Intermittent dosing with vemurafenib in BRAF V600E-mutant melanoma: review of a case series

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Andrew J. Dooley, Avinash Gupta, Madhumita Bhattacharyya and Mark R. Middleton

***Abstract*:** The selective BRAF inhibitors, vemurafenib and dabrafenib, yield high response rates and improved overall survival in patients with BRAF V600E-mutant metastatic melanoma. Acquired drug resistance and drug toxicity are key challenges when using these drugs. We investigated whether vemurafenib toxicity could successfully be managed with intermittent dosing, and if its therapeutic efficacy could be maintained on intermittent dosing. Six patients with BRAF V600E-mutated metastatic melanoma were treated with an intermittent dosing regimen of vemurafenib. In three patients, toxicities were successfully managed with an intermittent dosing regimen. In the other three patients, intolerable toxicities continued on intermittent dosing. Our experience shows that intermittent dosing can successfully manage vemurafenib toxicities where continuous dosing at a reduced dose does not. Intermittent treatment improves drug tolerability and can achieve or maintain melanoma shrinkage. We recommend that in clinical practice, intermittent dosing should be considered as an alternative to dose reduction/termination in the management of vemurafenib toxicity.

Keywords: melanoma, vemurafenib, intermittent, toxicity, resistance

Introduction

The v-raf murine sarcoma viral oncogene homolog B1 (*BRAF*) gene is mutated in 40–60% of melanomas, the most common being the V600E mutation, which leads to activation of the mitogen-activated protein kinase (MAPK) pathway [Davies *et al.* 2002; Fecher *et al.* 2008]. The selective BRAF inhibitors, vemurafenib and dabrafenib, yield high response rates and improved overall survival in patients with BRAF V600E-mutant metastatic melanoma [Chapman *et al.* 2011; Hauschild *et al.* 2012]. However, acquired drug resistance and drug toxicity are key challenges when using these drugs. Resistance to vemurafenib usually develops within 6–8 months [Sullivan and Flaherty, 2013]. Animal models suggest that intermittent dosing of vemurafenib can forestall the emergence of resistance [Das Thakur *et al.* 2013]. In the BRAF Inhibitor in Melanoma-3 (BRIM-3) trial, 38% of patients receiving vemurafenib required dose modifications because of toxicity [Chapman *et al.* 2011]. Management of toxicity typically involves stopping vemurafenib until resolution, before restarting at a lower dose, or permanently ceasing vemurafenib therapy. In one case report, toxicity was managed with dose interruptions alone, with resumption of treatment on disease progression. A response to treatment was noted each time vemurafenib therapy was restarted [Koop *et al.* 2014].

Intermittent dosing of BRAF inhibitors is not described for any solid tumours. However, intermittent dosing of both targeted and systemic therapies are used in standard practice to treat various solid tumours. Sunitinib is a multitargeted receptor tyrosine kinase inhibitor used to treat renal-cell carcinoma. The standard regimen is a dose of 50 mg in 6-week cycles consisting of 4 weeks of treatment followed by 2 weeks without treatment (4/2 schedule) [Motzer *et al.* 2007]. The reasoning behind this choice of regimen, as opposed to continuous dosing, was to allow patients to recover from potential bone marrow and adrenal toxicities observed in animal models [Faivre *et al.* 2006]. A recent phase II trial showed no benefit in terms of safety and efficacy for low-dose continuous dosing over the

Correspondence to:
Mark R. Middleton,PhD, FRCP
Department of Oncology, NIHR Biomedical Research Centre, Oxford Cancer and Haematology Centre, Churchill Hospital, Old Road, Headington, Oxford, OX3 7LE, UK
mark.middleton@oncology.ox.ac.uk

Andrew J. Dooley, BA
University of Oxford, John Radcliffe Hospital, Oxford, UK

Avinash Gupta, MRCP
Department of Oncology, NIHR Biomedical Research Centre, Oxford Cancer and Haematology Centre, Churchill Hospital, Oxford, UK

Madhumita Bhattacharyya, PhD, MRCP
Department of Oncology, Royal Berkshire Hospital, Reading, UK

approved high-dose intermittent (4/2 schedule) dosing [Motzer *et al.* 2012]. Intermittent dosing of capecitabine chemotherapy is used in treating breast cancer to improve tolerability while maintaining efficacy [Blum *et al.* 2001]. A variety of different dosing regimens are used, and the dose and schedule can be tailored to optimize treatment for each individual patient [Naughton *et al.* 2010].

