

LETTER TO THE EDITOR

Management of Vemurafenib Induced Severe Arthralgia and Pyrexia in a Patient with BRAF V600E Mutated Melanoma: First Experience with a Switch to Dabrafenib

Lars Alexander Schneider^{*1}, Peter Paschka², Karin Scharffetter-Kochanek¹, Verena Gaidzik², Nicolai Treiber¹ and Margit Anna Huber¹

¹*Skin Cancer Center Ulm, University Department of Dermatology and Allergology Ulm, Germany*

²*Department of Haematology and Oncology, University of Ulm, Germany*

Abstract: The invention of targeted therapy for BRAF mutated advanced stage melanoma has given the patients the perspective of a possible longer remission of the disease based on taking several pills a day without a further hospital stay. That is the ideal situation. However, the new drugs are not without side effects. Amongst them, fever and acute arthralgia are well known. We report on a patient in which these effects were so severe under vemurafenib that we had to stop the drug twice in the induction phase. Only with concomitant administration of corticosteroids finally a third induction worked. After 6 months on this therapy we switched the patient to dabrafenib and observed that in this case dabrafenib was much better tolerated. This is the second report on such a switch between the two licensed BRAF inhibitors because of side effects so far.

Keywords: Arthralgia, BRAF V600E, dabrafenib, fever, malignant melanoma, side effects, vemurafenib.

DEAR EDITOR,

Recognition of the genetic profile of the *BRAF* V600E driver mutation [1-3] in malignant melanoma has led to the development of inhibitors blocking specifically mutated *BRAF* [4]. The first one of this new line of drugs for metastatic melanoma, vemurafenib, is an EMA licensed systemic therapy for three years now and dabrafenib followed recently last year [5, 6]. BRAF inhibitors have shown very high response rates of up to 80% in the clinical phase III studies and mean a gain of lifetime for all these patients [7, 8]. However, the BRAF inhibitors are drugs with considerable side effects. Amongst those new cutaneous side effects like the induction of squamous cell carcinomas are challenging new class effects. They occur in around 10-20 % of treated patients and result from the paradoxical activation of signalling pathways under the BRAF inhibition [9]. Su *et al.* found that BRAF inhibition leads to increased MAPK (mitogenactivated protein kinase) signaling and secondary tumor development when another oncogene, HRAS, is activated. This results from the "paradoxical" activation of MAPK [10, 11]. However, The underlying mechanisms of other relevant side effects of BRAF inhibitors, e.g. pyrexia, joint pains or gastrointestinal side effects, still remain to be elucidated [9].

For both substances, toxic effects were a common incident in the various phase III trials, affecting every second treated patient [6, 12]. Table 1 summarizes the side effects and shows the difference in the spectrum between the two substances. It becomes evident, that the first in class drug vemurafenib has a higher percent rate for side effects, especially skin rashes, pyrexia and arthralgia compared to the successor drug dabrafenib. However, the data for dabrafenib is mainly based on one, namely the BREAK-3 licensing trial, whereas that for vemurafenib is based on already 4 large phase 3 trials [5, 6, 9, 12, 13]. However, irrespective of which BRAF inhibitor we choose, our clinical experience with these new drugs is still limited when it comes to clinical management of severe adverse reactions that require hospital admission and discontinuation of treatment. We report our experience with a 53 year old female patient with BRAF V600E positive malignant melanoma that had spread diffusely with soft tissue metastases in the left thigh after several repeated operations. She developed repeatedly severe joint pains, myalgia, fatigue, generalised skin eruption and fever upon starting her on vemurafenib so that admission to hospital and a 5 day course of prednisone 80mg/day were required and the drug had to be stopped twice completely in the initiation phase after 10 days. After these two frustrating attempts with vemurafenib we administered a full course of ipilimumab as the next step. However, the staging CT afterwards showed a further progress of disease and thus we developed the idea to restart her again a third time on vemurafenib with

