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Cytokine Release Syndrome During Sequential Treatment With Immune Checkpoint Inhibitors and Kinase Inhibitors for Metastatic Melanoma

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Summary: Switching from immunotherapy to targeted therapy in metastasized melanoma can be complicated by a cytokine release syndrome (CRS). CRS is a serious complication, which is induced by high levels of circulating cytokines, associated with T-cell engagement and proliferation, and results in a constellation of symptoms with variable organ involvement. We report 2 patients with BRAF V600 mutant melanoma who were previously treated with anti-PD-1 ± anti-LAG-3 antibodies and were switched to BRAF/MEK-inhibitors because of progressive disease. Both cases depict the complexity of interactions occurring during sequential treatment with immune checkpoint inhibitors and kinase inhibitors. Early identification and management of CRS is crucial to decrease its toxicity and improve safety of further drugs to be given in a therapeutic ladder.

Key Words: melanoma, immunotherapy, targeted therapy, cytokine release syndrome

(*J Immunother* 2018;00:000–000)

Current developments in immunotherapy and targeted therapy in advanced melanoma have dramatically improved progression-free survival and overall survival of treated patients.[1] However, remodeling of the treatment landscape has resulted in a new management complexity. Approximately 40%–65% of melanoma patients treated with anti-programmed death receptor-1 (anti-PD-1) agents as first-line fail to elicit an antitumor response (primary resistance); hence, further strategies are important in order to attain an efficient treatment.[2] In contrast, approximately 50% of the melanoma cases harbor an activating mutation in the BRAF oncogene, leading to the dilemma which drug group should be used first in these patients.[3] Eventually, patients have to switch from immunotherapy to targeted therapy. Because of the long half-life of immune checkpoint inhibitor antibodies, these patients are exposed to up to 4 drugs simultaneously, which can generate critical side effects.

Cytokine release syndrome (CRS) is thought to be a non–antigen-specific toxicity that can occur during treatment of immune-checkpoint inhibitors and BRAF/MEK-inhibitors (BRAFi/MEKi) when combined or applied shortly after immune checkpoint inhibitors.[4] Here, we report the cases of 2 patients with BRAF V600 mutant melanoma, who were treated with anti-PD-1 ± anti-LAG-3 checkpoint inhibitors and developed CRS after switching to BRAFi/MEKi.

CASE 1

A 47-year-old man presented with stage IV BRAF V600E mutated melanoma with multiple metastases of the right axillary lymph nodes and the lesser trochanter of the right side, which were documented by positron-emission tomography (PET-CT) in November 2016. He was enrolled in the Keynote-252 Study (NCT02752074), a phase 3 clinical trial of pembrolizumab (anti-PD-1) in combination with epacadostat (IDO-1 inhibitor) or placebo and randomized in the placebo arm. After 4 treatment cycles, a rapid progression of the disease was diagnosed in February 2017, prompting a therapy switch to the kinase inhibitors in March 2017.

Three weeks after treatment initiation with BRAFi/MEKi (vemurafenib 960 mg/BID and cobimetinib 60 mg/QD) the patient presented to our emergency department with pyrexia > 40°C, chills, and a diffuse maculopapular skin rash, without mucosal involvement (Fig. 1). Nikolsky's sign for skin fragility was negative. Clinical performance status was good (ECOG 1), despite hypotension and tachycardia, which was also accompanied by ventricular extrasystoles, renal insufficiency (creatinine, 206 μmol/L; N = 62–106 μmol/L) and liver abnormalities (grade 2 increase of ALT and AST up to 214 U/L and 145 U/L, respectively, N < 35 U/L). No complete blood count abnormalities were documented. Blood, urine, and stool cultures, as well as swabs for virus (HSV1/2, VZV, HHV-6) and bacteria were negative. Further serological investigations revealed increased CRP levels (max. 201 mg/L; N < 5 mg/L) and increased levels of IL-6 (66.4 pg/mL; N < 3.1 pg/mL), IFN-γ (312.7 ng/L; N < 15 ng/L) and TNF-α (6.50 pg/mL; N < 6.30 pg/mL). The histopathology of a skin biopsy showed an intact epidermis, with superficial cutaneous perivascular, lymphohistiocytic inflammation, and perifolliculitis (Fig. 1). The patient was treated with local and systemic corticosteroids. After 10 days, he was rechallenged with vemurafenib/cobimetinib in reduced dose in an in-patient setting, which caused a new fever episode with diarrhea and mild rash. After the third reexposition, no signs of intolerance were observed. The following staging showed a complete response. The dose of kinase inhibitors therapy could steadily be raised, and the patient remained on vemurafenib 960 mg/BID and cobimetinib 60 mg/d since.

