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Toxicities with targeted therapies after immunotherapy in metastatic melanoma

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Abstract

Over the last decade melanoma treatment has taken rapid strides with the advent of immunotherapies and targeted agents. With these new agents there has been a significant improvement in patient survival. However, these new treatment options may sometime lead to unanticipated side-effects which make these treatments challenging to administer and monitor. In preclinical studies, BRAF and MEK inhibitors have shown to modulate tumor microenvironment and potentiate immunotherapies. Therefore, sometimes patients who progressed on immunotherapies develop immune toxicities with these targeted agents due to the long half-life of monoclonal antibodies. Herein we present our institutional experience with regards to these unexpected toxicities with targeted agents in patients who had prior treatment with immunotherapies. This case series lays out the various side-effects along with details of their management, outcomes and patient response.

Keywords

Melanoma; immunotherapy; BRAF inhibitor; MEK inhibitor; immune toxicities

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Conflicts of Interest

ADB has received honorarium from Novartis and Roche. He is on advisory board of Novartis and Roche and travel support from Novartis and Roche. YZ is on advisory board of Amgen, Castle Biosciences, Eisai, Exelixis, Novartis, Pfizer and Roche/Genentech. He has travel support from Newlink Genetics. MM is on advisory board for Bristol-Myers Squibb, Eisai, EMD Serono, Genentech/Roche, Novartis and Blueprint Solutions. NG and US did not declare any competing conflicts of interest.

Introduction:

The advent of immune checkpoint inhibitors and agents targeting BRAF-MEK pathway has revolutionized the management of metastatic melanoma.[1] Nivolumab and pembrolizumab, two monoclonal antibodies targeting programmed cell death 1 (PD-1) protein have been approved as a single agent for metastatic or unresectable melanoma.[1,2] Nivolumab is also approved in combination with ipilimumab, a monoclonal antibody targeting cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) as a frontline treatment for metastatic melanoma.[1,2] In patients with activating $BRAF^{V600}$ mutation, vemurafenib and dabrafenib, two BRAF inhibitors are approved both as single agents as well as in combination with MEK inhibitors (vemurafenib with cobimetinib and dabrafenib with trametinib).[1,2]

Due to availability of two different class of agents as first line in patients with activating $BRAF^{V600}$ mutated melanomas, there exists a dilemma with regards to how to sequence these agents in clinical practice. A recent retrospective review did not find any difference sequencing anti-PD1 therapies either before or after BRAF inhibition.[2] However, we noticed many patients who received targeted therapies after progression on anti PD-1 based agents developed significant toxicities some of which mimicked immune reactions. We conducted a review of patients treated at our institution to identify and characterize these toxicities.

Methods and Materials:

The medical records of all metastatic melanoma patients enrolled in Melanoma, Skin & Ocular Repository (MAST) at the University of Iowa between 1/1/2012 and 7/31/2017 were reviewed. Individuals who had previously been on immunotherapy were identified and then a thorough chart review was performed to identify patients who had been treated with BRAF and MEK inhibitors following immunotherapy.

Results:

Of 1264 patient charts reviewed, 20 patients received BRAF/MEK inhibitors after anti PD-1 therapy (of which 18 patients received it within 3 months of the last dose of anti-PD-1 therapy) and 11 patients developed toxicities. These patients are presented below. Rest 2 patients received them after 6 months of the last dose of immunotherapy and therefore were excluded from analysis.

Case Reports:

Patient 1

A 48-year-old male was treated with pembrolizumab after diagnosis of $BRAF^{V600E}$ positive metastatic melanoma. He progressed after 4 cycles and thereafter was treated with pembrolizumab in combination with CMP-001, a Toll-Like Receptor 9 (TLR9) agonist. He again progressed after 4 cycles. He was subsequently started on vemurafenib and cobimetinib, and developed grade 3 rash twelve days after initiation of therapy. Vemurafenib and cobimetinib were stopped and prednisone 1 mg/kg was initiated. After 3 weeks prednisone, the taper was started. After one week of initiation of taper, the patient started

vemurafenib only at 960 mg twice daily. However patient developed grade 3 rash just after one dose of vemurafenib. Prednisone 1 mg/kg was restarted and vemurafenib was discontinued. Follow up CT scan 2 months after initiation of treatment showed partial response. He developed progressive disease in brain after 85 days.

