

CASE REPORT

Treatment with combined dabrafenib and trametinib in *BRAF*^{V600E}-mutated metastatic malignant melanoma: a case of long-term complete response after treatment cessation

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Abstract

Here, we report the case of a patient, diagnosed with *BRAF*^{V600E}-mutated metastatic malignant melanoma M1a, who achieved a complete metabolic response after 7 months of treatment with the combination of dabrafenib and trametinib. After 31 months, the treatment was interrupted for patient's decision. To date October 2017, 18 months after the interruption of the treatment with the combination of dabrafenib and trametinib, follow-up Positron Emission Tomography (PET) scans are still documenting complete metabolic response.

Keywords: case report, complete remission, dabrafenib, drug combination, melanoma, neoplasm metastasis, vemurafenib.

Citation

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Introduction

Several studies have identified different genetic profiles in patients affected by malignant melanoma [1–3]. Approximately 50% of cutaneous melanomas harbor activating *BRAF* mutations and the most frequent is *BRAF*^{V600E} [4,5]. *BRAF* is a member of the RAF kinase family, with a role in the ERK/MAP kinase pathway, a signaling cascade that regulates cell proliferation, differentiation and survival [6].

Although *BRAF* inhibitors, such as dabrafenib and vemurafenib, have shown a promising activity in melanoma management [7], all patients eventually develop a drug resistance at some time after treatment start [5,8,9]. The addition of a MEK inhibitor, such as trametinib or cobimetinib, to *BRAF* inhibitors mitigates one pathway of resistance, increasing response rates with improved overall survival (OS) without relevant cumulative toxicity [10,11]. In a recent exploratory analysis of survival data from selected clinical trials in metastatic melanoma with a long-term follow-up [12], mean survival curves, obtained by weighted averaging, revealed that the combination treatment with *BRAF* plus *MEK* inhibitors is clearly superior to *BRAF* inhibition alone in first-line treatment as well as in second line or higher line. The superiority of the

combination of *BRAF* plus *MEK* inhibitors remained consistent over time in both progression-free survival (PFS) and OS with follow-up times of up to 28 months. On the other hand, *MEK* monotherapy resulted to have only a limited efficacy (similar to chemotherapy as second line or beyond). The same analysis showed a superiority of the combination of *BRAF* plus *MEK* inhibitors within the first 6 months after treatment onset. After 6 months, a clear superiority of PD-1 blockers alone or in combination with CTLA-4 blockers was found. These findings are of high importance and reflect the clinical phenomena of acquired resistance – which is common in *MAP* kinase inhibition – and account for two phenomena: (a) the strong decline of the respective mean survival curves at 6 months of treatment; (b) primary resistance, which is common in immune checkpoint inhibition and accounts for the steep decline of the respective mean survival curves directly after therapy onset. These results indicate the usefulness of therapeutic approaches providing an intended switch from *MAP* kinase inhibition to immune checkpoint blockade to achieve the highest benefit from both therapeutic strategies. For this reason, data from the daily clinical practice by combining *BRAF* and *MEK* inhibitors may be useful to improve our knowledge in this disease setting.

We describe the case of one patient with *BRAF*^{V600E}-mutated melanoma treated with the combination of dabrafenib and trametinib and achieving a long-term complete response (CR). Written informed consent was obtained from the patient for publication of this case report.

Case report

In August 2002, a 57-year-old Caucasian man was referred to our institution for excision of a cutaneous lesion on the left parasternal region, which was diagnosed as a superficial spreading melanoma with invasion of the papillary dermis to a depth of 0.3 mm, Clark level III, 1 mitosis/mm², Stage IB pT1b,N0,M0 [13], with active chronic inflammation, capillary neogenesis and pigmented histiocytes in the dermis.

From 2003, the patient suffered from a controlled type 2 diabetes. In 2008, he underwent transurethral resection of the prostate for benign prostatic hyperplasia.

The patient was kept under regular follow-up every 6 months with clinical evaluation and complete skin examinations, blood tests (complete blood count [CBC], liver function tests [LFT], lipid profile and lactate dehydrogenase [LDH] level) ultrasound of regional lymph node and of the abdomen and optional X-ray diagnostics. Until 2012, no relevant abnormalities were found at follow-up visits excepting for an intermittent neutropenia with lymphocytosis.

At the beginning of 2013, owing to recurrent lymphadenitis, he was referred to a rheumatologist to exclude common rheumatic diseases. No alterations in the level of inflammatory biomarkers, such as erythrocyte sedimentation rate (ESR)

and C-reactive protein (CRP), were found; serum LDH levels were normal. In November 2013, ultrasonography of the left axillary region demonstrated three hypoechoic lymphnodes with abnormal vascularity on color Doppler and sharp border. Cytological examination confirmed the presence of melanoma metastases. The evaluation of tumor-infiltrating lymphocytes TILs revealed augmentation of CD4⁺ helper with an increased CD4/CD8 ratio. An exon 15 *BRAF*^{V600E} mutation was detected.

