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ORIGINAL ARTICLE

Adjunction of a MEK inhibitor to Vemurafenib in the treatment of metastatic melanoma results in a 60% reduction of acute kidney injury

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Abstract
Introduction A combined therapy MEK inhibitor, Cobimetinib (CB) and BRAF inhibitor, Vemurafenib (VMF), results in an improvement in progression-free survival among patients with BRAF V600-mutated metastatic melanoma. VMF skin adverse effects attributed to ERK paradoxical activation are decreased by the adjunction of CB. The aim of this study was to determine if this combination also improved the renal side effects of VMF.
Patients and methods To investigate the incidence of acute kidney injury (AKI), we conducted a retrospective observational monocentric study in Lyon Sud University Hospital in France. We included 38 patients with metastatic BRAF-mutated melanomas treated by VMF and CB between March 2015 and June 2016. According to the NCI-CTCAE classification, AKI was defined as an increase in serum creatinine exceeding the baseline concentration by 1.5-fold. Serum creatinine was measured before treatment, then on a monthly basis during treatment, and 1 month after treatment discontinuation. Patients were divided into two main groups: AKI-positive (AKI+) and AKI-negative (AKI−), and further subdivided into three groups according to AKI severity (stage 1–5).
Results Of 38 patients, 29 (76%) were AKI−, and all 9 AKI+ patients (24%) were diagnosed within the first trimester of treatment. Three-quarters of AKI ($n=7$, 77%) had stage 1 AKI and the remaining 23% stage 2 AKI. Pre-treatment renal function was significantly better in AKI+ group: 105 vs. 80 ml/min/1.73m² AKI−, $p=0.009$. Compared to previous results, the AKI incidence under the combined VMF–CB vs. VMF monotherapy was reduced by 60%.
Conclusion We reported a reduced incidence and severity of nephrotoxicity of the association inhibitors of BRAF and MEK compared to a BRAF inhibitor monotherapy.

Keywords Melanoma · Combined modality therapies · BRAF inhibitor · MEK inhibitor · Nephrotoxicity

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Introduction

The discovery of BRAF inhibitor therapies has dramatically improved the prognosis of patients with advanced BRAF V600 mutated melanoma [1]. The tolerance of BRAF inhibitor is mild, particularly regarding skin toxicity [2]. Recently, renal toxicity of Vemurafenib (VMF) has been documented and characterized by frequent, mild and reversible acute kidney injury (AKI) [3, 4].

However, the duration of response of BRAF inhibitors is short and limited by acquired drug resistance, resulting in disease progression after 6–8 months [5]. Reactivation of MAPK signaling pathways during a single agent BRAF

inhibitor therapy is the major mechanism for acquired resistance [5]. The MAPK reactivation mechanisms most commonly include emergence of RAS mutations, mutant BRAF amplification, and utilization of different RAF isoforms bypassing BRAF. Particularly, MEK phosphorylation despite BRAF inhibition is linked to MAPK reactivation [6–8]. With this evidence, BRAF inhibitor has been combined with MEK inhibitor. Inhibition of both MEK and mutant BRAF results in a significant improvement in progression-free survival (mean 9.9 vs 6.2 months) among patients with BRAF V600-mutated metastatic melanoma, as a first line of treatment in a phase III trial [9, 10]. No renal toxicity has been reported in these trials.

Moreover, cutaneous toxicities under BRAF inhibition, most notably squamous cell carcinomas and keratoacanthomas, are considered as a related class effect mechanism of BRAF inhibitors, and may be explained by a paradoxical activation of the MAPK pathway in wild-type BRAF cells, particularly by ERK phosphorylation [10]. This hypothesis is strengthened by a decreasing number of secondary cutaneous cancers with the combination therapy [9]. The combination of BRAF inhibitor with MEK inhibitor also improved clinical response and skin toxicity profile.

The role of ERK in the pathophysiology of tubular damage has been evoked, via its stimulatory effect on inflammatory cytokine production [11]. To date, no data are available regarding the effect of the combination of BRAF and MEK on renal toxicity. The objective of this study was to determine if the combination of BRAF and MEK inhibitor was less toxic for the kidney than BRAF inhibitor monotherapy.