CASE 2

A 48-year-old woman presented with stage IV BRAF V600E mutated melanoma of unknown primary with a tumor mass on her right thigh and several subcutaneous and lymph node metastases in the right groin. She was enrolled in the Keynote-034 study (NCT 02263508), a phase 3 clinical trial of talimogene laherparepvec (T-VEC) in combination with pembrolizumab from November 2016 until July 2017. Because of disease progression, a therapy switch to nivolumab (anti-PD-1) with an anti-LAG-3 antibody (BMS-986016) was initiated (NCT01968109). After 2 therapy cycles, she developed a generalized maculopapular rash, accompanied by pyrexia > 39°C, chills, tachycardia (111 bpm), and hypotension (88/44 mm Hg) (SIRS criteria 3/4) (Fig. 2). Clinical and radiologic signs suggesting infectious causes could be excluded. Blood and urine cultures were taken and an empiric antibiotic treatment with ciprofloxacin and clindamycin was initiated. The histopathology of a skin biopsy showed apoptotic keratinocytes with perivascular lymphohistiocytic inflammation. Liver function tests showed a grade 3 increase of ALT and AST (up to 404 U/L and 468 U/L, respectively; N < 35 U/L). A liver biopsy was performed, showing discrete liver inflammation with prominent periportal microvesicular steatosis and isolated ballooned hepatocytes. Laboratory renal function tests and complete blood count were normal, including both leukocytes and eosinophils. Further laboratory results revealed high CRP levels (max. 170 mg/L; N < 5 mg/L) and elevated circulating levels of IL-6 (38.4 pg/mL; N < 3.1 pg/mL) and IFN-γ (143.2 ng/L; N < 15 ng/L), indicating a possible CRS. High doses of oral and intravenous steroids (80 mg/d; 1 mg/kg/KG) were initiated. The inflammation parameters normalized steadily. The immunotherapy was permanently discontinued. The following staging showed progressive disease, prompting therapy switch to dabrafenib 175 mg/BID and trametinib 2 mg/QD in November 2017.

After 10 days, she presented again with the same clinical symptoms of pyrexia > 39°C, tachycardia (126 bpm) and leukopenia (1.64 G/L; N = 3.0–9.6 G/L) (SIRS criteria 3/4) (Fig. 2). A transient generalized macular rash occurred 2 days afterwards, accompanied by oral erosive mucositis, without evidence of skin fragility. A concomitant infection was excluded (cultures and radiology). Blood cytokine levels were drastically elevated; IL-6 > 300 pg/mL (normal N < 3.1 pg/mL), IFN-γ > 1000 ng/L (N < 15 ng/L), and TNF-α 15.6 pg/mL (N < 6.3 pg/mL). High dose of systemic corticosteroids was administrated intravenously (methylprednisolone 2 mg/kg/KG) and the inflammatory parameters normalized quickly. Dabrafenib and trametinib were discontinued. A treatment with alternative kinase inhibitors (vemurafenib 960 mg/BID and cobimetinib 60 mg/QD) was steadily initiated, in an in-patient setting.

