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

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Chapter 8c

Successful self-initiated intermittent symptom-based vemurafenib treatment for metastatic melanoma

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Introduction

Single observations by clinicians can lead to major breakthroughs, and some foresee even a renaissance period for clinical medicine [1]. In this context, we would like to share a clinical observation underscoring a preclinical finding.

Daily administration of the BRAF inhibitor vemurafenib leads to tumor shrinkage in over 90% of the patients with a mutation in the *BRAF* gene. These effects are however short lived, with for these patients a median progression-free survival of 5.3 months [2]. Therefore, mechanisms responsible for BRAF inhibitor resistance development receive much attention. The effect of various dosing schemes was studied in a human melanoma xenograft mouse model [3]. Lethal vemurafenib resistance developed within 100 days in mice on daily dosing, while no resistance was seen after 200 days with an on-and-off schedule. Intermittent vemurafenib dosing has not yet been studied in clinical trials.

Case report

Interestingly, we describe a 76-year-old female patient who used vemurafenib intermittently on her own initiative. She presented with cerebral, osseous, pulmonary and lymph node melanoma metastases, harboring a V600E mutation in the *BRAF* gene. She only had complaints from a painful lymph node metastasis in her right groin which disappeared within 2 days after initiation of vemurafenib (Figure 1A). However, she experienced dyspepsia, myalgia, itching and fatigue even at a 50% dose reduction, which she judged unacceptable. In absence of tumor-related symptoms, she therefore discontinued treatment. Thereafter, she monitored the inguinal lesion by palpation and intermittently took vemurafenib at progression. Radiological response measurement after 2 months showed near-

complete remission of the brain metastases (Figure 1B), and partial remission of the other metastases. The serum S-100B level decreased from 0.65 µg/L at baseline to 0.04 µg/L at 2 months and decreased further to < 0.02 µg/L at 4 months. She experienced an ongoing intra- and extracranial response for ~11 month, both radiological as by a persisting S-100B level < 0.02 µg/L, thereby exceeding the median PFS reported in trials. Overall, she took 208 vemurafenib tablets over 49 days during this period. The cost of this treatment was €8,330, while the projected cost of standard treatment would have been over €106,000.

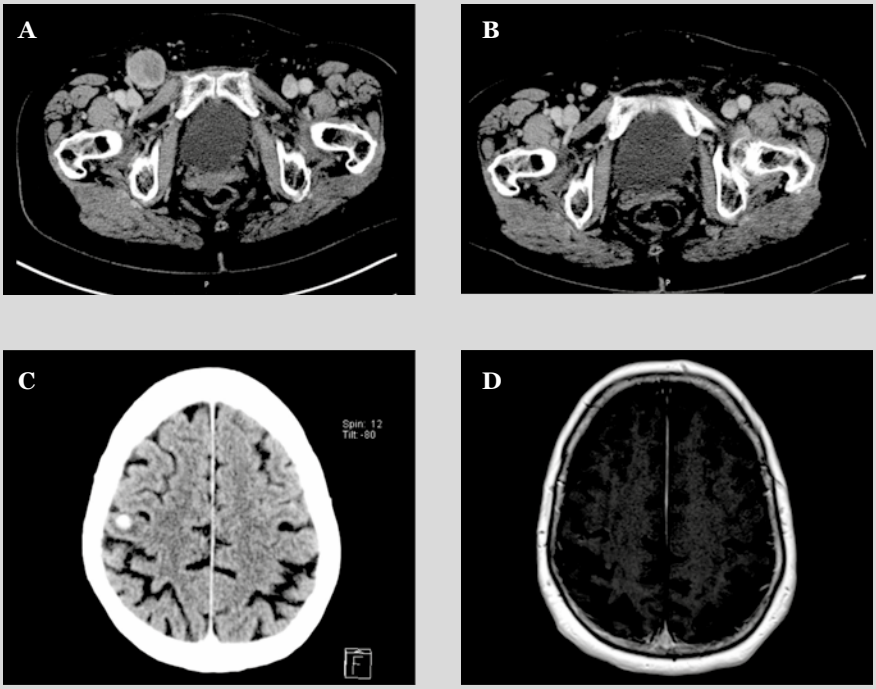

Figure 1: Radiologic response assessment.
(**A**) CT slice at baseline of the right-sided inguinal lymph node metastasis, which the patient used to monitor her tumor response. (**B**) CT slice of the same lesion after 2 months treatment with on-and-off vemurafenib. (**C**) CT slice prior to vemurafenib, with an example of a brain metastasis responding to intermittent vemurafenib. (**D**) MRI slice of the same area 2 months after intermittent vemurafenib treatment.

Discussion

Two other patients, a 78-year-old and an 88-year-old male, also underwent the symptom-based intermittent approach with vemurafenib. They both had palpable metastases on which they based their on-and-off scheme. Both were treated until disease progression

occurred. The 78-year-old male had a V600R mutation in BRAF and was treated for 5 months. The 88-year-old male was treated for 11 months and had a V600E mutation in BRAF. A case study supporting our hypothesis reported that patients who progressed during BRAF inhibition after an initial good response can experience objective tumor regression again at rechallange with BRAF inhibition after a treatment-free interval (a so-called 'BRAF-holiday') [4].

These cases illustrate that intermittent vemurafenib dosing is feasible and can relieve disease-related symptoms with an acceptable toxicity profile.
Interestingly, a phase II trial comparing intermittent sunitinib treatment versus a continuous dosing schedule in patients with advanced renal cell carcinoma showed a median time to tumor progression of 9.9 months for intermittent treatment and 7.1 months for continuous dosing (p = 0.090). Overall survival – 23.1 versus 23.5 months – was similar, but the intermittent group had a significantly superior outcome for time to deterioration [5].

In view of the above results, a prospective randomized clinical trial including an intermittent dosing schedule of vemurafenib in *BRAF* mutation positive metastatic melanoma patients is worth considering. The 4-weeks on, 2-weeks off model, reflecting the preclinical setting, would be an option [3]. However, even intermittent symptom-based BRAF inhibitor treatment is also worth considering.

References

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