Methods

Patients

We retrospectively analyzed data from 46 patients with metastatic melanoma carrying the V600E BRAF mutation, who have been receiving VMF (ZELBORAF®, Roche, Basel, Switzerland) and Cobimetinib (CB) (COTELLIC®, Roche, Welwyn Garden City, Great Britain) in Lyon Sud University Hospital, France, between March 2015 and June 2016. CB was delivered as early access program until market authorization in November 2015. The clinical data collected included demographics and medical history of high blood pressure (HBP), diabetes, nephropathy, and cardiovascular events (heart attack, myocardial infarction, carotid atheroma, occlusive arterial disease, and stroke). Cutaneous rashes were also recorded. Data on concomitant medications were collected, and included non-steroidal anti-inflammatory drugs, renin–angiotensin–aldosterone system blockers, and diuretics. Antibiotics and inhibitor of the proton pomp were also collected. All patients had been exposed to iodinated contrast media, since standard total-body computed tomography scan (CT scan) had been performed during the diagnosis of metastatic melanoma, and then every 3 months during treatment to evaluate patient response. Patients with a cause of AKI non-attributable to treatment were excluded.

Biological evaluation

Pre-treatment serum creatinine (SCr) concentrations (baseline concentrations) were measured with an isotope-dilution mass spectrometry using the traceable enzymatic method (Roche) in the central laboratory of the hospital, on the day preceding treatment initiation. SCr was then determined on a monthly basis during treatment and 1 month after treatment discontinuation. The SCr concentration of each patient was measured before their CT scan, in the same laboratory. The baseline glomerular filtration rate (eGFR) was estimated using the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) formula [11]. For classification of Chronic Kidney Disease (CKD), we used the Kidney Disease Improving Global Outcomes (KDIGO) containing five stages [12].

Classification of AKI severity

The primary outcome was the development of AKI, defined as a 1.5-fold increase in SCr from baseline, according to the NCI-CTCAE, last version [13]. Patients were initially classified as being either AKI+ or AKI−, and further subdivided according to disease severity, as defined by NCI-CTCAE. Indeed, patients with SCr exceeding baseline values by 1.5- to 2.0-fold, by 2- to 3-fold, or by over 3-fold or >4.0 mg/dl were considered as stage 1 AKI, stage 2 AKI, and stage 3 AKI, respectively. Patients with life-threatening consequences or with dialysis recovering were considered stage 4 AKI and stage 5 AKI was defined by patient's death. Complete recovery (reversibility of AKI) was defined as a decrease in SCr concentration by 1.1-fold compared to the baseline value, within 1 month of treatment discontinuation.

Treatment

Patients received VMF initiated at a dose of 960 mg twice daily, in combination with CB at a dose of 60 mg once daily. Patients received CB for the first 21 days of each 28-day cycle. Treatment was temporarily suspended in the event of an adverse effect grade 3 (Common Terminology Criteria for Adverse Events) and was reintroduced at a lower dose [2 or 3 tablets twice daily and 2 or 1 tablet(s) once daily, respectively] after symptoms

regressed to at least grade 1. Treatment was definitely discontinued if a grade 3 adverse event occurred despite decreasing the dose to two tablets twice daily and one tablet once daily, respectively, or if a grade 4 adverse event occurred. The administration of combined VMF and CB was also stopped if the tumor progressed, in accordance with the Scan Response Evaluation Criteria in Solid Tumors (RECIST) or until unacceptable toxicity. The common adverse effects of combined VMF and CB are similar as met with single therapy VMF (cutaneous reactions including skin rash, photosensitivity, alopecia, squamous cell carcinomas and second primary melanomas), pyrexia, arthralgia, asthenia, and liver function abnormalities [9]. CB is associated with serous retinopathy and cardiomyopathy [14]. Each patient had a cardiac evaluation with pre-treatment ultrasound and CB dose was adapted to systolic left ventricular function.

Statistical analysis

The demographic, treatment and clinical characteristics of the patients were described by median and quartiles for quantitative variables, and number and percent for categorical variables. Association with the AKI status was tested using the Wilcoxon test for quantitative data, and the Fisher's exact test for categorical data, as appropriate. Similarly, incidence rates of AKI in the two studies, VMF monotherapy and association of VMF and CB, were compared with the Wilcoxon test for quantitative data, and the Fisher's exact test for categorical data. Statistical significance was defined as $p < 0.05$. Statistical analysis was conducted using R software (R 3.0.2, 2013) [15].