She relapsed again with a third episode of pyrexia > 39 degrees and tachycardia (128 bpm) 10 days later (SIRS criteria 2/4). Her skin rash was accompanied with blisters and bullae, as well as erosive stomatitis, without circulating skin autoantibodies (Fig. 2). The histopathology of a skin biopsy showed an intact epidermis with isolated apoptotic keratinocytes, discrete perivascular edema and eosinophilic granulocytes. The laboratory results lacked again of peripheral eosinophilia. Taking into consideration that several drugs can elicit various immune-mediated responses, and because of the fact that dabrafenib, trametinib, and vemurafenib show a structural relationship to sulfonamides, which are known as possible inducers of drug hypersensitivity reactions, a lymphocyte transformation test (LTT) of the medications was performed, which showed no T-cell proliferation in vitro. A genetic susceptibility to drug hypersensitivity could also be excluded (HLA-B 38 negative). Elevated cytokine levels were again documented; IL-6 67.5 pg/mL (normal N < 3.1 pg/mL) and IFN-γ 2236 ng/L (N < 15 ng/L). TNF-α was normal (5.73 pg/mL; N < 6.3 pg/mL). After the exclusion of a concomitant infection (cultures, radiology), high doses of systemic steroids were administered again, but without any normalization of the skin condition. On January 04, 2018 and still under steroids, the patient received a dose of tocilizumab 400 mg, with a dramatic improvement of the inflammatory condition. Vemurafenib and cobimetinib were permanently discontinued. The following staging showed a stable disease.

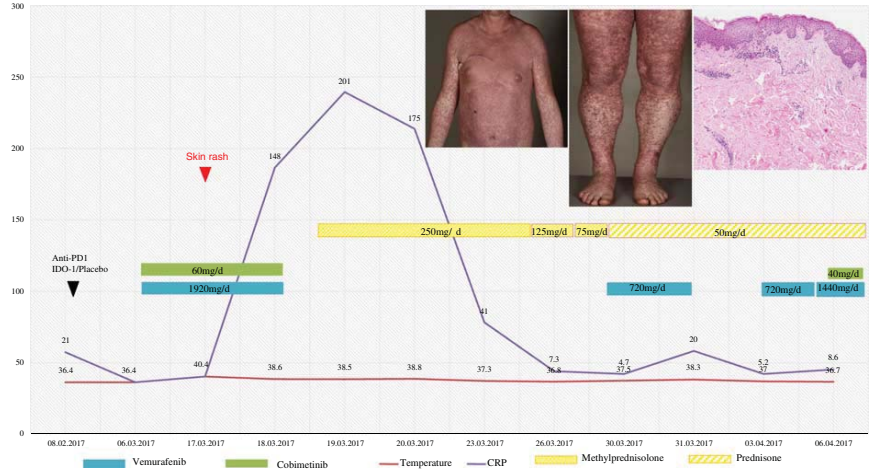

FIGURE 1. Temporal demonstration of temperature-raise and c-reactive protein (CRP)-raise in association with anti-PD-1 and BRAFi/MEKi treatment. The skin lesions included multiple erythematous macules and papules, without mucosal involvement. Histopathology showed intact epidermis, with superficial cutaneous perivascular, lymphohistiocytic inflammation, and peri/folliculitis.

DISCUSSION

We describe 2 cases of CRS defined by an extensive cutaneous rash, organ dysfunction (renal, cardiac, and hepatic), and increased serum cytokines (IL-6, IFN-γ, and TNF-α) induced by immune checkpoint inhibitors and further facilitated by targeted therapy following immune checkpoint blockade (anti-PD-1). Both cases had a strong immune activation with elevated circulating levels of several proinflammatory cytokines, which increase the susceptibility to systemic reactions (CRS).