Staging with positron emission tomography Positron Emission Tomography (PET) indicated melanoma metastatic to right paratracheal lymph nodes and left axillary region (Figure 1). CT scan of the brain showed no metastases and LDH levels were normal M1a [13].

According to the *BRAF*^{V600E} mutation evidence, at the end of January 2014, we proposed to the patient a treatment with oral vemurafenib 1920 mg daily. The drug administration was stopped after three days owing to an intense cutaneous (allergic reaction/immune system disorders G2 CTC AE 4.03) and respiratory hypersensitivity reaction, treated with steroids and anti-histamines. After this hypersensitivity episode was resolved, we tried to restart vemurafenib at the reduced dose of 1440 mg daily, but palatal edema and swelling with pain was observed (allergic reaction/immune system disorders G2 CTC AE 4.03). After hypersensitivity resolution, vemurafenib was restarted at the dose of 960 mg daily, but a new allergic reaction led to a definitive treatment stop.

In March 2014, after the patient received overall only seven doses of vemurafenib, PET scan revealed a partial response (PR) (Figure 2). Considering the good response to the treatment with vemurafenib, we assumed a high efficacy of BRAF inhibitors.

Figure 1. PET staging 2013 indicating melanoma metastatic M1a.

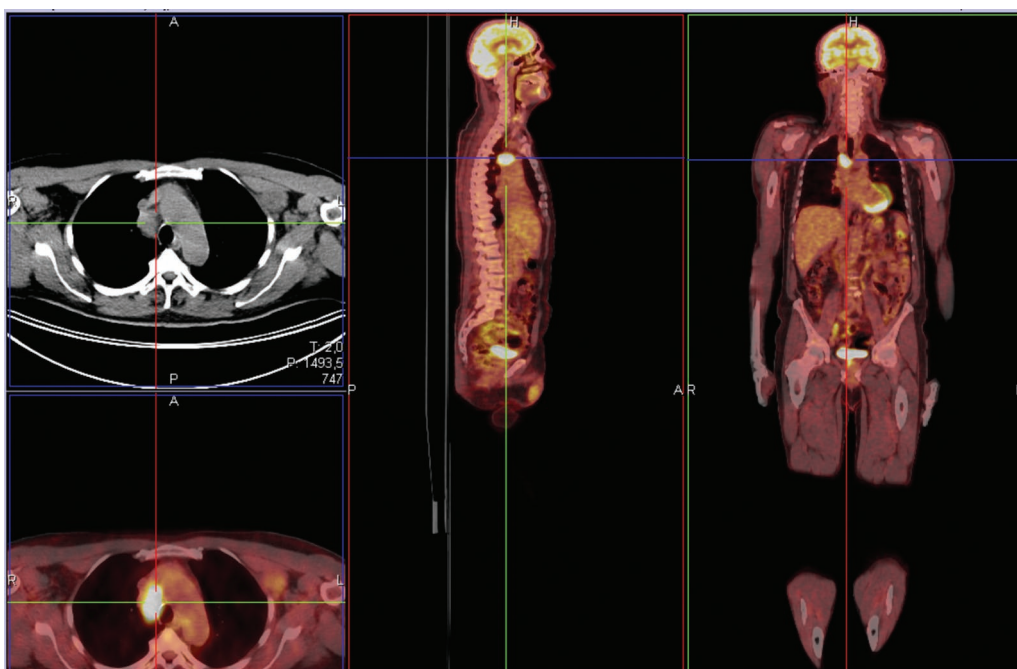
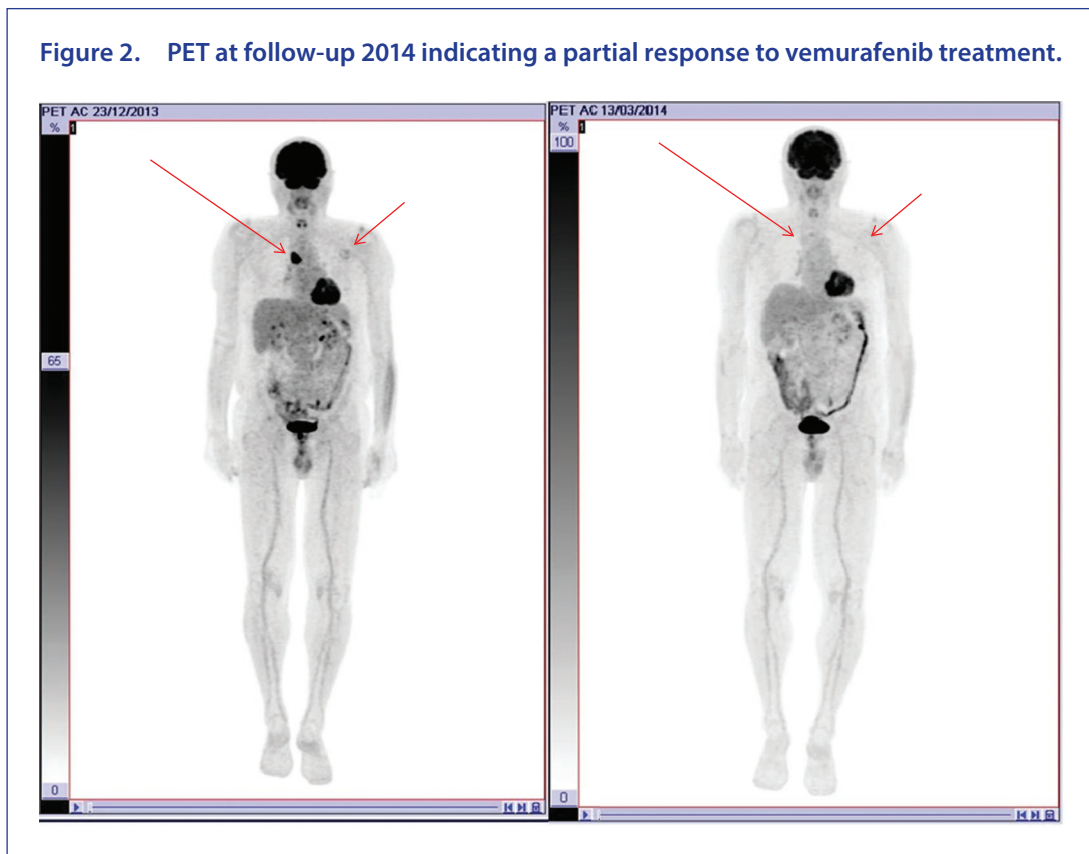