*Address correspondence to this author at the Department of Dermatology and Allergology, Albert-Einstein- Allee 11, D89081 Ulm, University of Ulm, D-89081 Ulm, Germany; Tel: 0049 731500-57605; Fax: 0049 731500-57666; E-mail: Lars-alexander.schneider@uni-ulm.de

concomitant cortical steroids in a dose of initially 25mg/day prednisone to buffer the onset of joint pain episodes mimicking Löfgren's syndrome. And this finally worked. Fig. (1) shows the clinical history as well as the CT scans of the inguinal region before treatment with a BRAF inhibitor and ten months later. Under this regime joint pains, fever and plantar erythrodysesthesia were bearable, but still present despite the steroid medication. We could therefore only to taper the dose of prednisone down to a minimum of 20mg/day and maintain vemurafenib on a scheme of 66% of the regular dose. Otherwise the side effects became again unbearable. Furthermore, CT-staging 3 and 6 months after initiation of this combined regime showed its success with a stable partial remission of the soft tissue metastases in the left thigh. However, the side effects still persisted even after months on this therapy. This prompted us to switch the patient after the new release of dabrafenib September 2013 to the alternative substance and surprisingly this worked very well. From the first day onwards dabrafenib was tolerated much better. We could immediately use the full dose of dabrafenib. The prednisone dose was also reduced to 10mg/day, and it could be tapered to 7.5mg/day within 8 weeks of switching treatment. Joint pains and fever subsided almost completely and prompted the decision to stay on dabrafenib. Using this regime we achieved a stable situation

for more than 12 months before further progress occurred, which is now treated with a new anti-PD-1 antibody (pembrolizumab).

Table 1. Comparison of the reported side effects in phase III studies for vemurafenib [5, 9, 12, 13] and dabrafenib [6] and demonstrating the variable spectrum of expectable adverse reactions.

Side Effect Any Grade	Vemurafenib	Dabrafenib
Skin rash	30-50%	15 %
Photosensitivity reaction	15-40%	5 %
Arthralgia	35-65%	15 %
Nausea	25-40%	10%
Pyrexia	15-20%	15%
Erythrodysesthesia	15-25%	20%
Cutaneous Squamous cell carcinoma	10-18%	7%

This case demonstrates that the new BRAF inhibitors have to be managed with care in clinical practice. Their therapeutic potential is vast, but we also need to develop

Case history

- 2/1995 C43.7 lower left leg pT2cN0cM0
- 8/2007 Lymph node metastasis left groin
- 2/2010 Relapse left groin
- 7/2011 Relapse left groin
- 2/2012 Relapse left groin, test: BRAF V600E+
- NCI CTC grade IV Arthralgia, Fever, Fatigue
- NCI CTC grade IV Arthralgia, Fever, Fatigue
- 9/2012 Progress of in transit metastases
- 2/2013 Progress two new lung metastases
- NCI CTC grade II Arthralgia, Rash
- NCI CTC grade II Arthralgia, Rash
- NCI CTC grade I Arthralgia, no fever no dysgeusia, no rash

- 2/1995 Wide excision
- 8/2007 Therapeutic dissection + Kirkwood
- 2/2010 Therapeutic dissection
- 7/2011 Therapeutic dissection
- 2/2012 Therapeutic dissection with combined arterio/venous graft R2
- 3/2012 Start Vemurafenib and STOP
- 4/2012 Re-start Vemurafenib and STOP
- 9/2012 Ipilimumab 4 infusions
- 2/2013 Re-start Vemurafenib half dose + prednisone 25mg/day initially
- 4/2013 Increase Vemurafenib to 2/3 dose + prednisone 20mg/day
- 10/2013 Switch Vemurafenib to Dabrafenib full dose + prednisone 10mg/day

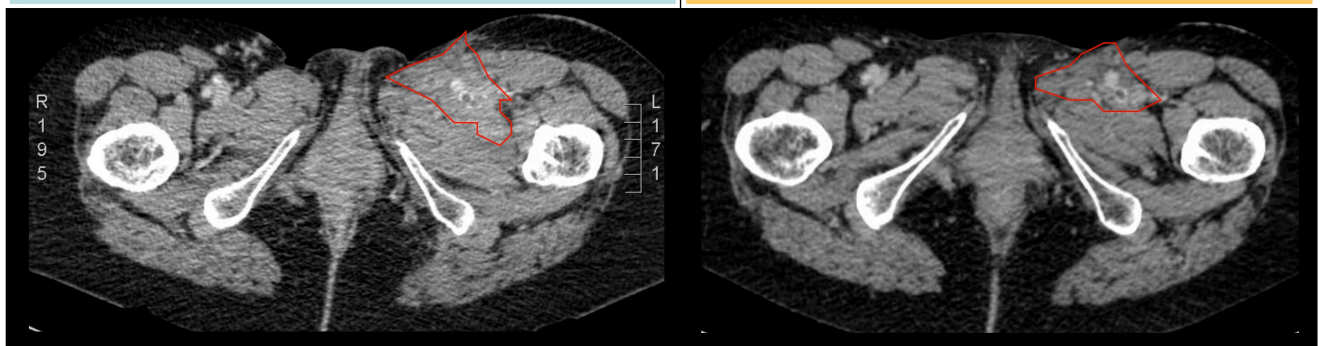


Fig. (1). Clinical course and respective clinical therapeutic management of the patient reported. The bottom part shows the CT scan from 1-2013 and for comparison the CT scan from 10-2011. The encircled area is the soft tissue metastases bulk in the left inguinal area.