CRS is characterized by the release of a variety of cytokines, such as INF-γ, TNF-α, IL-1β, IL-2, and IL-6

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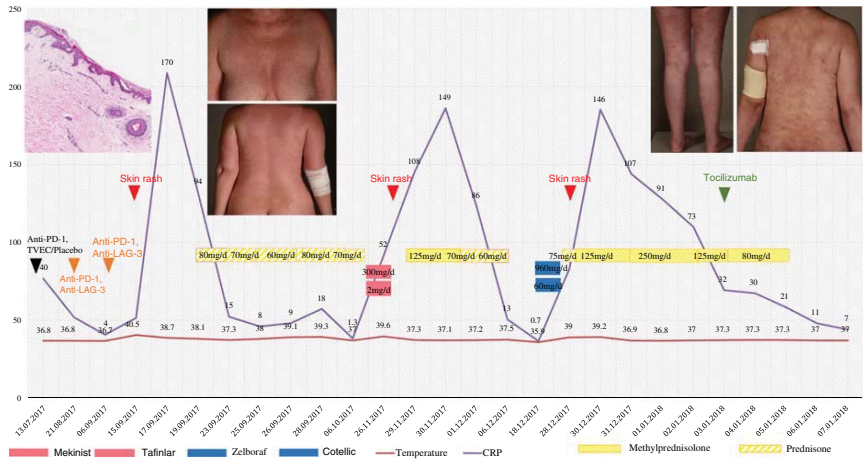

FIGURE 2. Temporal demonstration of temperature-raise and c-reactive protein (CRP)-raise in association with anti-PD-1, anti-LAG-3, and BRAFi/MEKi treatment. Skin lesions with erythematous macules and papules (first episode), compared with hyperpigmented macules after the administration of tocilizumab (third episode). Histopathology with apoptotic keratinocytes with perivascular lymphohistiocytic inflammation (first episode).

caused by an overshooting immune response mediated by T cells, B cells, NK cells, and macrophages.[5] This cytokine storm can induce endothelial and organ damage, resulting in microvascular leakage, heart failure, and even death. It is clinically defined by a constellation of inflammatory symptoms such as nausea, headache, tachycardia, hypotension, rash, and shortness of breath [according to the CTCAE version 4.0 (National Cancer Institute Common Terminology Criteria for Adverse Events)].

In both cases, because of the constellation of symptoms including skin rash, fever, and organ involvement, a diagnosis of a delayed hypersensitivity syndrome to the kinase inhibitors [drug rash with eosinophilia and systemic symptoms (DRESSs)] was initially proposed.[6] It is known that dabrafenib, trametinib, and vemurafenib have common structural properties with sulfonamides, which are important potential triggers of DRESS. Although we know that both reactions share a common pathophysiologic pathway of T-cell and innate immune cell activation, immunologic stress, and release of common key cytokines, our understanding of the exact mechanisms that promote these phenomena remains poor. CRS represents an aberrant immune response because of provoking constellation at the interface between immunotherapy and targeted therapy, whereas a DRESS is a severe allergic (type IV) drug-induced reaction probably as a result of modification of host antigens by haptens or through viral triggers. In both patients, the laboratory results lacked the frequently observed eosinophilia of DRESS as well as other blood abnormalities, and there was no reactivation of human herpes virus 6 (HHV-6) or lymphadenopathy, which would be typical for DRESS. Furthermore, the reaction in both patients occurred about 14 days after starting the medication with kinase inhibitors, which would be a very short and untypical time span for the development of a DRESS. Also, the LTT, which was performed in one patient, was negative. Because of these reasons the diagnosis of a CRS was much more likely than the one of a DRESS. The differential diagnosis also included a systemic inflammatory response syndrome (SIRS). The SIRS criteria were in both cases met; yet the definition of SIRS simply reflects a clinical expression of an adaptive response to inflammation with inadequate specificity and sensitivity. A sepsis could also be excluded. All in all, the sequence of the drug administration and the laboratory constellation with rapid increase of serum cytokines, particularly of IFN-γ, are strong indicators that support the CRS diagnosis.

