Melanoma Patients under Vemurafenib: Prospective Follow-Up of Melanocytic Lesions by Digital Dermoscopy

Marie Perier-Muzet[1,2], Luc Thomas[1,2], Nicolas Poulalhon[1], Sébastien Debarbieux[1], Pierre-Paul Bringuier[2,3,4], Gerard Duru[2], Lauriane Depaepe[4], Brigitte Balme[4] and Stephane Dalle[1,2,3]

Second primary melanomas (SPMs) induced by vemurafenib have been recently described. The aim of this study was to define the dermoscopical signs of melanoma in this context. Patients underwent a total body examination before receiving vemurafenib. Each single melanocytic lesion was registered before therapy by digital dermoscopy (DD), and then repeated monthly until therapy disruption. Forty-two patients were included, the mean duration of follow-up was 6.7 months, and a mean number of 51 lesions per patients were captured and followed. A total number of 2,155 lesions were recorded, of which 56.1% presented at least one change during the study. More common changes concerned the color of the lesions (up to 15%) and appearance or disappearance of globules (14.6%). Thirty-six of the melanocytic lesions were surgically excised, 21 were classified as a nevus, 1 was a lentigo, and 14 as a second new primary melanoma (occurring in 21% of our patients). DD allowed us to excise only 36/2,155 (1.6%) of the lesions and permitted us to detect 14 SPM in the 42 patients with a highly efficient malignant/benign ratio of 63.6%. Although vemurafenib is now tested in an adjuvant setting DD should be systematically used in order to accurately detect SPM and reduce the number of unnecessary excisions.

Journal of Investigative Dermatology (2014) **134,** 1351–1358; doi:10.1038/jid.2013.462; published online 5 December 2013

INTRODUCTION

Vemurafenib was approved in 2011 for the treatment of metastatic or unresectable melanoma ([No authors listed], 2011; da Rocha Dias *et al.*, 2013), as a selective inhibitor of the V600E mutated BRAF kinase. This activating mutation of the gene encoding for BRAF is present in approximately 50% of human melanomas (Davies *et al.*, 2002; Curtin *et al.*, 2005), leading to over activity in the mitogen-activated protein kinase pathway and uncontrolled cell growth. It occurs in 92% within the kinase domain, with a substitution of valine for glutamate at codon 600 (Takata and Saida, 2006). In previously published clinical trials, 6 months overall survival was estimated at 84% in the vemurafenib group and 64% in the dacarbazine group, response rates being 48% and 5%, respectively (Chapman *et al.*, 2011). Common observed adverse events included arthralgia, fatigue, nausea, diarrhea, and unspecific skin rash. These adverse effects require dose modifications in 38% of the patients (Anforth *et al.*, 2012; Boyd *et al.*, 2012; Chu *et al.*, 2012; Dummer *et al.*, 2012; Huang *et al.*, 2012; Hwa *et al.*, 2012; Zimmer *et al.*, 2012b; Kim *et al.*, 2013; Lacouture *et al.*, 2013; Villani *et al.*, 2013). Squamous cell carcinomas, usually well differentiated, are observed in 26% of the patients under treatment (Sosman *et al.*, 2012). Changes in pre-existing pigmented lesions under vemurafenib and dabrafenib were more recently reported. The first reports indicated either the regression or darkening of nevi (Chu *et al.*, 2012; Haenssle *et al.*, 2012) or the appearance of new nevi (Ma *et al.*, 2012; Schmitt *et al.*, 2013). Acquired atypical dermoscopic features within pre-existing nevi were subsequently reported (Gerami *et al.*, 2012; Haenssle *et al.*, 2012). Along with others, we mentioned the occurrence of second primary melanomas (SPMs) under vemurafenib (Dalle *et al.*, 2011; Zimmer *et al.*, 2012a; Debarbieux *et al.*, 2013) corresponding either to newly developed pigmented lesions, or rapidly changing pre-existing melanocytic lesions. To the best of our knowledge, a prospective follow-up of all nevi modifications on various patients under BRAF blockers has never been published before. We report herein a longitudinal study of dermoscopic changes occurring on the pigmented lesions of 42 patients receiving vemurafenib for advanced melanoma. Our aim was to better understand the impact of vemurafenib on pre-existing melanocytic lesions.

RESULTS

Forty-two unselected consecutive patients were prospectively included in this study, 13 women (31%) and 29 men (69%),

[1]*Department of Dermatology, Centre Hospitalier Lyon-Sud, Hospices Civils de Lyon, Lyon, France;* [2]*Université Claude Bernard Lyon 1, Lyon, France;* [3]*Cancer Research Center of Lyon, Lyon, France and* [4]*Unit of Pathology, Centre Hospitalier Lyon-Sud, Hôpital Edouard Herriot, Hospices Civils de Lyon, Lyon, France*

Correspondence: Stephane Dalle, Service de Dermatologie, Centre Hospitalier Lyon Sud, 69495 Pierre Bénite, France. E-mail: stephane.dalle@chu-lyon.fr

Abbreviations: DD, digital dermoscopy; SPM, second primary melanoma

Received 9 July 2013; revised 12 September 2013; accepted 24 September 2013; accepted article preview 7 November 2013; published online 5 December 2013

whose mean age was 60.5 (range from 29 to 87 years). The mean duration of follow-up was 6.7 months (1–19 months), and the mean number of followed up pigmented lesions per patient was 51.3, ranging from 7 to 143 (Table 1). A total number of 2,155 lesions were initially recorded. According to the patient outcome, eventual treatment discontinuation, and lost-from-follow-up-patient's missing data (the main reason for these was the poor general condition of progressing patients ethically incompatible with the relatively long systematic skin examination), the total number of captured lesions decreased over the time. After 1 month, 1,791 were recorded, decreasing to 791 lesions after 6 months and 381 lesions after 12 months. Most of the changes were observed within the first 5 months of treatment (from 26.1 to 30%), and with a peak of frequency of 49.9% during the second month (Figure 1). Overall, 56.1% of the lesions were modified during the follow-up.