Patient 2

A 54-year-old female was started on vemurafenib and cobimetinib for treatment of $BRAF^{V600E}$ positive metastatic melanoma after progression on pembrolizumab with SD-101, a TLR9 agonist, of which she had previously received three cycles. She developed grade 3 rash nine days after initiation of treatment. She was initially treated with oral steroids and vemurafenib and cobimetinib were held for 49 days, with resolution of rash. She was started on vemurafenib 960 mg twice daily only and again developed diffuse erythematous reaction, with facial swelling and ocular irritation after just one dose. Vemurafenib was held. One week later after resolution of symptoms she was again started on vemurafenib 240 mg BID which led to recurrence of diffuse erythematous reaction, with facial swelling and ocular irritation which occurred just after one dose. Five weeks later a trial of one dose of 240 mg vemurafenib with 20 mg cobimetinib was made which led to recurrence of whole body rash. Vemurafenib and cobimetinib were ultimately discontinued. Two weeks later she was started on dabrafenib and trametinib, with no recurrence of toxicities. She had a partial response to treatment, with progression-free survival of 195 days and is currently undergoing treatment.

Patient 3

A 54-year-old female with $BRAF^{V600E}$ positive metastatic melanoma was treated with pembrolizumab with IDO inhibitor. She developed progressive disease after five months of therapy. She was subsequently started on vemurafenib 960 mg twice daily and cobimetinib 60 mg daily but developed grade two nausea and vomiting after 49 days of therapy. Her nausea and vomiting initially resolved after holding vemurafenib and cobimetinib for ten days. Upon restarting these medications, the dose of cobimetinib was reduced to 40 mg daily. She had no recurrence of toxicities following this dose reduction. She had partial response to therapy and remains on vemurafenib and cobimetinib with progression-free survival of 136 days (treatment ongoing).

Patient 4

A 73-year-old male was started on dabrafenib 150 mg BID and trametinib 2 mg daily for treatment of $BRAF^{V600E}$ positive metastatic melanoma that progressed after four cycles of pembrolizumab with IDO inhibitor. Twenty-two days after starting this medication regimen, he developed grade 2 fever, requiring interruption of the treatment. Dabrafenib and trametinib were held for 14 days and then restarted with dose reduction to dabrafenib 100 mg BID and trametinib 1.5 mg daily. Fever completely resolved with the aforementioned dose reductions. He had partial response to therapy. He later developed new brain lesion. The progression-free survival was 111 days.

Patient 5

A 31-year-old female with a history of $BRAF^{V600E}$ positive melanoma with peritoneal and brain metastasis was treated with two cycles of ipilimumab and nivolumab. She was admitted with abdominal pain and was subsequently started on trametinib 2 mg daily and dabrafenib 150 mg twice daily along with 60 mg prednisone. She developed grade 3 pneumonitis just after one day of starting combination treatment with BRAF and MEK inhibitors. She required intensive care monitoring for acute respiratory failure. Prednisone was changed to intravenous 125 mg methylprednisolone daily. Dabrafenib was held for three days and trametinib was discontinued entirely, as there was concern that they were responsible for the pulmonary toxicity. After one week of high dose steroid treatment (125 mg IV methylprednisolone), she was restarted on prednisone 60 mg daily. After fourteen days she was started on a prednisone taper and then was re-admitted to the hospital for hypoxia, so prednisone 1 mg/kg was restarted. Over the following three weeks, the steroids were tapered off without worsening of pneumonitis or development of hypoxia. Follow-up PET and brain MRI showed partial response to therapy. She had a progression-free survival of 68 days.