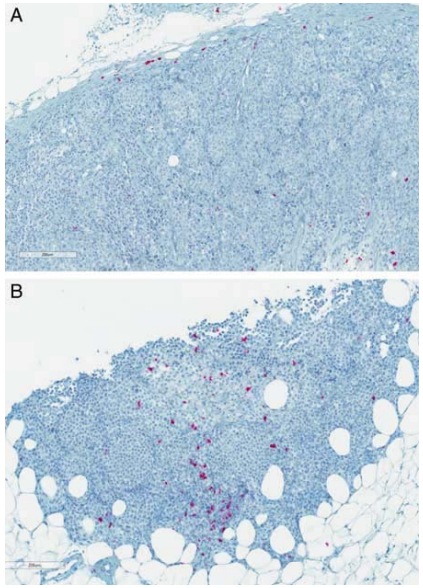

FIGURE 3. Comparison of immunohistochemical stainings for $CD8^+$ during anti-PD-1 therapy (A) and after starting kinase inhibitors therapy (B). The second finding shows increased $CD8^+$ T-cell infiltrates and numerous activated macrophages.

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Currently, there is increasing evidence implying that the sequential combination of immunotherapy and targeted therapy in advanced stage melanoma patients may be associated with an exaggerated immune response.[7] In vivo and in vitro data suggest, that MAPK pathway inhibition treatment is associated with increased melanoma antigen expression, increased $CD8^+$ T-cell infiltration, decreased immunosuppressive cytokine production, and increased PD-L1 expression, thus having an immunomodulatory effect on the tumor microenvironment.[4] In the first case, we ran serial biopsies comparing the histopathologic findings during the immunotherapy and after starting the kinase inhibitors, which showed an increased T-cell infiltrate and increased $CD8^+$ T cells, thus confirming this theory (Fig. 3). In contrast, cancer immunotherapy intends to boost host immune responses against tumors by blocking T-cell inhibitory molecules. Targeting the inhibition of either the cytotoxic T-lymphocyte-associated protein (CTLA-4) or the PD-1 has resulted in durable responses in the treatment of melanoma.[8] Further combination of immunotherapies with several checkpoint inhibitors, including lymphocyte activation gene-3 (LAG-3), may provide a synergistic improvement in T-cell activity.[9]

The management and treatment of CRS can be very challenging. Administration of methylprednisolone intravenously is the recommended first-line treatment in patients with mild to moderate symptoms. Several cytokine antagonists have been described as potential therapeutic candidates. IL-6, a pleiotropic, acute phase cytokine that augments the immune response through B-cell differentiation and autoantibody production, has been firstly described as a therapeutic target. High IL-6 levels have been described in patients with severe CRS as a sequence of the T-cell proliferation because of T-cell engaging treatment and inflammatory process.[5] The use of monoclonal antibodies blocking IL-6 receptors, such as tocilizumab, is recommended for the management of severe symptoms, causing an immediate and full inhibition of c-reactive protein (CRP) production.[10] Other therapeutic approaches targeting TNF-α (etanercept), IL-2R (daclizumab), and IL-1 (anakinra, IL-1RA) may also have a potential role in managing of the syndrome, but their indication, efficacy, and limitations have not been evaluated yet. However, the use of tocilizumab is recommended, regardless the levels of TNF-α or IL-1.[5]

To date, multiple studies are being conducted to investigate combination treatment with BRAF/MEK-inhibitors and checkpoint inhibitors, either administered simultaneously or in sequence (NCT02130466, NCT02967692, and NCT02908672). However, whether this combination will improve the (complete) response rate and the median survival in melanoma patients needs to be further elucidated. Although combination of different therapeutic agents seems to increase efficacy, they are also expected to be associated with higher toxicity, thus requiring close monitoring of patients.

CONFLICTS ON INTEREST/FINANCIAL DISCLOSURES

R.D. has intermittent, project focused consulting and/or advisory relationships with Novartis, Merck Sharp & Dhome (MSD), Bristol-Myers Squibb (BMS), Roche, Amgen, Takeda, Pierre Fabre outside the submitted work. J.M. has temporary advisory relationship and receives travel support from MSD and Merck. M.U.-M. has received honoraria from Bristol-Myers Squibb (BMS), Novartis, Amgen and Roche. The remaining authors declare that they have nothing to disclose.

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