COMPLEMENT AS THE ENABLER OF CARFILZOMIB INDUCED THROMBOTIC MICROANGIOPATHY

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SUMMARY: Carfilzomib has been associated with thrombotic microangiopathy (TMA) development in relapsed-refractory multiple myeloma patients. Direct toxicity and immune-mediated endothelial damage are the causes suggested for this TMA pathogenesis, but no effective treatment is available, yet. After limited successful experiences with the use of eculizumab, it seems that complement pathway could be involved. However, there is a scarce data, and, until now, no reliable techniques for complement assessment. We have evaluated the potential role of terminal complement in four patients with carfilzomib-induced TMA. Membrane attack complex (C5b-9) deposition on endothelial cells in culture exposed to plasma from patients during the acute phase of the disease uncovered complement overactivation as a potential endothelial damage mechanism, in 3 out of 4 patients. Three patients were treated with plasma exchange and, despite final clinical remission, all required temporary hemodialysis and two of them an additional cycle of therapy because disease recurrence. The fourth patient was treated with eculizumab after confirming C5b-9 deposition on endothelial cells. This treatment approach resulted in full clinical recovery and C5b-9 deposits normalization after 3 weekly doses. If confirmed in larger cohorts, C5b-9 evaluation will allow early identification of patients that could benefit from complement blockade and treatment monitoring.

METHODS:

Complement activation was assessed exposing by endothelial cells (EC) to patients' sera or to patients' plasma samples mixed with a control sera pool (1:1). C5b9 deposits on EC were analyzed through immunofluorescence and expressed as fold increase vs control samples. EX VIVO INDUCTION DEPOSITION OF C5B9 OVER EC <u>SERA</u> Patient Activated HMEC-1 with ADP PFA 3% (4h 37°C) Primary antibody (C5b9) Secondary Antibody **PLASMA** (Alexa 590) Pacient DAPI Control

Sera





We assessed C5b-9 deposition induced by plasma samples from the 4 CFZ-induced TMA patients at disease onset. Plasma from 3 out of the 4 patients induced significant C5b-9 deposition on ECs (fold increase of 6.5 ± 1 for patient 1; 6.8 ± 1.4 for patient 2; and 4.1 ± 0.3 for patient 4, *p*<0.01 for all values vs. controls) (Figure 1A). The only patient showing results equal to control results (patient 3, fold increase of 0.8 ± 0.2), already had thrombocytopenia before disease onset, was analysed after three plasma exchange (PLEX) sessions and showed pancytopenia despite kidney recovery and haemolysis resolution. To avoid the comorbidities associated with PLEX together with a central line placement, and after confirmation of C5b-9 deposition on ECs, patient 4 received early treatment with eculizumab (3 days after disease onset). An excellent clinical response was observed with an improvement of haemolysis parameters and a rise in platelet count after the second dose of eculizumab and especially after the third, followed by progressive recovery of kidney function, avoided the need for haemodialysis and PLEX (Figure 1B).

CONCLUSIONS:

In summary, C5b-9 deposition in 3 out of 4 patients with CFZ-induced TMA suggests the potential role of the terminal complement pathway in the pathogenesis of this CFZ-induced TMA. Only if confirmed in larger cohorts, this evaluation would offer new opportunities for the early identification of patients who could benefit from complement blockade in this clinical setting.