CASE REPORT

Challenges in the use of immunotherapy in metastatic melanoma

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SUMMARY

A 65-year-old man with metastatic melanoma was started on immunotherapy, switched to alternative targeted therapy and developed disseminated intravascular coagulation. This case underscores the complexity of interpreting and managing side effects of novel therapies in cancer care, identification of progression versus pseudoprogression and challenges in sequencing treatments in metastatic melanoma.

were notable for worsening transaminitis and significant elevation of alkaline phosphatase and total bilirubin. Other laboratory results demonstrated a leucocytosis, as well as a normocytic anaemia requiring two transfusions. Magnetic resonance cholangiopancreatography (MRCP) showed a significant increase in tumour burden and mild left hepatic ductal dilation without any obvious obstruction (see [figures 1 and 2](#)).

BACKGROUND

Recent discoveries in cancer therapy generate enthusiasm and new challenges in management. Specifically, immunotherapy is increasingly used across all malignancies with impressive results. Starting with melanoma, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) checkpoint inhibitors and programmed cell death 1 (PD-1) checkpoint inhibitors provide more treatment options in the setting of metastatic disease. These treatments can provide dramatic improvements in progression free and overall survival, as shown by recent clinical trials that demonstrate durable responses among metastatic patient populations that previously carried grim prognosis.^{1–4} Furthermore, the addition of targeted molecular therapies, with BRAF inhibitors, has changed the landscape of management of metastatic melanoma. Along with the excitement of new therapeutic options also comes challenges with management. Specifically, managing side effects and monitoring progression leave many unanswered questions. We report the case of a man with metastatic melanoma who helps to underscore the challenges in proper management in the era of targeted treatment options.

CASE PRESENTATION

A 65-year-old man was diagnosed with recurrent maxillary sinus melanoma extending to adjacent facial and cranial structures. Imaging was notable for innumerable hepatic masses, consistent with metastasis on liver biopsy, which confirmed stage 4 disease. He underwent palliative treatment with excision of his primary tumour and five cycles of radiation postoperatively. Given the extent of disease burden in the liver and high lactate dehydrogenase (LDH, 1085 U/L), he was started on dual therapy with ipilimumab and nivolumab. Two weeks after cycle 1 of immunotherapy, he presented to the hospital for symptoms of generalised fatigue and right upper quadrant abdominal pain. On presentation, he was noted to have new ascites and labs

OUTCOME AND FOLLOW-UP

Owing to the worsening severity of his hepatic tumour load, the decision was made to switch chemotherapy to dabrafenib and trametinib, as prior studies were positive for BRAF V600 mutation. [Table 1](#) shows the relevant laboratory studies. Following initiation of therapy, the patient clinically improved and his liver function tests improved. On day 5 of therapy, however, he was noted to have an acute anaemia and thrombocytopenia without evidence of haemolysis. Labs were also significant for prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT) with decreased fibrinogen and elevated D-dimer, concerning for disseminated intravascular coagulation (DIC). However, clinically, the patient appeared well, with stable haemodynamics and without signs of infection. He required multiple transfusions, including packed red blood cells (6 units), and cryoprecipitate (70 units) over the course of 3 days. He was started on high dose steroids (prednisone 2 mg/kg) due to concern for an autoimmune-mediated process. Therapy with dabrafenib and trametinib was continued. He achieved dramatic improvement in all parameters over the next several days, for which his steroid doses were tapered, and he was discharged shortly thereafter to a rehab facility. The following week, he was seen in an outpatient clinic without any symptoms or significant abnormalities in his laboratory values.

DISCUSSION

The treatment strategies for metastatic melanoma have evolved rapidly in recent years. Treatment is no longer limited to chemotherapy, but now includes targeted therapies such as BRAF and MEK inhibitors, as well as immunotherapies such as PD-1 and CTLA-4 checkpoint inhibitors. Significant improvement in patient outcomes was initially seen with monotherapy of these new agents.^{1–4} However, during the last 2 years, multiple studies have been published using combinations of targeted agents or immunotherapies.^{1 5–7} These combinations have been shown to result in even more improvements in

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Figure 1 Abdominal MRI pretreatment.

progression-free survival, overall response rates and, in some cases, overall survival.

Along with these significant advances in patient outcomes, there are additional management challenges, specifically a new spectrum of side effects not previously seen with cytotoxic therapies, pseudoprogression of disease on radiologic imaging and difficulty in determining the appropriate sequence for the use of these therapies. These challenges are underscored in the management of the case report presented here. This patient received two different combination therapies and developed significant life-threatening side effects, including DIC and pancytopenia, and was treated with steroids with complete recovery of his blood counts.

First, it is well known that immunotherapies produce side effects, often referred to as immune-related adverse events (irAEs), which are not seen with historical cytotoxic chemotherapies. The most common side effects reported in melanoma patients treated with combination CTLA-4 and PD-1 receptor antibodies include diarrhoea, rash, fatigue and pruritus. Immune-related side effects may occur with a lower frequency, but can be life-threatening if not diagnosed and treated early. These typically include immune effects on the skin, gastrointestinal tract, endocrine organs and liver.⁶ Immune-related haematological adverse events were not reported in the initial trials, but have been published in recent case reports, including red cell aplasia, neutropenia and

pancytopenia.^{8–10} Treatment of irAEs typically involves cessation of immune therapies and treatment with local or systemic immunosuppression with steroids.