Patient 6

A 37-year-old male with $BRAF^{V600E}$ positivemetastatic melanoma was initially treated in a clinical trial of pembrolizumab with IDO inhibitor. He progressed after 15 cycles with development of multiple new brain lesions. After whole brain radiation, he was switched to another clinical trial composed of vemurafenib 960 mg BID, cobimetinib 60 mg daily, and decitabine 0.1 mg/kg twice weekly. He developed grade 3 elevation of liver enzymes 41 days after initiation of therapy. He was started on dexamethasone 4 mg daily and the treatment was held for 16 days and then restarted at reduced dose of vemurafenib 720 mg BID and cobimetinib 40 mg daily. Dexamethasone was tapered and then discontinued after 23 days. Twenty-eight days after restarting therapy he again developed a grade 3 elevation of liver enzymes. This was again managed by holding therapy for 21 days and then restarting with dose reductions of medications, including vemurafenib to 480 mg BID and cobimetinib 20 mg daily. After 35 days of therapy, he again developed grade 3 LFT elevation, so medications were held for 21 days. He was then restarted on single-agent therapy only with vemurafenib 480 mg BID, due to persistently elevated liver enzymes. Cobimetinib 20 mg daily was added to this regimen after 21 days but had to be changed to 20 mg every other day after one week of therapy due to repeated elevation of liver enzymes. With this medication regimen, he had no further development of toxicities. He had stable disease with progression-free survival of 238 days before undergoing disease progression in brain.

Patient 7

An 82-year-old male with $BRAF^{V600R}$ positive melanoma was started on dabrafenib 150 mg BID and trametinib 2 mg daily for treatment of stage IV disease after progression on 7 cycles of pembrolizumab with IDO inhibitor and then 11 cycles of pembrolizumab with CMP-001, a TLR9 agonist. He developed grade 2 nausea, poor appetite, and chills after 42 days of therapy. This was managed by holding dabrafenib and trametinib for 9 days and then restarted at full dose. However, these were discontinued again after 2 weeks due to nausea

and chills. At that point, the BRAF and MEK inhibitors were discontinued for approximately seven months, at which point a CT scan showed a new posterior neck mass. Given these findings, dabrafenib 150 mg BID and trametinib 2 mg daily were restarted. After 21 days he developed diarrhea and dabrafenib and trametinib were held for three days. They were restarted with dose reduction of dabrafenib 100 mg BID and trametinib 1.5 mg daily. Dabrafenib and trametinib were ultimately discontinued 39 days later due to nausea, poor appetite, and weakness. He had a partial response to therapy. He progressed after 408 days.

Patient 8

A 73-year-old female was started on vemurafenib 960 mg BID and cobimetinib 60 mg daily after progression of $BRAF^{V600E}$ positive metastatic melanoma on ipilimumab and 34 cycles of pembrolizumab (31 cycles of pembrolizumab alone, 3 cycles of pembrolizumab + CMP-001). She developed a grade 3 cytokine release syndrome consisting of mucositis, oral candidiasis, facial rash, and weakness after 15 days of oral therapy. Her home hydrocortisone, which she was on for management of adrenal insufficiency was increased from 40 mg BID to 100 mg q8h x 48 hours and then 50 mg q8h. In addition, vemurafenib and cobimetinib were discontinued. By 19 days after developing cytokine release syndrome, her hydrocortisone was able to be tapered down to 20 mg daily. Toxicities resolved after steroid treatment and discontinuing vemurafenib and cobimetinib and these medications were not restarted. She had a partial response to therapy, with progression-free survival of 181 days while off treatment (no progression to date).

Patient 9

A 54-year-old male with $BRAF^{V600E}$ positive metastatic melanoma who progressed after 6 cycles of pembrolizumab with IDO inhibitor and 3 cycles of ipilimumab with IDO inhibitor combination was started on vemurafenib 960 mg BID, cobimetinib 60 mg daily, and decitabine 0.1 mg/kg twice weekly. He developed grade 3 cytokine release syndrome with altered mental status 17 days after starting this new therapy. He was admitted to the hospital and started on hydrocortisone 100 mg q8h initially, which was then transitioned to prednisone 1 mg/kg daily. Vemurafenib, cobimetinib, and decitabine were held. However, on prednisone 1 mg/kg daily he developed fever, diffuse rash, and erythema of the face. This resolved with increasing prednisone to 1 mg/kg twice daily. Steroid taper was started after 10 days and completed after 56 days. After holding the treatment for 39 days, vemurafenib, cobimetinib, and decitabine were restarted with dose reduction of vemurafenib to 720 mg twice daily and cobimetinib to 40 mg daily. Twenty-two days after restarting these medications he developed arthralgia, hypotension, weakness, and fever. He was again started on hydrocortisone 100 mg q8h with resolution of toxicities after 2 doses. This was continued for 48 hours and then transitioned to prednisone 60 mg daily, which was tapered off over 12 days. Vemurafenib, cobimetinib, and decitabine were discontinued indefinitely. He had partial response of disease to treatment and remains progression free for 422 days.

