 5/10$ high-powered fields) with or without necrosis [2,3]. Anaplasia confers a poorer progression-free and overall survival, although less reliably than in astrocytomas [7]. This aggressive variant of PXA has been recognized as a separate clinical entity in the recently published 2016 WHO Classification of Tumors of the CNS, termed ‘anaplastic PXA’, and now classed as a grade III tumor, having previously been categorized as a grade II tumor in the 2007 edition [8,9].

Typical treatment is gross total resection if feasible, followed by radiotherapy and cytotoxic chemotherapy at recurrence. Five-year overall survival is 76–80% in all patients with PXA, and 57% in those with anaplasia [1,3].

• BRAFV600 mutations

A seminal study investigating the MAPK signal-transduction pathway identified mutations in BRAF as a key driver of oncogenesis in a number of human cancers, most notably melanoma [10]. More than 95% of BRAF mutations are a substitution of valine by glutamate at amino acid position 600 (BRAF V600) that initiates constitutive and proneoplastic activation of the MAPK pathway [10,11]. The BRAFV600 mutation is found in 38–60% of patients with PXA [1,12–15]. It is unclear whether a BRAF mutation alone affects prognosis [1]. In glioma mouse models, BRAF mutation alone is insufficient to initiate tumorigenesis. However, the combination of cyclin-dependent kinase inhibitor 2A loss with mutated BRAF generates malignant transformation [16]. Concomitant cyclin-dependent kinase inhibitor 2A deletion and BRAF mutation have been frequently identified in PXA [11].

• BRAF inhibition

The introduction of drugs that inhibit mutant BRAF has dramatically changed the clinical outcomes of patients with BRAF-mutated tumors. The most robust data of efficacy are from large clinical trials in patients with metastatic melanoma.

A pivotal Phase III randomized trial compared the BRAF inhibitor vemurafenib with

dacarbazine (standard therapy) in 675 patients with BRAFV600-mutated metastatic melanoma [17]. There were superior response rates (48 vs 5%), progression-free survival (5.3 vs 1.6 months [HR: 0.26; 95% CI: 0.2–0.33, $p < 0.001$]) and 6-month survival (84% [95% CI: 78–89%] vs 64% [56–73]) in the vemurafenib arm. A further large Phase III randomized trial compared the BRAF inhibitor dabrafenib with dacarbazine in 250 patients with previously untreated BRAFV600 mutant metastatic melanoma with improved response rates (50% [42.4–57.1] vs 6% [1.8–15.5]) and progression-free survival (5.1 vs 2.7 months [HR: 0.3; 95% CI: 0.18–0.51, $p < 0.001$]) in the dabrafenib arm [18]. The most frequent side effects of BRAF inhibitor therapy were arthralgia, rash, fatigue, cutaneous squamous cell carcinoma and keratoacanthoma. Comparing the two trials, dabrafenib appeared to be better tolerated than vemurafenib, with a lower incidence of skin toxicity. Treatment of melanoma patients with brain metastases demonstrated the efficacy of BRAF inhibitors in the CNS, with similar responses in intracranial and extracranial disease [13].

There is some evidence for the use of BRAF inhibitors in BRAFV600 mutant PXA. A Phase II ‘basket’ study of vemurafenib in 122 patients with nonmelanoma cancers with BRAFV600 mutations included four patients with PXA [19]. Of these, 3/4 patients had a partial response and 1/4 patient had a best response of stable disease. In a case series of four patients with PXA (one with anaplasia) with BRAFV600 mutations treated with salvage vemurafenib, best response assessments were partial response in one patient, stable disease in two patients and progressive disease in one patient [20]. The median overall survival was 8 months (range: 4–14 months), and median progression-free survival was 5 months (range: 2–10 months). All patients previously had surgical resection, radiotherapy and chemotherapy (PCV or temozolomide). Three case reports describe treatment with vemurafenib in three separate patients with anaplastic PXA [21–23]. All of these patients had been previously treated with surgical debulking, radiotherapy and chemotherapy. Two cases report tumor regression on MRI (one near complete response) and the third case reported stable disease on follow-up imaging. The reported toxicities are consistent with those characterized in clinical trials in patients with melanoma described above.

There is a single published case report of dabrafenib use in PXA. A patient with primary meningeal PXA with anaplastic features was commenced on dabrafenib following surgery and radiation, with subsequent significant improvement in tumor-related symptoms and reduction in disease on imaging [24]. The patient developed progressive disease 3.5 months later (although therapy was withheld for several weeks due to an intracranial hemorrhage) and died a few weeks later.

Case

A 21-year-old university student initially presented in June 2014 with a 1-month history of crescendo headache, vomiting, blurred vision and somnolence. MRI of the brain demonstrated a large mass with a pleomorphic appearance within the right middle cranial fossa. There was a large enhancing soft tissue nodule at the medial inferior aspect, a large cystic component and surrounding vasogenic edema with midline shift (**Figure 1**).

