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Asian Case of Metastatic Melanoma in Which a Complete Response Was Maintained after Discontinuation of Dabrafenib and Trametinib

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Abstract

A 54-year-old man diagnosed with metastatic melanoma of the right inguinal node with occult primary developed liver and bone metastases. The combination of dabrafenib plus trametinib was initiated, and a complete response (CR) was achieved 24 months after starting treatment. One month later, the target therapy was discontinued at the patient's decision, and he has remained free from progression for 21 months since discontinuation. To the extent of our knowledge, real-world data in Asian melanoma concerning the discontinuation of dabrafenib plus trametinib after achieving CR have not been published; therefore, our case is a meaningful one for considering to cease target drugs and to rescue their financial toxicity.

Keywords

Metastatic Melanoma, Dabrafenib, Trametinib, Complete Response, Discontinuation

1. Introduction

We herein report a rare Japanese malignant melanoma patient who experienced a long-lasting completely tumor-free status without continuous dabrafenib and trametinib treatment. The COMBI-v and COMBI-d trials verified the superiority of the combination of BRAF inhibitor (BRAFi) and MEK inhibitor (MEKi) to BRAFi alone for metastatic melanoma treatment [1]. A better outcome when using the combination approach was also found in daily clinical practice. However, there are few reports following up patients who experienced a complete response (CR) with the combination therapy and consequently interrupted any anti-tumor treatment.

We herein report the real-world data of a single Asian melanoma patient who maintained a long-term CR after the discontinuation of dabrafenib plus trametinib treatment as the first-line therapy. We obtained the patient's written informed consent to publish this report.

2. Case Presentation

The patient was a 54-year-old man who had taken oral cyclosporin due to severe atopic dermatitis. He noticed a right inguinal subcutaneous mass that was diagnosed as malignant melanoma of unknown origin. Shortly after lymph node dissection and subsequent pegylated interferon were performed as adjuvant therapy based on the IIIC staging in the AJCC 7th edition, liver and bone metastases were detected (**Figure 1(a)**, **Figure 1(b)**). Since the resected metastatic lymph node carried a BRAF-V600E mutation, targeting therapy with 300 mg/day of dabrafenib plus 2 mg/day of trametinib was started. The metastases showed a shrinking trend, and then the liver lesions completely disappeared; the vertebrae lesions remained sclerotic from osteolytic 23 months after the initial treatment (**Figure 1(c)**). One month later, we verified CR achievement, *i.e.* CR-in, without the active accumulation of fluorodeoxyglucose in any metastatic lesions (**Figure 1(d)**). He consistently declined not only the dose reduction of dabrafenib and trametinib but also further anti-cancer treatment, including immune-checkpoint inhibitors, because of the inducible severe fatigue and pruritic condition. Atopic erythema was not exacerbated and well-controlled by topical use of steroid ointment at the time. Then, he has experienced no disease relapse for the 21 months after treatment cessation.

