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New approaches and consequences for elderly cancer patients with focus on melanoma
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Vemurafenib-Induced Disseminated Intravascular Coagulation in Metastatic Melanoma

Introduction

The selective *BRAF* serine-threonine kinase inhibitor vemurafenib is currently part of the standard treatment arsenal of patients with advanced *BRAF*-mutated melanomas. The most common adverse effects of vemurafenib are cutaneous events, arthralgia, and fatigue. Neutropenia is observed in fewer than 1% of the patients, and no disseminated intravascular coagulation (DIC), thrombocytopenia, or clotting disorders have been reported in the main clinical trials.^{1,2} In this article, we report on a case of vemurafenib-induced DIC in a melanoma patient and combine our findings with information obtained from pharmacovigilance databases.

Case Report

A 53-year-old man was diagnosed with synchronous metastasized cutaneous melanoma. After excision of the primary tumor, he received dacarbazine, which induced a partial response. Because of rapidly progressive disease 8 months later, he was referred to our hospital. Restaging showed an asymptomatic solitary 9 mm brain metastasis and high hepatic tumor load. The cobas 4800 *BRAF* V600 Mutation Test (Roche Molecular Diagnostics, Rotkreuz, Switzerland) was positive. Chemistry showed a serum lactate dehydrogenase (LDH) of 3,101 U/L (normal value < 250 U/L) and a serum S100 calcium binding protein B (S-100B) of 14.65 $\mu\text{g/L}$ (normal value < 0.20 $\mu\text{g/L}$). For additional laboratory studies see Table 1. Vemurafenib 960 mg twice daily orally was started. Six days later, he presented at the emergency room with general malaise, deterioration, and loss of energy due to anemia. Blood tests showed an anemia without evidence of hemolysis, a thrombocytopenia of $37 \times 10^3/\mu\text{L}$, a prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT) with decreased fibrinogen and strongly elevated D-dimers (Table 1).

Vemurafenib was then interrupted and 6 RBC concentrates were administered over 3 days. All laboratory values normalized spontaneously. His serum LDH and S-100B decreased to 1,154 U/L and 1.74 $\mu\text{g/L}$, respectively, suggesting a massive tumor response.

On day 14, vemurafenib was restarted at a 50% dose (480 mg). Approximately 12 hours after taking the first dose of vemurafenib, his platelets dropped from $247 \times 10^3/\mu\text{L}$ to $98 \times 10^3/\mu\text{L}$, and the PT and aPTT were again prolonged; decreased fibrinogen and elevated D-dimers indicated acute recurrent DIC. Twelve hours later he developed hemiparesis. According to computed tomography imaging, this was caused by bleeding in his known brain metastasis. All medical treatments were stopped, and the patient died within 24 hours.

Table 1. Relevant Laboratory Studies

Vemurafenib	Days				
	0 Start	6* Termination	10	14† Restart	15
Leukocytes ($4\text{-}10 \times 10^3/\mu\text{L}$)	15.4	16.3	12.9	12.8	
Hemoglobin (14.0-17.1 mg/dL)	10.6	6.6	9.5	11.3	9.5
Platelets ($150\text{-}350 \times 10^3/\mu\text{L}$)	336	37	214	247	98
Reticulocytes (8-26%)		55			
Creatinine (< 110 $\mu\text{mol/L}$)	73	104	85	74	71
Alkaline phosphatase (< 120 U/L)	469	682	527	712	686
Lactate dehydrogenase (< 250 U/L)	3,101	4,361	1,436	1,531	2,353
Aspartate transaminase (< 40 U/L)	170	1,153	115	134	244
Alanine transaminase (< 45 U/L)	110	395	136	111	125
Bilirubin (< 17 $\mu\text{mol/L}$)	21	29	39	49	98
S-100B (< 0.20 $\mu\text{g/L}$)	14.65		1.74		
Uric acid (0.20-0.45 mmol/L)		0.53			
Creatine kinase (< 200 U/L)		28			
Prothrombin time (9-12 sec)		25.4	12.3	13.4	15.9
aPTT (23-33 sec)		45	29	26	33
Antithrombin (80-120%)		91			
Haptoglobin (0.3-2.0 g/L)		2.3			
Fibrinogen (1.7-4.0 g/L)		0.6	2.0	1.1	0.7
D-dimer (< 499 ng/mL)		7,603		7,363	7,643

Abbreviations: S-100B = S100 calcium binding protein B; aPTT = activated partial thromboplastin time.
 *On day 6 the patient presented at the emergency room and vemurafenib was stopped.
 †On day 14 vemurafenib was restarted at 50% and administered only once.