Clinical Management

strategies to handle their adverse effects similar as it was the case for ipilimumab. Otherwise, we gain lifetime without life quality for our patients and this is very important in the palliative situation of advanced melanoma. A strategy to administer a BRAF inhibitor combined with systemic steroids has not been reported so far. Our case may serve as a first proof of concept and open a perspective for other patients affected severely by the side effects of the new drugs. Furthermore, we can show here for the first time that a switch between the two available substances in order to achieve better tolerability in the individual situation can be an option that may improve the clinical situation for the individual patient. This is the second new aspect of BRAF inhibitor therapy that we report here for the first time. A last interesting aspect is further, that the remission of metastases was here observed after a sequential administration of ipilimumab followed by a BRAF inhibitor plus corticosteroids. The steroid medication would be expected to counteract the potential ipilimumab effect if present. One may speculate whether all of the regression we observed is due to the BRAF inhibitor effect alone or maybe the combination of the whole. This last question cannot be conclusively answered and has to remain open.

ABBREVIATIONS

CT = Computer tomography
EMA = European Medicines Agency

CONFLICT OF INTEREST

M.A. Huber and L.A. Schneider received travel grants from the Roche, MSD and Bristol Myers Squibb.

L. A. Schneider and M. A. Huber served in advisory boards for the Roche and Bristol Myers Squibb.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

- [1] Fecher LA, Amaravadi RK, Flaherty KT. The MAPK pathway in melanoma. *Curr Opin Oncol* 2008; 20(2):183-9.
- [2] Curtin JA, Fridlyand J, Kageshita T, *et al.* Distinct sets of genetic alterations in melanoma. *N Engl J Med* 2005; 353(20): 2135-47.
- [3] Dankort D, Curley DP, Cartlidge RA, *et al.* Braf(V600E) cooperates with Pten loss to induce metastatic melanoma. *Nat Genet* 2009; 41(5): 544-52.
- [4] Flaherty KT, Hodi FS, Bastian BC. Mutation-driven drug development in melanoma. *Curr Opin Oncol* 2012; 22(3):178-83.
- [5] Chapman PB, Hauschild A, Robert C, *et al.* Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med* 2011; 364(26): 2507-16.
- [6] Hauschild A, Grob JJ, Demidov LV, *et al.* Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. *Lancet* 2012; 380(9839): 358-65.
- [7] Chapman PB, Hauschild A, Robert C, *et al.* Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med* 2011; 364(26): 2507-16.
- [8] Flaherty KT, Puzanov I, Kim KB, *et al.* Inhibition of mutated, activated BRAF in metastatic melanoma. *N Engl J Med* 2010; 363(9): 809-19.
- [9] Larkin J, Ascierto PA, Dreno B, *et al.* Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. *N Engl J Med* 2014; 371(20): 1867-76.
- [10] Su F, Viros A, Milagre C, *et al.* RAS mutations in cutaneous squamous-cell carcinomas in patients treated with BRAF inhibitors. *N Engl J Med* 2014; 366(3): 207-15.
- [11] Weeraratna AT. RAF around the edges--the paradox of BRAF inhibitors. *N Engl J Med* 2012; 366(3): 271-3.
- [12] Sosman JA, Kim KB, Schuchter L, *et al.* Survival in BRAF V600-mutant advanced melanoma treated with vemurafenib. *N Engl J Med* 2012; 366(8): 707-14.
- [13] Robert C, Karaszewska B, Schachter J, *et al.* Improved overall survival in melanoma with combined dabrafenib and trametinib. *N Engl J Med* 2014; [Epub ahead of print].

Received: November 10, 2014

Revised: December 28, 2014

Accepted: December 30, 2014

© Schneider *et al.*; Licensee Bentham Open.

This is an open access article licensed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0/>) which permits unrestricted, non-commercial use, distribution and reproduction in any medium, provided the work is properly cited.