Results

Patient characteristics

We included 38 patients (18 women) with an average age of 56.4 ± 13.9 year, ranging from 33 to 84 year (Table 1). Three patients were excluded because they had AKI with an obvious cause (hypovolemia) and four because treatment time was less than 1 month for severe extra renal intolerance. One patient was excluded because of a thrombotic microangiopathy. The average treatment duration was 4.6 ± 2.8 months. The combined treatment was the first-line treatment for 78.9% ($n = 30$) of patients (Table 1). 15.8% ($n = 6$) had been receiving a single therapy VMF 2 years ago and almost half of patients ($n = 18$, 47%) received VMF 1 month before the market authorization and availability of CB.

Patients with acute kidney injury

A quarter of patients ($n = 9$, 24%) presented with AKI (Table 1). AKI developed during the first trimester for all patients, divided equivalently (33% during first, second and third month). The severity of kidney injury was predominantly moderate, since 88% ($n = 8$) were classified as stage 1 AKI, and the remaining 12% ($n = 1$) as stage 2 AKI. There were no cases of stage 3, 4 or 5 AKI. Among the 9 AKI+, no urinary analysis was available. Kidney biopsies were not performed.

Evolution of renal function and reversibility of acute kidney injury

There was no interruption of treatment because of renal dysfunction. The reversibility of AKI was evaluated in four of the nine patients who presented AKI and had discontinued their treatment, and who had SCr results available 1 month after discontinuation. The SCr returned to a baseline level ($\pm 10\%$) for three of the four patients (75%) in the month following treatment discontinuation. The remaining five AKI+ patients pursued VMF–CB treatment.

Comparison of AKI incidence with the combined treatment compared with a VMF monotherapy cohort (Table 2)

Recently we studied a cohort of 74 patients treated by VMF monotherapy for metastatic melanoma. 59.5% developed mild and reversible AKI within the first trimester of treatment [3].

The incidence rates of AKI in the two studies, VMF monotherapy and the combined association of VMF and CB were compared. They were patients from the same hospital. The dose of VMF was the same in the two studies.

The two cohorts differ significantly on the AKI prevalence ($p < 0.001$). Patients under VMF monotherapy significantly developed more AKI (+150%) than patients under the combined association of Vemurafenib–Cobimetinib (VMF–CB) with a treatment duration significantly longer under VMF monotherapy (+100%). The reduction of AKI incidence under the combined VMF–CB vs VMF monotherapy was 60%.

We found here a significant correlation between AKI and best pre-treatment renal function. Patients who developed AKI were, not significantly, younger and less comorbid than patients who have benefited most from protector effect of MEK inhibitor.

Table 1 Characteristics of included patients with (AKI+) and without (AKI−) acute kidney injury

	Total ($n=38$)	AKI+ ($n=9$)	AKI− ($n=29$)	p value
Age (years)	55 (45.7–70)	50 (43–54)	57 (49–71)	0.08
Gender				
Men	20 (52.6)	5 (55.5)	15 (51.7)	1
Women	18 (47.4)	4 (44.5)	14 (48.3)	1
Treatment line				
First line	30 (78.9)	9 (100)	21 (72.4)	
Second line	3 (7.9)	0	3 (10.3)	
Third line	3 (7.9)	0	3 (10.3)	
Fourth line	2 (5.3)	0	2 (7)	
Treatment duration (months)	4.5 (2–6.7)	5 (5–6)	4 (2–7)	0.161
Anthropometry				
Body mass index (kg/m²)	26.3 (24.2–30.14)	25.1 (24.2–26.4)	26.9 (24.2–30.4)	0.37
Vemurafenib before Vemurafenib + Cobimetinib	18 (47.4)	3 (33.3)	15 (51.7)	
Renal parameters				
Known nephropathy	11 (29)	3 (33.3)	8 (27.6)	1
Baseline creatinine (µmol/L) before Vemurafenib–Cobimetinib	74.5 (74.2–88.2)	64 (54–74)	79 (70–97)	0.009
Baseline eGFR before Vemurafenib–Cobimetinib (ml/min/1.73 m²)	82 (70.5–93)	105 (94–114)	80 (69–90)	0.001
GFR > 90	17 (46.1)	9 (100)	8 (27.6)	
60 < GFR < 90	17 (43.6)	0	17 (58.6)	
45 < GFR < 60	3 (7.7)	0	3 (10.3)	
30 < GFR < 45	1 (2.6)	0	1 (3.5)	
15 < GFR < 30	0	0	0	
GFR < 15	0	0		
Pre-treatment comorbidities				
High blood pressure	10 (26.3)	2 (22.2)	8 (27.5)	1
Diabetes	2 (5.2)	0	2 (0.7)	1
Cardiovascular risk factor or disease	5 (13.1)	0	5 (16.7)	1
Nephrotoxic medications				
Non-steroidal anti-inflammatory drug	2 (5.3)	0	2 (6.9)	1
Renin–angiotensin–aldosterone system blocker	9 (23.7)	2 (22.2)	7 (23.3)	1
Diuretics	4 (10.5)	0	4 (13.8)	1
Proton pump inhibitor	13 (34.2)	3 (33.3)	10 (26.3)	1
Antibiotics	10 (26.3)	3 (33.3)	7 (24.1)	1
Skin rash	26 (68.4)	8 (88.9)	18 (62.1)	
Liver cytolysis	5 (13.1)	2 (22.2)	3 (10.3)	