Changes related to the color of the entire lesion were most commonly noticed. These changes occurred early with up to 15% modifications during the first 2 months (Figure 2). It is noteworthy that high percentages of modification within month 16 are probably related to a bias of rank size (<80 pigmented lesions and five patients were still under follow-up at month 16). Modifications related to the globular structures (appearance of new globules or disappearance of pre-existing globules) were seen in 14.6% of the lesions and more common between months 3 and 6. Appearance of new globules was observed in 11.5% of the melanocytic lesions, whereas disappearance was only seen in 5.3%. Besides the color changes affecting the entire lesion, focal changes, either hyper or hypo-pigmentation (7.3%), and onset of dark structureless areas (5.1%) were frequently observed. Increase in diameter (4.6%) and changes concerning the dermoscopic network (4.4%) were less frequent (Supplementary Figures S1 and S2 online). The onset of superficial hyperkeratosis (1.46% of the pigmented lesions), geometrical changes (asymmetry), and vascular changes were uncommon and observed in 0.23 and 0.15% of melanocytic lesions, respectively. Rates of changes on the 10 dermatologic criteria are summarized in Figure 3.

Aside from the global analysis considering every single pigmented lesion as the statistical object, inter individual differences were studied at the patient level. Accordingly, frequency of change in one given patient varied from 8.2 to 93.8%. We therefore identified three groups of patients, those who presented few changes of their pigmented lesions (group 1, ranging from 0 to 39.9% of changing lesions at least on one dermoscopical criterion, $n=11$, 26.2% of patients, average change rate of 22.7%), those who presented rates of changes from 40 to 59.9% (group 2, $n=12$, 28.6% of patients, mean change rate of 46.9%), and those who showed a high frequency of pigmented lesion modifications (group 3, 60% or more, $n=19$, 45.2% of patients, mean change rate of 78.3%; Figure 4). Patients bearing an atypical nevus syndrome were at higher risk of change and represented 25% of patients in group 2 and 21.1% in group 3, whereas they were absent in group 1 (Supplementary Table S1 online). On the other hand, past history of intense sun exposure was less associated with modifications under treatment (60% of patients in group 1 reported chronic sun exposure, whereas 61.1% of patients in group 3 did not).

Thirty-six (1.7%) of the melanocytic lesions were surgically removed. After independent pathology examination by at least two of us (BB and LD); 21 were classified as melanocytic nevi (of which 9 were dysplastic), 1 was a lentigo, and 14 SPMs (average thickness of 0.27 mm, ranging from *in situ* to 0.85 mm). BRAF genotypic status, when determined, was always of the wild type. Fourteen SPMs were excised in 9/42 patients (21%). The mean delay between the initiation of therapy and SPM diagnosis was at 4.1 months. Pathology reports are mentioned in Table 1. Studying the dermoscopic features between excised atypical/activated nevi and melanomas (Table 2), we were not able to differentiate significant differences regarding homogeneous darkening of color, decreasing of size, pattern change, onset of dermoscopic signs of regression, keratosis, or new vessels. This was expected as all lesions were excised because of a high suspicion of melanoma and, considering this, our false-positive cases (22/36) and our malignant/benign ratio (63.6%) were very comparable to previously published data on digital dermoscopy (DD) performances in referral pigmented lesion clinics (Lacouture *et al.*, 2013).

Comparing the group of excised lesions and the group of modified-but-non-excised ones, no statistical difference was observed according to the number of changes occurring during the period of follow-up (mean number of changes of 3.1 and 2.9, respectively, $P=0.28$). However, during the first month, appearance of localized changes in pigmentation, structureless dark areas, or globules were more frequently observed in the excised lesions than in the only modified ones ($P=0.006$, 0.001, and 0.041, respectively). Changes in black structureless areas, in network, and in diameter were the dermoscopic features that led more frequently to excision during the second month ($P=0.049$, 0.029, and 0.002, respectively), whereas localized changes in pigmentation and in diameter were the most decisive criteria within the third month ($P=0.038$ and 0.035). No difference was observed between these two groups according to changes in global color, hyperkeratosis, vessels, dermoscopic pattern, or symmetry, or for any given criteria after the third month.

Considering the body areas for melanomas and modified nevi, occurrence 86% and 90%, respectively, occurred on skin areas protected from chronic exposure, whereas 14% and 10% occur on chronically sun-exposed skin (Table 1).

DISCUSSION

Modifications in pigmented lesions have been reported less frequently than the onset of squamous cell carcinomas under blockers of the mitogen-activated protein kinase pathway, including the non-selective BRAF inhibitor sorafenib (Bennani-Lahlou *et al.*, 2008; Kong *et al.*, 2008) and the selective BRAF inhibitor vemurafenib (Chu *et al.*, 2012). This question became, however, crucial with the observance of SPMs in patients treated by vemurafenib (Dalle *et al.*, 2011; Zimmer *et al.*, 2012a; Debarbieux *et al.*, 2013), raising the question on the long-term impact of BRAF inhibitors on pre-malignant or dormant malignant pigmented lesions. Although several hypotheses were suggested regarding the mechanisms of primary and secondary resistance to vemurafenib, it has