SHORT COMMUNICATION

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Development of Cutaneous Toxicities During Selective Anti-BRAF Therapies: Preventive Role of Combination with MEK Inhibitors

Gamze ERFAN[1,2], Susana PUIG[1,3,4], Cristina CARRERA[1], Ana ARANCE[5], Lydia GABA[5], Ivan VICTORIA[5], Adriana GARCIA-HERRERA[6], Llucia ALOS[6,4] and Josep MALVEHY[1,3]

[1]Dermatology Department, [5]Oncology Service and [6]Pathology Department, Melanoma Unit, Hospital Clinic & IDIBAPS (Institut d'Investigacions Biomèdiques August Pi i Sunyer), Villarroel 170, ES-08036 Barcelona, Spain, [2]Dermatology Department, Namık Kemal University Faculty of Medicine, Tekirdag, Turkey, [3]CIBER de Enfermedades raras, Instituto de salud Carlos III, [4]Universitat de Barcelona, Barcelona, Spain. E-mail: susipuig@gmail.com

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Activated *BRAF* mutations affecting the mitogen-activated protein kinases (MAPK) pathway are present in 50% of metastatic melanomas. Targeted therapies have been developed to block such mutations (1, 2). There is a risk of other components of the MAPK signalling pathway, such as MEK, being reactivated after the use of BRAF inhibitors (3–5). Given the evidence of drug resistance and side-effects of BRAF inhibitors, combined treatments with BRAF and MEK inhibitors are being tested in clinical trials for metastatic melanoma. Trametinib is one of these MEK inhibitors. Skin toxicities from BRAF inhibitors, such as photosensitivity, palmoplantar keratoderma (PPK) and keratosis pilaris (KP), have been reported (4, 6–11). Also, non-melanoma skin cancers (NMSC) are considered one of the most significant side-effects (3, 11). We report here the profile of skin toxicities from vemurafenib, dabrafenib alone, or dabrafenib and trametinib combined treatment.

MATERIALS AND METHODS

A total of 59 patients (47 treated with only vemurafenib (71%) or dabrafenib (9%) and 12 with dabrafenib and trametinib in combination (20%)) were seen in the Hospital Clinic, Barcelona, Spain. All patients underwent dermatological evaluation at baseline and monthly during treatment, or whenever patients presented with a complaint. All skin toxicities, including squamous-proliferative, keratinizing, inflammatory, follicular/adnexal disorders, were evaluated clinically and/or histopathologically. Any patients presenting new melanocytic tumours or changes in their pre-existing naevi were excluded from the current study. The study was approved by the ethics committee and patients gave their written informed consent.

Statistical analysis with significant value ($p \leq 0.05$) was performed with paired-sample Student *t*-test for differences between the duration of toxicities and Pearson χ^2 with 95% confidence interval (95% CI) for analysing the significance of the existence of each side-effect.

RESULTS

Demographics and all skin toxicities reported in our series are listed in Table SI[1]. Only 2 patients (3.4%) had a previous history of actinic keratosis (AK). Twenty patients (33.8%) had seborrhoeic keratoses (SK) at baseline. At least one skin toxicity was diagnosed in 53 (89.8%) patients. Risk of presenting skin toxicities was not related to sex, age, duration, or type of treatment.

Fourteen patients (23.7%) developed more than one NMSC during treatment. The patients with keratoacanthoma (KA) and squamous cell carcinoma (SCC) were significantly older than those without KA and SCC ($p=0.03$ and $p=0.02$, respectively). A total of 32 KAs were detected in 12 patients (mean 2.7 per patient). Patients with SCC had a higher number of KAs ($p=0.002$). NMSC diagnosis was related to neither sun-exposed areas nor history of NMSC. Development of NMSC-including or not including AK, and KA was higher in patients with only single treatment (odds ratio [OR]-combined: 0.5 $p=0.02$, OR: 0.74 $p=0.05$ and OR-combined: 0.75 $p=0.05$). All patients with SCC were treated with only one drug (OR: 0.9 $p=0.29$). The proportion of patients who developed NMSC, KA and/or AKs was lower in combined therapy (OR: 0.5, $p=0.02$, OR: 0.74, $p=0.05$ and OR: 0.66, $p=0.01$).