The patient had an emergency drainage of the large temporal cyst with initial histology reported as glioblastoma. Eleven days later she underwent a right temporal craniotomy and gross total resection. Final histology was reported as PXA with anaplastic features, and a BRAFV600 mutation was identified. Her symptoms resolved.

The patient received adjuvant RapidArc intensity modulated radiotherapy (54.9 Gray in 33 fractions), completed in August 2014. In September and October 2014 she had several stereotypical episodes which “felt like being washed over with hot and cold water,” with a “feeling” in her abdomen. These were diagnosed as temporal lobe seizures and she was commenced on lamotrigine.

An MRI scan in November 2014 (**Figure 2**) identified an increase in the volume of enhancing tissue in the surgical bed, suspicious for disease progression. The patient had a second right temporal craniotomy and complete resection. Histology was consistent with tumor recurrence. She was subsequently commenced on vemurafenib 960 mg twice daily in December 2014. Eleven days later she developed a widespread macular rash throughout her trunk and limbs. She stopped vemurafenib, commenced hydrocortisone cream and her rash subsequently resolved. Vemurafenib was recommenced at a 25% dose reduction 17 days later. The following day she developed a similar widespread rash. Vemurafenib was stopped and the rash again resolved. An MRI in February 2015 showed slight thickening in enhancement in the floor of the right middle cranial fossa. At this point she was commenced on dabrafenib 150 mg twice daily which she continues to take. In her last

Figure 1. MRI performed at initial presentation. (A) Axial T1 sequence with Gadolinium. (B) Axial T2 sequence.

Figure 2. Axial MRI with gadolinium. (A) Enhancing tissue within surgical bed, suspicious for tumor recurrence. **(B)** No evidence of recurrence after resection and 18 months of BRAF inhibitor therapy.

review in June 2016 she was well, with mild fatigue, but no other toxicities of dabrafenib or symptoms of her tumor. Serial MRI has shown no recurrence of her PXA.

Discussion

Our case is the second report of dabrafenib treatment in PXA, the first of successful treatment in PXA with dabrafenib following intolerance to vemurafenib and adds to the growing literature on the successful use of BRAF inhibitors in patients with PXA.

In clinical trials of BRAF inhibitors in metastatic melanoma while initial response rates are impressive, acquired resistance to BRAF inhibitors occurs in a significant proportion of patients. One of the most frequent causes of acquired resistance is reactivation of the MAPK pathway [25,26]. Furthermore, paradoxical activation of the MAPK pathway in cells without BRAF mutations has been implicated in the development of secondary skin tumors in patients treated with BRAF inhibitors [27,28]. MEK is an essential component of the MAPK pathway [29]. Trametinib, a MEK inhibitor, in combination with dabrafenib was superior to BRAF inhibition alone in two Phase III clinical trials in metastatic melanoma, with similar toxicity profiles [30,31]. Combination BRAF and MEK inhibition is now the standard treatment

in BRAFV600 mutant metastatic melanoma [32].

Conclusion

In conclusion, all patients with PXA should be tested for the BRAFV600 mutation. If present we advocate that they should be commenced on combination BRAF and MEK inhibition with dabrafenib and trametinib.

Acknowledgements

The authors are grateful to BUPA for providing dabrafenib.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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.