Patient 10

A 67-year-old male with $BRAF^{V600K}$ positive metastatic melanoma developed progressive disease with brain metastasis after 7 cycles of pembrolizumab alone and 8 cycles of

pembrolizumab with CMP-001. After completing whole brain radiation he was started on vemurafenib 960 mg BID only. One week later he developed grade 1 acute kidney injury, grade 2 hypercalcemia, and fatigue. Intravenous fluids and pamidronate were administered. Vemurafenib was held for 3 days after which it was restarted at 960 mg twice daily with cobimetinib 60 mg daily. He developed grade 3 rash 22 days after re-initiation of therapy. This was treated with prednisone 60 mg daily for 7 days and BRAF and MEK inhibitors were held for one week. Rash resolved with steroids. Treatment was reinitiated with a reduced dose of vemurafenib of 720 mg twice daily and cobimetinib 40 mg daily and rash did not recur. His disease remained stable for 104 days before progression of metastatic lesions.

Patient 11

A 28-year-old female with stage IV $BRAF^{V600E}$ positive melanoma had disease progression after 4 cycles of ipilimumab and 5 cycles of pembrolizumab. She developed brain metastasis which was treated with radiation therapy. She was started on dabrafenib 150 mg twice daily and trametinib 2 mg daily. She developed a grade 3 rash only 14 days after starting therapy. However, treatment was discontinued as patient continued to have numerous seizures secondary to metastatic brain lesions. She was subsequently enrolled in hospice care.

Discussion:

In phase III studies combination of BRAF and MEK inhibitors has been associated with significant grade 3 and 4 toxicities in the range from 32% to 75%.[3–5] However certain toxicities like cytokine release syndrome and pneumonitis are unusual with these targeted agents and are more consistent with immune toxicities. We hypothesize that these toxicities ranging from nausea, vomiting, and fatigue to rash, pneumonitis and cytokine release syndrome might just be different parts of an extended spectrum of immune-mediated reaction.

In preclinical studies, BRAF inhibitors have shown to modulate the tumor microenvironment to potentiate immunotherapy by improved antigen presentation, increase in expression of melanoma antigens like gp100 and MART1, decreased tumor-secretion of immune suppressive cytokines, increased T-cell recognition of tumor antigens and enhanced migration of immune effector cells to tumors.[6,7] Similarly, MEK inhibitors have shown to increase effector CD8+ T-cells within the tumor, protect tumor-infiltrating $CD8^+$ T cells from death from chronic T cell receptor stimulation while preserving their cytotoxic activity and upregulate tumor antigen expression and preservation.[6]

Pembrolizumab and nivolumab have a long half-life which ranges from 12–22 days.[8,9] Therefore modulation of tumor microenvironment by BRAF and MEK inhibitors in patients with prior exposure to immunotherapy, can result in immune-mediated responses or toxicities even months after immunotherapy exposure. In a prior report, three patients received BRAF inhibitor either alone or in combination with MEK inhibitor following unsuccessful treatment with immunotherapy.[10] All these three patients not only developed autoimmune symptoms ranging from vitiligo to rash and hypophysitis but also achieved rapid durable complete response.[10]

This retrospective chart review identified twenty patients with BRAF mutated metastatic melanoma who were treated at the University of Iowa Hospitals and Clinics with immunotherapy followed by BRAF and MEK inhibitor therapy. Of those twenty patients, eighteen patients received BRAF/MEK inhibitor therapy within three months of immunotherapy, with a median duration of 28 days (range 8 to 82) in between therapies. The other two patients received BRAF/MEK inhibitors more than 6 months later and were considered outliers. Of these 18 patients, 11 developed toxicities needing dose modifications or delays. Of the evaluable 10 patients (excluding 1 patient who was discharged to hospice due to uncontrolled seizures), 8 had partial response and two had stable disease. Similarly, of the 7 patients who did not develop adverse reactions, there was one complete response, three partial responses, one stable disease, and two patients had progressive disease. Therefore, responses were seen in both cohorts.