The most common side effects seen in trials with the combination of BRAF and MEK inhibitors are fever, fatigue, headache, nausea, vomiting, diarrhoea and chills.^{5 11} In the initial trial published in *NEJM* in 2014, there were three grade 4 haematological events, including anaemia, decreased lymphocyte count and pancytopenia. Additional details about these haematological events were not reported, so the outcomes and treatment in these patients are unknown. Generally, side effects with targeted therapies improve with cessation of therapy or decrease in dosage of the BRAF and/or MEK inhibitor.

In the case discussed above, we noted that the patient developed cytopenias, with evidence of DIC (low fibrinogen, elevated D-dimer, reduced platelet count and prolonged PT and PTT). There are several possible explanations for the DIC, notably the malignancy itself, occult infection or the treatment. An extensive infectious workup was completed with blood cultures, urine culture, sputum culture and imaging with CT scans. He did not exhibit clinical signs of sepsis, with temperature, blood pressure and heart rates in the normal range. There was an absence of known bone marrow involvement of his disease. Despite the possibility that the DIC was related to his treatment, it is not completely clear if this was a delayed side effect of the immunotherapy given 3 weeks earlier or related to the recent use of BRAF and MEK inhibitor given 5 days prior to the onset of haematological changes. The patient was treated with high dose prednisone and responded quickly and appropriately, giving the impression that this was an inflammatory or immune-related side effect, likely secondary to the prior immune therapy. In addition, despite extensive workup for other aetiologies, such as bleeding or infection, no other cause for his cytopenias was discovered.

Another challenge with the use of immune therapies is monitoring disease response with possibility of pseudoprogression and when to treat with high dose steroids. Traditionally, the RECIST criteria have been used to evaluate tumour response to therapy.¹² However, this has proven to be inadequate in the setting of new immunotherapies, which can cause an initial increase in the size of tumour lesions prior to subsequent improvement, a concept known as pseudoprogression. Therefore, new immune-related response criteria have been developed to determine therapy responses (irRECIST).^{13 14} This phenomenon was a concern in the patient above, who was noted to have an increase in liver masses after starting immune therapy. It is unclear if this was progression of disease or pseudoprogression. Unfortunately, due to compression of hepatic ducts, the initial immunotherapy could not be continued for fear of complete biliary obstruction.

Finally, this case also brings to light the challenge of sequencing new immunotherapies which have become available for metastatic melanoma and other malignancies. To date there have not been any trials that delineate the best sequence of treatment. In some subsets of patients, immunotherapies can lead to prolonged disease response, but the initial time to response is often longer than the time to response in patients treated with BRAF and MEK inhibitors. In patients who require immediate treatment, perhaps the faster acting BRAF and MEK inhibitors should be considered first. Patients must be stable and understand the risk of pseudoprogression on immunotherapy, which can lead to additional complications, as noted and discussed above. Patient-specific evaluations should be completed to determine if a patient will be able to tolerate any inflammation or

Figure 2 Abdominal MRI post-treatment.

Table 1 Relevant laboratory studies

	Days				
	–7 Prior to treatment	0 Therapy initiation	5 Event	11 Hospital discharge	18 Outpatient follow-up
Dabrafenib and trametinib*					
White cell count (WCC, 4.0–11.0 K/UL)	12.3	12.8	9	10.8	7.7
Haemoglobin (13.5–17.5 G/DL)	7.6	7.6	5.9	9.5	10.2
Platelets (150–400 K/UL)	230	218	85	106	314
Reticulocytes (0.8–2.6%)			4.4%		
Creatinine (0.7–1.3 mg/dL)	0.88		0.93		0.73
Alkaline phosphatase (25–100 U/L)	280	262	225	290	342
Lactate dehydrogenase (171–308 U/L)			3392		691
Aspartate aminotransferase (AST) (13–39 U/L)	272	228	170	55	41
Alanine aminotransferase (ALT) (9.0–67.0 U/L)	193	182	180	77	56
Total bilirubin (0.3–1.2 mg/dL)	3.5	4.2	6.5	4.1	3.2
Prothrombin time (PT) (9.2–13.5 S)	12.1		16.1	10.9	
Activated partial thromboplastin time (aPTT) (27–37 S)	26		37	28	
Haptoglobin (44–184 mg/dL)			205		
Fibrinogen (180–460 mg/dL)			114	188	
D-dimer (ref <243 ng/mL DDU)			>65 000		

*Ipilimumab and nivolumab were given 3 weeks prior to the initiation of dabrafenib and trametinib.

pseudoprogression prior to initiation of therapy, including but not limited to age, comorbidities and concerns or preferences regarding any further treatment in the setting of metastatic disease. This may be a risk worth taking in some patients, with the hope of obtaining a long-term response.

Immunotherapy continues to offer exciting new hope for individuals battling advanced malignancies, but also poses unique management challenges that require vigilance and ongoing research.

Learning points

- ▶ Continued research is needed to understand common and uncommon side effects of immunotherapy.
- ▶ Pseudoprogression identified a need to redefine imaging criteria for progression of disease in patients who are treated with immunotherapy.
- ▶ More research is needed to assist in understanding optimal sequencing of multiple lines of effective therapy in the era of multiple effective and targeted therapies in metastatic melanoma.

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