References

- Ida CM, Rodriguez FJ, Burger PC *et al.* Pleomorphic xanthoastrocytoma: natural history and long-term follow-up. *Brain Pathol.* 25(5), 575–586 (2015).
- Perkins SM, Mitra N, Fei W, Shinohara ET. Patterns of care and outcomes of patients with pleomorphic xanthoastrocytoma: a SEER analysis. *J. Neurooncol.* 110(1), 99–104 (2012).
- Gallo P, Cecchi PC, Locatelli F *et al.* Pleomorphic xanthoastrocytoma: long-term results of surgical treatment and analysis of prognostic factors. *Br. J. Neurosurg.* 27(6), 759–764 (2013).
- Dolecek TA, Propp JM, Stroup NE, Kruchko C. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2005–2009. *Neuro Oncol.* 14(Suppl. 5), v1–v49 (2012).
- Kahramancetin N, Tihan T. Aggressive behavior and anaplasia in pleomorphic xanthoastrocytoma: a plea for a revision of the current WHO classification. *CNS Oncol.* 2(6), 523–530 (2013).
- Crespo-Rodriguez AM, Smirniotopoulos JG, Rushing EJ. MR and CT imaging of 24 pleomorphic xanthoastrocytomas (PXA) and a review of the literature. *Neuroradiology* 49(4), 307–315 (2007).
- Giannini C, Scheithauer BW, Burger PC *et al.* Pleomorphic xanthoastrocytoma: what do we really know about it? *Cancer* 85(9), 2033–2045 (1999).
- Louis DN, Ohgaki H, Wiestler OD *et al.* The 2007 WHO classification of tumours of the central nervous system. *Acta Neuropathol.* 114(2), 97–109 (2007).
- 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.* 131(6), 803–820 (2016).
- Davies H, Bignell GR, Cox C *et al.* Mutations of the BRAF gene in human cancer. *Nature* 417(6892), 949–954 (2002).
- Schindler G, Capper D, Meyer J *et al.* Analysis of BRAF V600E mutation in 1,320 nervous system tumors reveals high mutation frequencies in pleomorphic xanthoastrocytoma, ganglioglioma and extra-cerebellar pilocytic astrocytoma. *Acta Neuropathol.* 121(3), 397–405 (2011).
- Dias-Santagata D, Lam Q, Vernovsky K *et al.* BRAF V600E mutations are common in pleomorphic xanthoastrocytoma: diagnostic and therapeutic implications. *PLoS ONE* 6(3), e17948 (2011).
- Gibney GT, Gauthier G, Ayas C *et al.* Treatment patterns and outcomes in BRAF V600E-mutant melanoma patients with brain metastases receiving vemurafenib in the real-world setting. *Cancer Med.* 4(8), 1205–1213 (2015).
- Bettegowda C, Agrawal N, Jiao Y *et al.* Exomic sequencing of four rare central nervous system tumor types. *Oncotarget* 4(4), 572–583 (2013).
- Tabouret E, Bequet C, Denicolai E *et al.* BRAF mutation and anaplasia may be predictive factors of progression-free survival in adult pleomorphic xanthoastrocytoma. *Eur. J. Surg. Oncol.* 41(12), 1685–1690 (2015).
- Robinson JP, Vanbrocklin MW, Guilbeault AR, Signorelli DL, Brandner S, Holmen SL. Activated BRAF induces gliomas in mice when combined with Ink4a/Arf loss or Akt activation. *Oncogene* 29(3), 335–344 (2010).
- Chapman PB, Hauschild A, Robert C *et al.* Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N. Engl. J. Med.* 364(26), 2507–2516 (2011).
- Hauschild A, Grob J-J, Demidov LV *et al.* Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, Phase 3 randomised controlled trial. *Lancet* 380(9839), 358–365 (2012).
- Hyman DM, Puzanov I, Subbiah V *et al.* Vemurafenib in multiple nonmelanoma cancers with BRAF V600 mutations. *N. Engl. J. Med.* 373(8), 726–736 (2015).
- Chamberlain MC. Salvage therapy with BRAF inhibitors for recurrent pleomorphic xanthoastrocytoma: a retrospective case series. *J. Neurooncol.* 114(2), 237–240 (2013).
- Hofer S, Berthod G, Riklin C, Rushing E, Feilchenfeldt J. BRAF V600E mutation: a treatable driver mutation in pleomorphic xanthoastrocytoma (PXA). *Acta Oncol.* 55(1), 122–123 (2016).
- Harada SFK, Reddy a, Nabors Lb. Molecular pathology: SC18–1. Interesting case-actionable mutation in a case with a recurrent pleomorphic xanthoastrocytoma with anaplastic features. *Pathology* 46(Suppl. 2), S28–S29 (2014).
- Lee EQ, Ruland S, Leboeuf NR, Wen PY, Santagata S. Successful treatment of a progressive BRAF V600E-mutated anaplastic pleomorphic xanthoastrocytoma with vemurafenib monotherapy. *J. Clin. Oncol.* 34(10), e87–e89 (2016).
- Usabalieva A, Pierson CR, Kavran CA *et al.* Primary meningeal pleomorphic xanthoastrocytoma with anaplastic features: a report of 2 cases, one with BRAF(V600E) mutation and clinical response to the BRAF inhibitor dabrafenib. *J. Neuropathol. Exp. Neurol.* 74(10), 960–969 (2015).
- Solir DB, Rosen N. Resistance to BRAF inhibition in melanomas. *N. Engl. J. Med.* 364(8), 772–774 (2011).
- Shi H, Hugo W, Kong X *et al.* Acquired resistance and clonal evolution in melanoma during BRAF inhibitor therapy. *Cancer Discov.* 4(1), 80–93 (2014).
- Robert C, Arnault JP, Mateus C. RAF inhibition and induction of cutaneous squamous cell carcinoma. *Curr. Opin. Oncol.* 23(2), 177–182 (2011).
- Carnahan J, Beltran PJ, Babji C *et al.* Selective and potent Raf inhibitors paradoxically stimulate normal cell proliferation and tumor growth. *Mol. Cancer Ther.* 9(8), 2399–2410 (2010).
- Chang L, Karin M. Mammalian MAP kinase signalling cascades. *Nature* 410(6824), 37–40 (2001).
- Robert C, Karaszewska B, Schachter J *et al.* Improved overall survival in melanoma with combined dabrafenib and trametinib. *N. Engl. J. Med.* 372(1), 30–39 (2015).
- Long GV, Stroyakovskiy D, Gogas H *et al.* Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, Phase 3 randomised controlled trial. *Lancet* 386(9992), 444–451 (2015).
- Garbe C, Peris K, Hauschild A *et al.* Diagnosis and treatment of melanoma. European consensus-based interdisciplinary guideline – update 2016. *Eur. J. Cancer* 63, 201–217 (2016).