To the best of our knowledge, intermittent dosing with vemurafenib has never been previously described. We investigated whether vemurafenib toxicity could successfully be managed with intermittent dosing, and if its therapeutic efficacy could be maintained on intermittent dosing.

Methods

A case series of six patients with BRAF V600E-mutated metastatic melanoma treated with vemurafenib is presented. Each patient was started on a dose of 960 mg twice daily (BD), but all required dose modifications due to toxicity. Following initial dose reductions, and faced with toxicity, we elected to treat them intermittently rather than lower the dose further or terminate the use of vemurafenib. Where grading of toxicities are stated, these are according to the Common Terminology Criteria for Adverse Events. These have been included wherever available data allowed.

Results

Case 1 was an 85-year-old woman with subcutaneous and lymph node disease. She responded well to treatment but required a reduction to 720 mg BD after 8 weeks due to persistent fatigue, anorexia and a 10 kg weight loss. These toxicities continued at reduced dosage. After 12 weeks of vemurafenib, a skin lesion was excised from her left lower limb, which proved to be a poorly differentiated squamous-cell carcinoma. Intermittent dosing began at 12 weeks (720 mg BD, on alternate weeks). A computed tomography (CT) scan confirmed a partial response at 16 weeks. Unacceptable weight loss continued on intermittent dosing. She felt well during the off-dose weeks, with improved energy and appetite, and decided to stop treatment completely at 20 weeks. A CT scan performed 6 weeks after ceasing vemurafenib showed stable disease. New symptoms appeared 24 weeks after ceasing vemurafenib; these were abnormal sensation and decreased dexterity in the right hand. A CT scan, performed 28 weeks after ceasing vemurafenib, showed new brain metastases, but no other new or enlarged metastases.

Case 2 was an 88-year-old woman with subcutaneous and lung metastases, who showed a good response to vemurafenib. She suffered from nausea, diarrhoea, poor appetite and arthralgia (all at grade 2), as well as grade 1 skin toxicities (dry skin and acneiform rash). At 5.5 months, vemurafenib was stopped for 1 week due to intolerable nausea, vomiting and fatigue. Vemurafenib was then reintroduced, at a lower dose of 720 mg BD, but due to the patient suffering from nausea, decreased appetite and feeling unwell despite the decreased dose, was stopped 2 weeks later. Vemurafenib was restarted a week later, at a dose of 480 mg BD on which the patient continued for 8 weeks. She suffered grade 2 toxicities (nausea, vomiting and fatigue), so vemurafenib was stopped for 2 weeks, before she was restarted on 480 mg BD. She continued on 480 mg BD for 8 weeks, but significant arthralgia and fatigue (both grade 2) continued. At this point, 10 months after first using vemurafenib, with CT and clinical evidence of a continued response to the drug, it was decided to recommence vemurafenib on an intermittent regime of 480 mg BD, on alternate weeks. The patient was continued on this regimen for 2 months, when treatment ceased due to persisting arthralgia. A further 16 months later she remains well, and progression free.

