New approaches and consequences for elderly cancer patients with focus on melanoma

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Chapter 8a

Effect of vemurafenib on a V600R melanoma brain metastasis

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This chapter refers to the paper '*BRAF inhibitor activity in V600R metastatic melanoma*' by Oliver Klein et al, published in the *European Journal of Cancer* (2013;49:1073-1079):

Introduction

We read with great interest the work of Klein and colleagues who described the results of treatment with dabrafenib or vemurafenib in nine melanoma patients with a V600R mutation in BRAF [1]. Five out six evaluable patients experienced a partial tumor response. However, no volume response was seen for the brain metastases in five patients. We therefore would like to present another 64-year-old patient, with a V600R mutation who did experience effect of vemurafenib treatment on a brain metastasis.

Case report

At referral to our hospital he was diagnosed 2 years earlier with primary cutaneous melanoma. He had undergone 2 months prior to referral whole brain irradiation, 20 Gy in 5 fractions, for a solitary cerebral metastasis, but had never received systemic anti-tumor treatment. His complaints consisted of progressive fatigue as well as neurological symptoms including dysarthria and dysphasia. He was wheelchair bound and had a paresis of his right arm.

Radiological staging showed subcutaneous, mediastinal and retroperitoneal lymph node metastases, as well as lung and spleen lesions. The solitary brain metastasis compressed his left lateral ventricle and induced a midline shift. The cobas® 4800 BRAF V600 Mutation Test was negative. However, sequence analysis of codon 600 of the *BRAF* gene

showed the V600R mutation (c.1798_1799 GT>AG; p.(Val600Arg)). No mutation in the *NRAS* gene was found. Based on preclinical data for vemurafenib in case of a V600R mutated melanoma model [2], we started treatment with 960 mg vemurafenib twice daily orally.

All his neurological symptoms improved within 3 weeks, which allowed the patient to walk short distances and facilitated him to communicate. Tumor response was assessed after 8 weeks, 16 weeks and 24 weeks according to RECIST 1.1. He experienced stable disease for non-cerebral target lesions for 24 weeks. The S-100B serum level lowered from 0.91 µg/L to 0.21 µg/L at 8 weeks and was 0.22 µg/L at 16 weeks. The solitary brain metastasis decreased from 43–29 mm to 30–19 mm at 8 weeks. However, at 16 weeks a new brain metastasis was detected. The patient underwent stereotactic radiotherapy for this new lesion and continued vemurafenib with clinical benefit. Eventually, at 24 weeks 2 more new brain lesions appeared and he died 7 months since start vemurafenib due to progressive intracranial disease.

Discussion

This is the first case reported in literature of a metastasized melanoma patient harboring a V600R mutation in the *BRAF* gene with reduction in size of a brain metastasis on vemurafenib in a previously irradiated lesion.

Recently, efficacy of dabrafenib in V600E and V600K mutated melanoma patients with brain metastases was evaluated. Intracranial response was observed in 39% of patients with a V600E mutation (n = 74) without, and 31% with previous local treatment (n = 65). These percentages were respectively 6.7 (n = 15) and 22 (n = 18) for patients with a V600K mutation [3].

The FDA approved vemurafenib only for metastatic melanoma patients with a V600E mutation in BRAF while the EMA approved it for other V600 mutations as well. Given our experience we would like to endorse the call by Klein et al. that patients with rare V600 mutations should be included in clinical trials, and we support their argument that mutation analyses of metastatic melanoma should test also for non-V600E mutations. In negative cases when using the cobas® 4800 BRAF V600 Mutation Test, it could therefore be considered to perform high resolution melting analysis, and in abnormal traces followed by DNA sequencing. This approach will likely detect more melanoma patients, including those with brain metastases, that possibly benefit from BRAF inhibitors.

References

1. Klein O, Clements A, Menzies AM, et al. BRAF inhibitor activity in V600R metastatic melanoma. *Eur J Cancer*. 2013;**49**:1073–1079.
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3. Long GV, Trefzer U, Davies MA, et al. Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): a multicentre, open-label, phase 2 trial. *Lancet Oncol* 2012;**13**:1087–1095.