PPK was associated with longer duration of treatments ($p=0.003$), but there was no difference between combined compared with single drug treatments (OR: 1.021, $p=0.99$). When comparing dabrafenib single drug against vemurafenib or combined treatments, the number of patients with PPK on dabrafenib single agent was higher than the other 2 (OR: 3, $p=0.01$ and OR: 3.8, $p=0.001$). The patients presenting with SK were older than the others ($p=0.003$). NMSC and AK were detected earlier and with higher number of KAs in patients with SK than those without (($p=0.006$, $p=0.02$) and ($p=0.03$)). The number of SKs was higher in patients with only dabrafenib treatment ($p=0.01$). Of patients with verrucous papillomas, 92.8% received single-drug therapy.

KP appeared in younger patients ($p=0.02$) and was not prevented by combined regimen (OR: 0.96, $p=1.00$). The number of SKs was lower in patients with KP ($p=0.05$). Acneiform eruption/folliculitis (AE-F) was more frequent in males (OR: 5.6, $p=0.02$ and OR: 1.37, $p=0.01$) and related to longer duration of treatments ($p=0.002$). Most of the patients presenting hair loss received combined therapy (OR: 1.6, $p=0.48$) (Fig. S1[1]). Photosensitivity was present in both single-drug treatments without any differences (OR: 1.12, $p=0.90$),

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and was not prevented by combined therapy (OR: 1.35, $p=0.71$). Skin rash presented earlier in patients under combined treatment, the same as in patients treated with dabrafenib alone ($p=0.01$ and $p=0.01$). Out of 5 patients presenting vitiligo, 3 of these (5.1%) were receiving treatment with only dabrafenib (Fig. S1[1]).

DISCUSSION

Our experience supports the view that skin toxicities are highly frequent during MAPK-target therapies, even under combined regimen with BRAF and MEK inhibitors. Similar to previous reports, single-drug treatment demonstrated a higher frequency and earlier appearance of NMSC-including or not including AK, than combined treatment (7–11). Indeed all SCCs were presented under this regime. Most importantly, patients presenting SCC and KA were older and there was no relationship between skin types or previous history of NMSCs. Our study demonstrated an association between the diagnosis of new SKs and early development of NMSC and an increased number of KAs. In accordance with previous reports our study shows that the number of SKs was higher in patients receiving dabrafenib treatment (12). Based on our findings and those of Hafner et al. (13), who suggested that SK could be the result of MAPK pathway mutations, patients with SK may develop NMSC sooner, and the number of KAs could be higher in these patients.

Our study supports the fact that photosensitivity occurs during the early stages of BRAF inhibitor treatments and, notably, demonstrates that combination with MEK inhibitors does not prevent photosensitivity. Despite the small sample size with dabrafenib in our series, which is a limitation of our study, there appears to be no difference in photosensitivity between the 2 selective BRAF inhibitors (8–11).

Several studies have described skin-rash as KP, follicolocentric and maculopapular (5, 8, 9, 14). We observed the maculopapular rash less frequently than other studies and at earlier onset in combination and dabrafenib-only treatments. In addition, KP was seen in younger patients and showed a negative relationship between the development of KP and the number of SKs.

In contrast to previous reports, PPK was diagnosed more frequently in patients on the dabrafenib regimen (8, 10, 12). Furthermore, the duration of treatment was longer in these patients. Importantly, our study found that combined therapy did not prevent PPK. Acneiform eruption/folliculitis was more frequent in our series and significantly seen in males (8, 10–12). Interestingly, gender was not related to any other specific toxicity. We hypothesized that this could be the result of longer duration of therapy follow-up in our series. In our experience vitiligo was more frequent with dabrafenib therapy, compared with 2 cases reported in the literature during vemurafenib treatment (15). Interestingly, for the first time, to our knowledge erythema of the conjunctiva has been seen as a toxicity developed during early stage of therapy.

In conclusion, combined treatment of MAPK inhibitors may prevent some of the skin toxicities, as expected. However, the most frequent side-effects, such as KP, PPK and photosensitivity, cannot be prevented.

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The authors declare no conflicts of interest.

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