Case 3 was a 58-year-old woman with bone metastases, previously treated with dacarbazine and ipilimumab. She had a background of glaucoma. The patient experienced skin toxicities when on vemurafenib 960 mg BD (squamoproliferative lesions, which were excised, and grade 2 photosensitivity). CT scans at 7 weeks and 15 weeks showed stable disease. After 24 weeks, vemurafenib was stopped due to decreased visual acuity. Anterior uveitis was diagnosed and treated with dexamethasone, cyclopentolate and timolol. Vemurafenib was restarted 4 weeks later at 720 mg BD, but stopped again after a further 13 weeks for recurrent uveitis. On recovery about 4 weeks later, she was restarted on intermittent dosing of 720 mg BD, on alternate weeks. This regimen was continued for a further 6 months, before being stopped because of progressive disease. Uveitis did not recur when on intermittent therapy.

Case 4 was a 79-year-old man, diagnosed with metastatic disease in the mediastinal lymph

nodes, lung and liver. Full-dose vemurafenib was poorly tolerated, causing skin toxicity and weight loss, so treatment was interrupted after 2 weeks. After recovery, he was restarted on 240 mg BD, increasing to 480 mg BD after 1 week, but was only able to tolerate the latter dose for 4 weeks. Dosage was again reduced to 240 mg BD, before switching to intermittent dosing 10 weeks after starting vemurafenib (480 mg BD, on alternate weeks). While on intermittent therapy, he suffered grade 1 erythema and had a squamous-cell carcinoma excised from his right hand, but he regained weight lost during continuous dosing. A partial response was seen on CT scan at 3 months, which was maintained at 6, 9 and 12 months. He has now been on an intermittent regimen (480 mg BD, on alternate weeks) for over 12 months. He currently continues on this regimen without suffering any significant toxicity.

Case 5 was a 53-year-old man with low-volume lung metastases, initially treated with dacarbazine and ipilimumab. Once he developed progressive disease he was started on vemurafenib 960 mg BD. After 2 weeks of treatment he developed skin toxicities (photosensitivity and a grade 2 rash). After 8 weeks, a CT scan showed a partial response, but skin toxicity continued. A 2-week break allowed toxicities to settle, before therapy was restarted at 720 mg BD. After 20 weeks, skin toxicity was ongoing, so he was switched to a 3-weeks-on, 1-week-off regimen at 720 mg BD. He tolerated this regimen better, with ongoing response confirmed on CT scans. Due to ongoing grade 1 skin toxicity (photosensitivity), and a planned holiday to the Middle East, the patient discontinued vemurafenib after 16 weeks of intermittent therapy. Two months after ceasing vemurafenib, there was rapid growth in a single lung lesion, which then responded to the introduction of dabrafenib.

Case 6 was a 78-year-old woman, with cutaneous, lymph node and adrenal metastases. Within 10 days of starting vemurafenib there was a significant reduction in the cutaneous lesions. By week 3 she had reduced oral intake and renal impairment, so treatment was interrupted for 1 week and then resumed at full dosage. By week 11 she was again unwell with diarrhoea, nausea and recurrent renal impairment, so treatment was interrupted for a further 2 weeks and then restarted on an intermittent regimen of 960 mg BD, 4 weeks on, 2 weeks off. This regimen was better tolerated. CT scans at 3 months and 6 months showed a partial response. After 10 months treatment was stopped due to progressive disease. She is now being managed symptomatically, but remains clinically stable.

Discussion

Adverse effects are common with vemurafenib treatment and more so in elderly and comorbid patients, who are not well represented in clinical trials. These effects are managed by dose interruption and/or a reduction, giving rise to concerns about the ability to adequately inhibit the MAPK pathway.

All the clinical trials of vemurafenib to date have mandated continuous dosing, but it is unclear whether this is necessary for clinical effectiveness. Preclinical data now suggest this is not the case and, indeed, that drug resistance might be delayed by intermittent treatment [Das Thakur *et al.* 2013]. The premise that continuous *BRAF* inhibition is a driver of acquired resistance is supported by cases of successful retreatment with vemurafenib or dabrafenib several months after stopping treatment [Seghers *et al.* 2012]. Data from the BRIM-3 trial has shown no differences in outcomes for patients requiring dose interruptions or reductions, compared with those treated continuously at the maximum dose [Chapman *et al.* 2011]. The development of many vemurafenib toxicities after several weeks of treatment also suggests that regular breaks in treatment might be an effective means of enhancing drug tolerability.