Data are presented as median ± (Q1–Q3) or n (%)

GFR Glomerular filtration rate estimated by CKD EPI ml/min/1.73m², *(Q1–Q3)* Quartile 1–Quartile 3

Discussion

Here we report for the first time the occurrence of acute kidney injury with the combined treatment BRAF and MEK inhibitors, VMF and CB. Although no nephrotoxicity has been described in previous safety studies for this association, one case of granulomatous interstitial nephritis and dermatitis has been reported with the association of Dabrafenib and Trametinib (BRAF and MEK inhibitors) [15].

In the present cohort we found that AKI occurred only in 24% of patients, being mild and of early setting. Kidney biopsies were not performed based on previous experience with VMF, as AKI was considered due to tubular damages caused by VMF [3].

By comparison with our previous cohort of patients treated with VMF as a monotherapy, we observed a 60% reduction of AKI occurrence after the adjunction of MEK inhibitor [3]. Such a reduction of adverse known BRAF inhibitor-induced lesions has been showed previously for cutaneous toxicity, with a significant decrease of hyper-proliferative skin lesions, cutaneous squamous cell carcinoma and keratoacanthoma when MEK inhibitor was added to

Table 2 Comparison of two cohorts of patients treated by BRAF inhibitor monotherapy or combined therapy with MEK inhibitor

	VMF monotherapy[a] $n=74$	VMF–CB $n=38$	p value	Total $n=112$
AKI	44 (59.5%)	9 (23.7%)	<0.001	53 (47.3%)
Age (years)	63.5 (48.2–71.5)	55 (45.7–70)	0.21	59.5 (48–70.2)
BMI (kg/m²)	25.05 (22.4–27.7)	26.30 (24.2–30.1)	0.051	25.65 (23–28.7)
Gender			0.53 (Chi^2)	
Female	29 (39.2%)	18 (47.4%)		47 (42.0%)
Male	45 (60.8%)	20 (52.6%)		65 (58.0%)
Treatment line			0.045 (Fisher)	
1	53 (71.6%)	30 (78.9%)		83 (74.1%)
2	18 (24.3%)	3 (7.9%)		21 (18.8%)
3	1 (1.4%)	3 (7.9%)		4 (3.6%)
4	2 (2.7%)	2 (5.3%)		4 (3.6%)
Initial dose of Vemurafenib			0.002	
2cp	3 (4.1%)	0 (0.0%)		3 (2.7%)
3cp	0 (0.0%)	5 (13.2%)		5 (4.5%)
4cp	71 (95.9%)	33 (86.8%)		104 (92.9%)
Treatment duration in months	9 (5–24.7)	4.5 (2–6.7)	<0.001	6.00 (3.75–14.25)
High blood pressure	22 (29.7%)	10 (26.3%)	0.875	32 (28.6%)
Cardio vascular factors or diseases	33 (44.6%)	5 (13.2%)	0.002	38 (33.9%)
Diabetes	8 (10.8%)	2 (5.3%)	0.49	10 (8.9%)
Diuretics	15 (20.3%)	4 (10.5%)	0.301	19 (17.0%)
Renin–angiotensin–aldosterone system blocker	9 (12.3%)	9 (23.7%)	0.205	18 (16.2%)
Non-steroidal anti-inflammatory drug	19 (25.7%)	2 (5.3%)	0.018	21 (18.8%)
CKD with eGFR ≤ 60	8 (10.8%)	4 (10.5%)	1	12 (10.7%)
CKD with eGFR ≥ 60	13 (17.6%)	11 (28.9%)	0.252	24 (21.4%)
Basal serum creatinine µmol/L	72 (62–83)	74.5 (64.2–88.2)	0.338	73.5 (63–84)

