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Title	Carfilzomib-Induced Thrombotic Microangiopathy Successfully Salvaged with Eculizumab
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Abstract

Introduction

Carfilzomib, a second-generation irreversible proteasome inhibitor, is commonly used in the management of multiple myeloma. Thrombotic microangiopathy is a rare but potentially life-threatening complication associated with carfilzomib. Prompt recognition and treatment are crucial to prevent further organ damage and improve patient outcomes. Eculizumab, a terminal complement inhibitor, has shown promising results in the management of carfilzomib-induced TMA.

We report a patient with IgA-kappa plasma cell myeloma who developed thrombotic microangiopathy (TMA) following treatment with carfilzomib and was successfully salvaged with eculizumab.

Case Presentation

A 62-year-old man with IgA-kappa plasma cell myeloma relapsed 3 years after autologous hematopoietic stem cell transplantation following induction with bortezomib, thalidomide and dexamethasone (VTD). He presented with profound pancytopenia and IgA-kappa paraproteinemia of 40g/L in 2023. Bone marrow examination showed diffuse sheets of clonal plasma cells with markedly suppressed trilineage haematopoiesis. Carfilzomib and dexamethasone (KD) were initiated as salvage therapy. Leukopenia and thrombocytopenia resolved after the first cycle of treatment and his IgA-kappa paraproteinemia dropped to 12g/L. However, after the 8th dose, he developed microangiopathic haemolytic anaemia, thrombocytopenia, and acute kidney injury with creatinine peaking at 842 umol/L. ADAMTS13 activity was only slightly reduced at 47.1%. A diagnosis of carfilzomib induced TMA was made and carfilzomib was discontinued.

He was given two sessions of haemodialysis and was treated with eculizumab shortly after the diagnosis of carfilzomib-induced TMA. After the 4th dose of eculizumab, his platelet was normalized and his renal function had significantly improved with creatinine down to 113 umol/L. He was given five doses of eculizumab in total.

Discussion

The mechanism of carfilzomib-induced thrombotic microangiopathy (TMA) is not fully understood. However, it is believed that complement activation of the alternative pathway plays a crucial role. Carfilzomib, as an irreversible proteasome inhibitor, may disrupt the normal turnover of complement regulators, leading to excessive complement activation and subsequent endothelial injury, formation of microvascular thrombi, and end-organ damage. Additionally, carfilzomib inhibits NFκB, reducing vascular endothelial growth factor (VEGF) levels and potentially causing glomerular endothelial injury and renal TMA [1].

Recognition of carfilzomib-induced TMA is essential, and discontinuation of the drug is the initial step in management. Eculizumab has shown promising results in rapidly improving haematological parameters and reversing renal dysfunction in some patients [2].

Conclusion

This case highlights carfilzomib-induced TMA as a potential complication of carfilzomib therapy in patients with multiple myeloma. Prompt recognition and early initiation of eculizumab can successfully salvage patients with this life-threatening condition. Further research is needed to better understand the underlying mechanisms and risk factors associated with carfilzomib-induced TMA and optimize its management.

References:
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