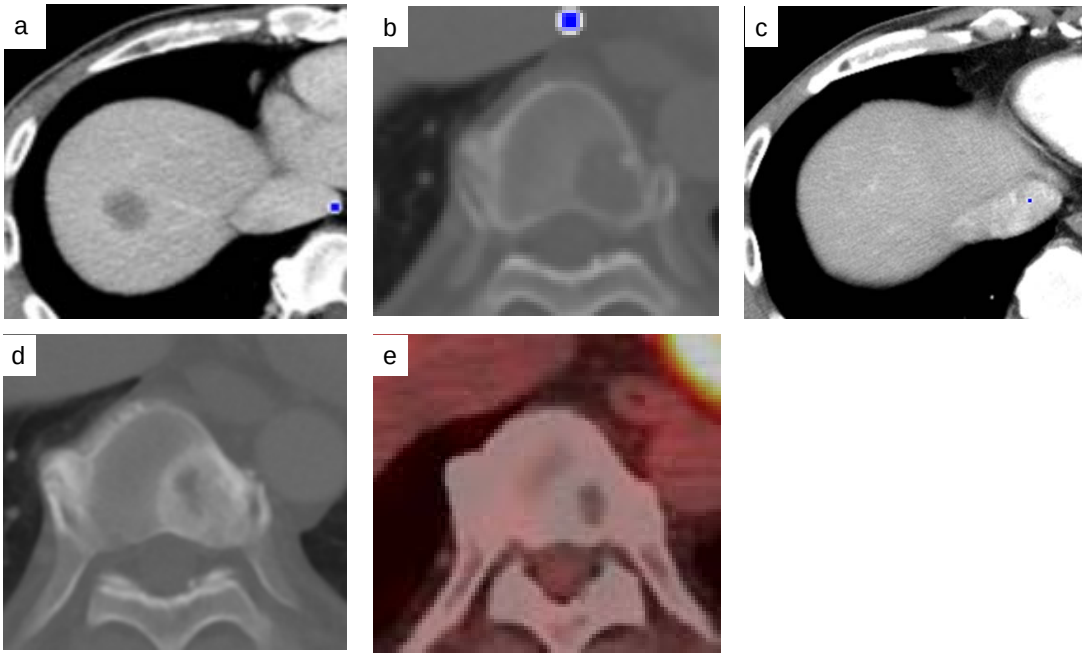

Figure 1. The metastatic lesions to liver (a) and vertebrae bone (b) were noted by contrast-enhanced CT. The bony lesion was osteolytic. (c) The liver lesion was completely disappeared. The bony lesion became sclerotic (d) and showed no pathologic accumulation of ^{18F}FDG on PET-CT (e).

3. Discussion

A COMBI-v and COMBI-d pooled analysis showed that the estimated 5-year overall survival (OS) and progression-free survival (PFS) were 34% and 19%, respectively. Of note, the CR-in group showed a markedly better status, with OS and PFS rates of 71% and 49%, respectively [1]. Of the 106 CR-in cases, 20 (19%) discontinued dabrafenib and trametinib, and 8 (40%) of those patients experienced disease progression or relapse with a median PFS of 40 days (range: 1 - 1144 days). This 40-day PFS might be a hallmark to decide until when an intense observation after CR-in is required [1].

Several previous publications have focused on disease relapse and rechallenge with BRAF inhibitor (BRAFi) monotherapy after achieving CR [2] [3] [4]. Among 12 patients who achieved CR with BRAFi treatment, 6 maintained CR for a median of 17 months after drug discontinuation, while the other 6 suffered a relapse within a median of 3 months [2]. The duration of BRAFi therapy before a CR tended to be longer in the relapsing group than in the non-relapsing group [4]. The present patient needed 23 months for CR-in, which was longer than the 2.5 months reported in the above-mentioned non-relapsing group. Regarding the effectiveness of rechallenge, of the six relapsed re-treated with BRAFi, three achieved CR, one showed stable disease, and one showed progressive disease, suggesting that rechallenge with BRAFi tends to be successful once CR has been achieved [2]. Theoretically, rechallenge with the combination is expected to elicit a more powerful and longer-lasting anti-tumor effect than BRAFi alone due to the dual signal blockade and substantially lower degree of drug resistance. Actually, 3 out of 6 patients who experienced disease relapse after treatment cessation subsequently received BRAFi and MEKi combination therapy, attributing to be a partial response [5]. Therefore, we consider to perform rechallange with the combination prior to the alternative induction of immune-checkpoint inhibitors if disease relapse will be found.

Although previous articles have showed real-world data on the discontinuation of BRAFi plus MEK inhibitor (MEKi) combination [5] [6], this is the 1st report to present the Asian patient who archived long-term relapse free status. The 21 months of follow-up after treatment cessation shown in the present case are valuable because the follow-up duration was a median of just 16 months in a large cohort and 18 months in another single case, making this a relatively long-term observation [5] [6].

4. Conclusion

We believe that the present case provides favorable evidence supporting the avoidance of the continuous use of expensive drugs in a dairy clinical practice. In addition, stratifying similar cases conducts to optimize the use of targeting drugs in BRAF-mutated Asian malignant melanoma.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Abbreviations

CR: complete response

PFS: progression-free survival

BRAFi: BRAF inhibitor

MEKi: MEK inhibitor