Data are presented as median ± (Q1–Q3) or *n* (%)

AKI acute kidney injury, *CKD* chronic kidney disease, *(Q1–Q3)* Quartile 1–Quartile 3, *eGFR* estimated glomerular filtration rate estimated by CKD EPI ml/min/1.73m²

[a] Teuma et al. [3]

BRAF inhibitor [9–15]. The potential beneficial effect is sought to be due to the inhibition of downstream ERK [16].

The present analysis suggests that nephrotoxicity of BRAF inhibitor is still present with the use of MEK inhibitor association, but occurs less frequently, with reduced severity and clinical side effects and is not a cause for treatment withdrawal. Patients known to be at risk of AKI (by age and comorbidities) might be more protected by inhibition of paradoxical ERK activation.

The pathophysiology of BRAF nephrotoxicity is still under study. The role of ERK is suspected in renal disease. ERK is expressed and phosphorylated in renal fibroblast and tubular epithelial cells. Activation of ERK in renal fibrosis has been demonstrated with in vitro model, with correlation between phosphorylated ERK and tubular epithelial proliferation [17]. ERK could also be involved via its stimulatory effect on inflammatory cytokine production. IL-6 and TNFα, in particular, are known to play a role in tubulointerstitial nephritis [18, 19]. A reduction of cisplatin-induced renal injury by decreasing ERK1/2 phosphorylation and renal TNF-alpha level has also been described with MEK inhibitor [20]. Since a paradoxical downstream activation of ERK under BRAF inhibitors occurs, renal toxicity could be explained by these mechanisms. Decreasing of nephrotoxicity with adjunction MEK inhibitor strengthens this hypothesis, as shown in Fig. 1.

Alternatively, a potential effect of VMF–CB on creatinine metabolism could be discussed. Indeed, a false renal function decrease might be attributed to the medications by blocking the active tubular secretion of creatinine and subsequently increasing SCr without effective change in GFR. This mechanism has been elegantly shown by Hurabielle et al. with VMF [21]. Whether this occurs with the association of VMF–CB has not been reported yet.

Interestingly, there is another association of BRAF and MEK inhibitors, Dabrafenib and Trametinib, which has also shown nephrotoxic effects such as hyponatremia [22]. AKI and hyponatremia have also been reported