All our patients (mostly elderly) suffered common side effects that required dose reductions. A recent open-label, multicentre, safety study on vemurafenib has recently been published. There was an increased incidence of grade 3 and grade 4 adverse events, and adverse events leading to discontinuation, in patients on vemurafenib aged 75 years and older compared with younger patients [Larkin *et al.* 2014].

In our case series, intermittent therapy was used to avoid further reducing vemurafenib dosage and/or stopping treatment altogether, as the minimum efficacious drug exposure is only reliably achieved at a dose of 240 mg BD [Flaherty *et al.* 2010]. In our experience, many patients treated with vemurafenib suffered with toxicities, which then improved rapidly during breaks from treatment. These toxicities then often returned with

continuous dosing at lower doses. This suggested that intermittent therapy, with breaks from treatment, might be better for maintaining certain patients on vemurafenib. We have used a variety of different dosing regimens in an attempt to manage toxicities. The design of the regimen chosen for each patient depended upon the severity of the toxicities, how quickly the toxicities resolved on ceasing vemurafenib, and on the length of continuous dosing needed for toxicities to appear/reappear. We recommend a similar approach be taken when designing an intermittent dosing regimen to manage vemurafenib toxicity. As such, we do not recommend any specific intermittent dosing regimen. However, clinical trials are in set up, which may determine the optimal intermittent dosing regimen for treating melanoma with vemurafenib.

In cases 1, 2 and 5 intolerable toxicities continued on intermittent dosing, which resulted in discontinuation of vemurafenib. In cases 3, 4 and 6, switching to intermittent dosing allowed daily doses to be maintained between 480 mg and 960 mg BD, and proved sustainable for between 2 months and 12+ months, where continuous therapy was not tolerated. In case 4, the patient continues on intermittent therapy with limited toxicity, but vemurafenib was ceased in cases 3 and 6 following disease progression.

Uveitis is a common adverse effect of vemurafenib [Larkin *et al.* 2014]. Uveitis recurred despite the reduction in continuous dosage in case 3, but did not recur when intermittent dosing was implemented. This is evidence that intermittent therapy can effectively prevent adverse toxicity where a reduction in continuous dosage does not. With cancer chemotherapy, the patient's willingness to accept side effects is a key factor in determining if treatment is continued. Intermittent therapy does not prevent toxicity, but breaks in treatment are an important factor in maintaining the tolerability of therapies used to treat other cancers [Adams *et al.* 2011].

Four patients (cases 1, 2, 5 and 6) showed objective responses to treatment before being switched to intermittent dosing, with another (case 4) showing a response after switching to intermittent dosing. One patient (case 3) had stable disease during continuous dosing, which was maintained on intermittent dosing for 6 months. In case 5, disease progressed soon after intermittent vemurafenib was ceased, which then responded to the introduction of dabrafenib. This suggests intermittent vemurafenib was an efficacious treatment in this case. In case 2, the prolonged period of response after stopping vemurafenib demonstrates long term dosing is not always necessary to achieve ongoing effect. In cases 3 and 6, intermittent vemurafenib was ceased following disease progression, 17 months and 10 months, respectively, after vemurafenib was first commenced. However, in all cases, progression-free survival was maintained beyond the median 5.3 months described in BRIM-3, which provides reassurance that our strategy does not result in loss of efficacy [Chapman *et al.* 2011]. There is no evidence from this case series that intermittent therapy is more effective than continuous therapy, or that it can prevent the appearance of drug-resistant disease.

Conclusion

Intermittent dosing with vemurafenib is an effective means of maintaining patients on the drug when faced with severe toxicity. Intermittent treatment improves tolerability and can achieve or maintain melanoma shrinkage. While awaiting information from clinical trials, we recommend that intermittent dosing should be considered as an alternative to dose reduction/termination in the management of vemurafenib toxicity.

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Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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