Cutaneous Side Effects of Single Versus Combined *BRAF* Inhibitors: A Comment to Erfan et al.

Rachael ANFORTH and Pablo FERNANDEZ-PENAS
Department of Dermatology, Westmead Hospital, 2145 Sydney, Australia

We read with interest the paper by Erfan et al. (1) on the cutaneous toxicities of anti-BRAF inhibitor therapy in 59 patients with metastatic melanoma. We note that their patient population was mainly treated with vemurafenib (71%) with only 9% receiving dabrafenib. This is of significance as the toxicities are slightly different between the two agents. The authors concluded that cutaneous squamous cell carcinomas (cuSCC) appeared in 23.7% of their patients. This figure is consistant with their population with the reported rate of vemurafenib induced cuSCC being higher than that of dabrafenib (19–26% versus 10–12 %) (2). Similarly they found that cuSCC were common in older patients and presented in both sun-exposed and non-sun-exposed sites.

In 2015, we published on a cohort of 134 patients who were treated with dabrafenib ($n=106$; 79%) and vemurafenib ($n=28$; 21%) (2). In this study we found that the only significant risk for development of cuSCC during treatment was age (>60 years old). The patient's sex or mutation status did not affect time to development of cuSCC. Interestingly patients on vemurafenib appeared to develop their cuSCCs earlier in the treatment course compared with dabrafenib.

As with Erfan et al., we also found that location of cuSCC varied. With 58% occurring on chronic sun-damaged skin and 33.3% occurring on low chronic sun-damaged areas (sun-protected). This correlates with Erfan et al's statement that only two patients had signs of sun damage (actinic keratoses) prior to treatment (1, 2).

The authors findings that photosensitivity is present in both treatment groups was interesting. Photosensitivity is a vemurafenib-specific toxicity and in our experience very rarely encountered in dabrafenib or dabrafenib and trametinib combination therapy (3). Perhaps, given the small population of dabrafenib in their cohort, it may be worth reviewing.

The addition of the MEK inhibitor trametinib to treatment has been shown to negate the majority of the single agents toxicities, in particular cuSCC and other hyperkeratotic conditions. It does this by preventing the activation of ERK, which in single agent treatment has been shown to be unregulated. It is therefore interesting that the authors found palmoplantar keratoderma persisted in their cohort treated with combination therapy. We reported on 30 patients treated with the combination of dabrafenib and trametinib and found a significant reduction in the number of PPK cases (47% in dabrafenib alone versus 5% in the combination group) (4). We too found that folliculitis was higher in the combination group, likely the result of the MEK inhibitor.

The consistency of cutaneous toxicities is reassuring as it will improve the clinical management of patients treated with BRAF inhibitors, with clinicians aware to pay closer attention to older patients and examine sun-protected areas.

Reply to the comments by Anforth and Fernandez-Penas

Gamze ERFAN[1], Cristina CARRERA[2–4], Josep MALVEHY[2–4] and Susana PUIG[2–4]
[1]Dermatology Department, Namık Kemal University Faculty of Medicine, Tekirdag, Turkey, [2]Dermatology Department, Melanoma Unit, Hospital Clinic & IDIBAPS (Institut d'Investigacions Biomèdiques August Pi i Sunyer, [3]CIBER de Enfermedades raras, Instituto de salud Carlos III, and [4]Universitat de Barcelona, Barcelona, Spain. E-mail: spuig@clinic.ub.es

First of all we really appreciate the comments by Anforth & Fernandez-Penas and their interest in our paper on the cutaneous toxicities of anti-BRAF inhibitor therapy in patients with metastatic melanoma (1). As they noted, our population was mainly treated with vemurafenib and only 9% received dabrafenib, which is the main limitation of the study. Besides pointing out this limitation and, similar to previous reports, we found that the development of new non-melanoma skin cancer and keratoacanthoma was significantly higher in patients with single anti-BRAF treatment (OR-combined: 0.5, $p=0.02$, OR: 0.74, $p=0.05$ and OR-combined: 0.75, $p=0.05$) also when comparing combined and single dabrafenib (OR: 0.6, $p=0.02$ and OR: 0.6, $p=0.02$) with no differences between single treatment of vemurafenib and dabrafenib. All patients with SCC were under single anti-BRAF treatment (OR: 0.9, $p=0.29$). Unlike the study of Anforth et al. (2) in our study we observed that the patients on dabrafenib appeared to develop their cuSCCs earlier in the treatment course compared with vemurafenib (mean days to cuSCC diagnosis with single dabrafenib was 48 days compared to 80.5 days in single vemurafenib).

As Anforth & Fernandez-Penas mention, in our study, photosensitivity was diagnosed in 26 (44.1%) patients

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and importantly 30.7% of them were under dabrafenib treatment, either alone or combined. According to our findings combination therapy did not prevent photosensitivity (OR: 1.35, $p=0.71$) and photosensitivity was present in both vemurafenib and dabrafenib single treatment without any differences (OR: 1.12, $p=0.90$). In previous reports, photosensitivity is a highly diagnosed side effect during BRAF inhibitor treatments. Rinderknecht et al. (5) mentioned that 57% of patients with vemurafenib treatment had photosensitivity and that it occurred during early stages of drug administration. Other studies also support these findings (6–8). Dummer et al. (9) stated that the minimal erythema dose of UVA reduces in patients with vemurafenib treatment. However, a few reports showed patients with photosensitivity under dabrafenib single or combined treatment (10, 11). Also, according to our findings, there is no statistically difference for this side effect between the two selective BRAF inhibitors.

In our study palmoplantar keratodermia (PPK) was diagnosed in 20 (33.9%) patients and 20% of them were under combined treatment. The duration of the treatment was longer in those patients with PPK (286.3 ± 45.8 vs 162.1 ± 16.2, $p=0.003$). We observed that combination therapy did not prevent this side effect compared to single therapy (OR: 1.021, $p=0.99$). On the other hand, when dabrafenib single and combination treatments were compared, the number of patients with this side effect subjected to dabrafenib single treatment was higher (OR: 3, $p=0.01$). Also, comparing dabrafenib and vemurafenib single treatments, the existence of foot-hand hyperkeratosis was higher in dabrafenib single treatment (OR: 3.8, $p=0.001$).

We agree that the limited number of patients on dabrafenib could have an effect on the diversity of cutaneous side effects seen in our study compared with the study by Carlos et al. (4) from Australia, in which more than 80% of the patients received dabrafenib, but also the differences between Spanish and Australian populations could account for these differences.

In summary, we must underline that the clinical management of patients treated with BRAF inhibitors alone or combined with MEK inhibitors requires the physician's attention regarding all reported side effects (4, 12).

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