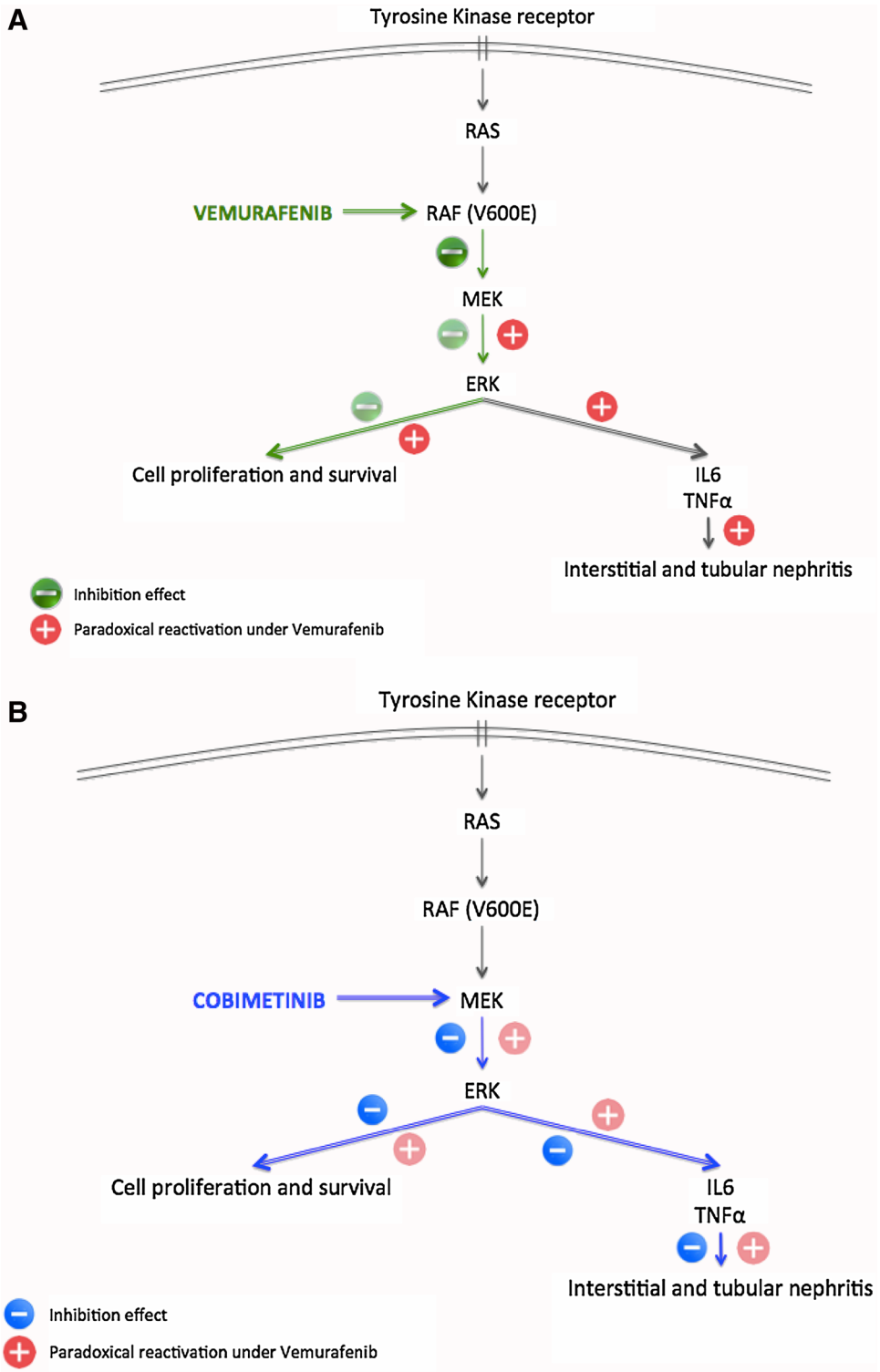

Fig. 1 Pathophysiology of AKI under Vemurafenib in Ras–Raf MAPK pathway (**a**) and how Cobimetinib association could reduce it (**b**). *AKI* acute kidney injury

under Dabrafenib monotherapy, suggesting a combined effect with the BRAF inhibitors rather than an isolated effect of a MEK inhibitor [23]. Granulomatous nephritis with Dabrafenib and Trametinib has been reported, suggesting side effects with different pathophysiologic mechanisms of toxicity [15]. The two-drug association has the same molecular targets and the same anti-tumor efficacy; so far there is no clear data of renal toxicity of Dabrafenib–Trametinib. This is the reason why it is difficult to speculate on potential renal toxic effect, which nevertheless could be comparable to that of VMF–CB.

This study has limitations. The retrospective design may lead to missing data concerning the confounding factors, in particular detailed renal investigations. Time after treatment withdrawal was too short to evaluate the potential reversibility of the nephrotoxicity. The sample size due to the monocentric nature of analysis also limited the statistical power. The present results were retrospectively compared to our prior cohort. However, this is the first cohort addressing the renal toxicity of a combined association of VMF and CB.

In conclusion, we report a reduced incidence and severity of nephrotoxicity of the association inhibitors of BRAF and MEK compared to a BRAF inhibitor monotherapy. When present, the acute kidney injury appeared early and of mild intensity, allowing to pursue the treatment. As renal toxicity is suspected to be linked to VMF tubular damages, our recommendations proposed in case of AKI with VMF can be used in case of AKI with combined VMF–CB [3].

Combined therapy with adjunction of MEK inhibitors also improve tumoral response and reduced occurrence of BRAF inhibitors' adverse effects, mediated by MEK paradoxical activation. Many other MAPK reactivation mechanisms are responsible for resistance to chemotherapy and tumoral escape. They represent new therapeutic targets to be explored and developed.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards All procedures in our study involving human participants were in accordance with the ethical standards with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Animal rights This article does not contain any studies with animals performed by any of the authors.

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