In our study patients, 8 and 9 who developed cytokine release syndrome continue to be progression-free months after discontinuing BRAF and MEK inhibitor. Similarly, patient 7 had a prolonged period of progression-free survival without any treatment. These durable responses are characteristic of immune agents. However, our retrospective analysis did not show that patients who developed toxicities always developed durable responses. For example, patient 3 who developed grade 3 pneumonitis just after one day of BRAF and MEK inhibitor treatment had progressive disease after 68 days. We found that in most cases disease progressed in the brain which is an immune privileged site.

Another interesting finding was in patient 2 who had to discontinue vemurafenib and cobimetinib due to toxicities but safely tolerated dabrafenib and trametinib. It is possible that different BRAF/MEK combinations have unintended unknown targets and toxicities and switching them in case of unacceptable toxicities is an option.

Multiple studies like NCT02130466, NCT02908672, and NCT02967692 are currently exploring the utility of a combination of immunotherapy and BRAF/MEK inhibitor therapy. It is thought that activating an immune response in addition to blocking oncologic signaling can induce a more durable response.[11] It might be possible that these combinations can lead to severe toxicities. A prior study of ipilimumab with vemurafenib was discontinued due to development of grade 3 elevations in aminotransferase levels.[12] Another interesting option might be intermittent BRAF and MEK inhibitors during immunotherapies to increase antigen presentation and modulate tumor microenvironment while avoiding development of resistance to BRAF/MEK inhibitors. In summary, further research needs to be done to better understand the interaction between immunotherapy and BRAF and MEK inhibitor therapy to determine what is the optimal way to treat patients with melanoma.

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2. Clinical data was obtained through the University of Iowa Melanoma, Skin & Ocular Repository (MaST), an Institutional Review Board–approved biospecimen repository.

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Table 1

Toxicities, outcomes, and patient response with BRAF and MEK inhibitors after immunotherapy

Pt. No.	BRAF status	Prior therapies	Duration between last anti PD-1 therapy and initiation of BRAF-MEK inhibitor (days)	Reaction	Immune mechanism as underlying cause	Duration between reaction and initiation of BRAF-MEK inhibitor	Response	Progression-free survival (days)	Overall survival (days)
1	V600E	Pembrolizumab, pembrolizumab+CMP001	21	G3 rash	Possible	12	PR	85	140
2	V600E	pembrolizumab+SD-101	27	G3 rash	Possible	9	PR	195*	NA
3	V600E	Pembrolizumab+IDO inhibitor	13	Grade 2 nausea and vomiting	Unlikely	49	PR	136*	NA
4	V600E	Pembrolizumab+IDO inhibitor	85	Grade 2 fever	Unlikely	22	PR	111	131
5	V600E	Ipilimumab and nivolumab	31	Grade 3 pneumonitis	Possible	1	PR	68	81
6	V600E	Pembrolizumab+IDO inhibitor	56	Grade 3 liver enzyme elevation	Unlikely	41	SD	238	398
7	V600R	Pembrolizumab with IDO inhibitor, pembrolizumab with CMP-001	12	Grade 2 nausea, poor appetite, and chills	Possible	42	PR	408	NA
8	V600E	Ipilimumab, pembrolizumab, pembrolizumab + CMP-001	27	Grade 3 cytokine release syndrome	Probable	15	PR	181+	NA
9	V600E	pembrolizumab + IDO inhibitor, ipilimumab +IDO inhibitor	28	Grade 3 cytokine release syndrome	Probable	17	PR	422+	NA
10	V600K	Pembrolizumab, pembrolizumab+CMP001	54	Grade 3 rash	Possible	22	SD	104#	110#
11	V600E	Ipilimumab, pembrolizumab	25	Grade 3 rash	Possible	14	NA	UNK	335

* - On treatment and continue to be progression-free

- Duration in days since starting vemurafenib

+ - Continue to be progression-free without any treatment