CLINICAL RESPONSE TO NOMACOPAN IN THE PAEDIATRIC HSCT-TMA SETTING

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INTRODUCTION

- HSCT-TMA (haematopoietic stem cell transplant associated-transplant microangiopathy) is a rare but devastating complication of HSCT, with a survival rate of around 20% in severely affected individuals (1-3).
- It is characterised by endothelial damage and complement activation resulting in microvascular thrombi, haemolytic anaemia, platelet consumption, hypertension, and organ dysfunction.
- Nomacopan, a novel bispecific inhibitor of complement C5 and the pro-inflammatory mediator leukotriene B4, has been proposed as a potential treatment (4).
- We report clinical and biochemical response to nomacopan in paediatric HSCT-TMA

METHODS

Patient X, a 6-year-old male underwent a 6/8 HLA-mismatched unrelated cord blood (CB) HSCT conditioned with fludarabine, treosulfan and thiotepa, for relapsed refractory AML in January 2022 post CB HSCT in April 2020. The patient received 7 granulocyte infusions peri-transplant as part of an experimental protocol to augment the graft-versus-leukaemia effect. His immediate post-transplant course was complicated by engraftment syndrome, acute gut GVHD grade 3 and CMV viraemia.

At day +66 (post-transplant) the patient developed features suggestive of TMA in the form of crampy abdominal pain with blood in stool, raised urine protein creatinine ratio, hypertension, schistocytes in the peripheral blood and elevated sC5b9. He was enrolled into AK901 and started treatment with nomacopan on day +74. A single age and weight based ablating dose was followed by maintenance twice daily dosing for 21 days.

RESULTS

- After initial pharmacodynamic analysis at day 14 of treatment, the patient was found to have predose terminal complement activity (TCA) slightly higher (value 14.4) than the LLOQ (CH50 >10 U Eq/ml). Although his TCA had been reduced by 95% from an unusually high baseline CH50 of 299.6U Eq/ml and sC5b9 had normalised, dose was increased in line with the protocol.
- A few days later the patient developed neurological symptoms following a period of hypertension and was diagnosed with posterior reversible encephalopathy syndrome (PRES). Nomacopan was stopped for 3 days and restarted after the diagnosis was deemed to be unrelated to nomacopan treatment.
- Treatment continued for a further 46 days until the end of the study with correction of the patients' urine protein creatinine ratio for ≥28 days. Gut pathology and thrombocytopenia resolved, and the patient remains well and in remission.
- No adverse events related to nomacopan were experienced during the 72-day treatment period.

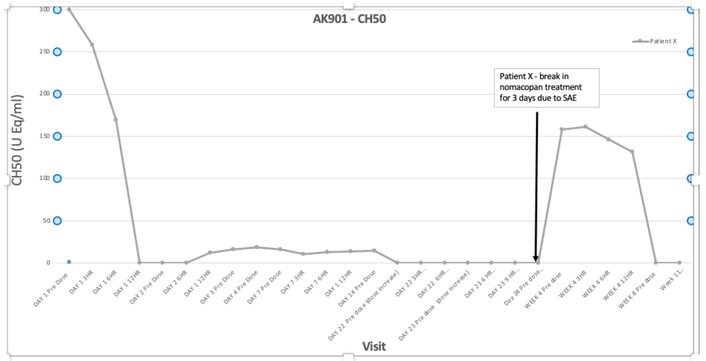

Figure 1: Clinical response to Nomacopan in patient X

CONCLUSION

The pathophysiology of HSCT-TMA is complex and multifactorial. It is important to be vigilant for clinical signs and symptoms of TMA and screen appropriately when suspicion arises so patients can receive prompt management and complement inhibition considered early. These data show that nomacopan had a favourable safety profile and controlled complement activity in this patient with severe HSCT-TMA.

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