Discussion

Cancer can lead to a hypercoagulable state, and venous thromboembolic events are seen regularly. DIC is a systemic condition involving pathological activation of coagulation, leading to consumption and depletion of clotting factors and thrombocytopenia, which in turn can lead to hemorrhagic and thrombotic complications. It can be initiated by several diseases, including cancer in approximately 7% to 24% of DIC cases.^{3,4} Necrotic tumor, advanced malignancy, male gender, and older age are independent factors correlated with DIC in patients with cancer.⁵

Melanoma can also induce thromboembolic events including DIC.⁶ DIC can be resolved by antitumor therapy.^{7,8} However, such treatment itself can also induce DIC. For example, four melanoma patients developed DIC shortly after intratumoral Bacillus Calmette-Guérin injections.⁹ The patient case presented here suggests that vemurafenib can also induce DIC in a melanoma patient. Thrombotic thrombocytopenic purpura can be excluded in the absence of hemolysis and the presence of abnormal coagulation tests. In our patient, the DIC improved spontaneously after vemurafenib treatment was stopped and returned at vemurafenib rechallenge.

However, several additional aspects should be considered. First, rapid tumor response to vemurafenib and high tumor load may be a contributing factor to DIC. Indeed, the rapid decline in serum tumor markers LDH and S-100B in our patient indicates that vemurafenib had potent antitumor activity. *BRAF* inhibition in *BRAF*-mutated metastatic melanoma often leads to extremely early tumor responses by rapid melanoma cell death.¹⁰ Consequently, massive degradation of vital tumor tissue might have resulted in a release of breakdown products, thus inducing DIC. Therefore, this may have been a contributing factor. DIC appeared to be unrelated to tumor load in our patient, as it reoccurred at vemurafenib rechallenge, when a lower tumor load compared to first starting dose was indicated by a more than eightfold reduction of S-100B on day 10 and two-fold lower LDH on day 14.

Second, a pre-existing coagulopathy may have existed. In that case, vemurafenib could have led to the thrombocytopenia, and not necessarily the DIC. We cannot totally rule this out, as no coagulation parameters (except a normal platelet count) were available before the start of vemurafenib treatment. However, considering the disease response and the fact that platelet counts and DIC parameters were both restored on discontinuation of the vemurafenib, this does not seem likely. Furthermore, the repeated vemurafenib administration not only caused a recurrence of thrombocytopenia, but also induced re-elevation of clotting times.

Third, elevated vemurafenib levels due to reduced hepatic clearance may have contributed to the thrombocytopenia. This cannot be ruled out, as no vemurafenib plasma levels were measured in our patient. The DIC, however, was not clearly vemurafenib dose dependent, since the DIC recurred even on a low single dose of 480 mg vemurafenib.

Only one other case of hemorrhage due to DIC with proteolysis of factors XII and XIII induced by vemurafenib has been published.¹¹ This patient did not recover after discontinuing vemurafenib and no follow-up information was reported. Interestingly, we retrieved important additional information from pharmacovigilance databases. The Adverse Event Reporting System of the US Food and Drug Administration contains 12 DIC cases that were vemurafenib related, of which five were fatal and three life threatening.¹² This is in total 0.36% of the most common vemurafenib adverse events reported to the US Food and Drug Administration. In the EudraVigilance SUSAR (Suspected Unexpected Serious Adverse Reaction) database of the European Medicines Agency, three reports are available with an unknown outcome.¹³ Together, this indicates a total of 17 melanoma patients in whom *BRAF* inhibition with vemurafenib induced DIC.

We want to emphasize the tentative nature of the information provided by this single patient case. Ideally, additional parameters should have been measured, such as coagulation parameters before the start of treatment. Nevertheless, given the high risk of fatal outcome in a total of 17 reported cases, it should be considered unsafe to restart vemurafenib treatment—even with dose reduction—in case of vemurafenib-induced DIC.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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