Figure 2. PET at follow-up 2014 indicating a partial response to vemurafenib treatment.

For this reason, we proposed to the patient a combination with dabrafenib and trametinib. In May 2014, the new treatment with dabrafenib 150 mg PO twice daily plus trametinib 2 mg PO daily was initiated. In July 2014, the treatment was suspended for a few days following a modest cutaneous allergic reaction (allergic reaction/immune system disorders G1 CTC AE 4.03) on the forearms. In December 2014, a new localized cutaneous reaction occurred (allergic reaction/immune system disorders G1 CTC AE 4.03). For this reason, a reduced dose of dabrafenib 100 mg PO twice daily and trametinib 1.5 mg daily of the combination treatment was indicated. In August 2014, PET scan showed a complete metabolic remission.

In April 2016, the treatment was interrupted for patient's decision. Since then, there have been regular follow-up every 3 months with clinical evaluation and PET scans.

At the time of manuscript preparation in October 2017, the clinical condition of the patient remains good with performance status=0. To date, PET scans have showed a complete metabolic remission and blood test results, including LDH levels, are normal.

Conclusions

This report presents the case of a patient affected by melanoma, metastatic to the lymph nodes, which showed a long-term CR to dabrafenib plus trametinib despite treatment interruption.

According to a recent landmark analysis at the 5-years landmark point [14], 5-year OS in patients with $BRAF^{V600}$ -mutant metastatic melanoma treated with dabrafenib plus trametinib was 28% (PFS rate was 13%) with a response rate of 76%. CR was observed in 17% of patients. In detail, in patients with CR, PFS rate at 3 years was 67%, at 5 year was 40%; whereas, the median PFS was 39.6 months. Currently, we have no indications on the duration of treatment of patients with $BRAF^{V600E}$ -mutated metastatic malignant melanoma that shows CR to treatment with MEK/BRAF inhibitors [15]. Particularly, it is unknown whether patients who achieve CR can safely discontinue treatment [16]. Data from retrospective studies indicate that approximately 50% of patients achieving CR with dabrafenib plus trametinib relapse after treatment discontinuation [16,17]. Furthermore, the duration of treatment with MEK/BRAF inhibitors does not influence the rate of relapse following treatment cessation [16].

Higher percentages of relapses are observed in patients treated with MEK/BRAF inhibitors compared to patients treated with immunotherapy that discontinued the treatment following a CR [18]. This finding may indicate the importance of immune-mediated mechanisms of action.

In the absence of evidence-based clinical guidance on treatment duration, it is also important to consider individual preferences of patients with complete remission that integrates survival advantage as well as disease-associated and adverse-event-associated symptoms when making a decision on whether or not to halt the treatment with

MEK/BRAF inhibitors. Our patient decided to discontinue the treatment following modest grade 1–2 cutaneous and mucosal side effects. Although combined use of BRAF and MEK inhibitors is well tolerated by many patients, it is not devoid of side effects. Several clinical trials reported that diarrhea, anorexia, nausea, and vomiting are common adverse events frequently associated with the use of a combination of BRAF and MEK inhibitors in daily clinical practice, thus requiring early and appropriate managements to avoid unnecessary dose reductions and transitory or definitive treatment discontinuations [19]. Therefore, there is a need to master the characteristic features, incidence, and relative risk (RR) of

significant adverse events to take adequate prevention and intervention as early as possible [20].

In conclusion, we present the case of a patient with prolonged CR to treatment with dabrafenib plus trametinib despite treatment interruption. Our findings confirm similar long-term results of clinical trials indicating that that durable survival is achievable with dabrafenib plus trametinib in patients with BRAF^{V600}-mutant metastatic melanoma [21]. However, case reports and case series may offer ‘real-life’ information on how to treat the selected population of long-term survivors with metastatic melanoma.

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