DO C1Q-POSITIVE DONOR SPECIFIC ANTIBODIES HAVE PROGNOSTIC EFFECT IN PATIENTS WITH RESISTANT ANTIBODY-MEDIATED REJECTION TREATED WITH BORTEZOMIB? SINGLE-CENTRE EXPERIENCE

Janka Slatinska1, Eva Honsova1, Tomas Rohal1, Iva Kratochvilova1, Petra Hruba1, Petra Hruba1, Ondrej Viklicky2
1Department of Immunology, IKEM, Prague, Czech Republic; 2Department of Nephrology, IKEM, Prague, Czech Republic

INTRODUCTION AND AIMS: Donor-specific antibodies (DSAs) examination is a crucial part of antibody-mediated rejection (AMR) diagnosis. C1q-positive (+) DSAs are associated with poor graft survival. We analyzed results of patients treated for resistant AMR by a bortezomib-based regimen with retrospectively performed C1q assay. The aim of this work was to analyze the treatment effect on DSA levels and potential effect of C1q+ DSAs on graft survival.
METHODS: We retrospectively analyzed documentation of 772 patients who underwent renal transplantation between 1/2012-6/2015. Novel therapeutic approach to resistant acute AMR in kidney transplant recipients was applied in 23 patients (3%) based on administration of bortezomib [1 cycle of 4 doses of bortezomib (1.3 mg/m2)], small doses of intravenous corticosteroids, plasmapheresis and a dose of rituximab (375mg/m2). This protocol was administered after conventional treatment had failed. Resistant AMR was defined as persisting deterioration or non-function of renal allograft in patients with histological verification of AMR, positive C4d staining and detection of donor specific antibodies (DSA) receiving standard antirejection treatment with PP + IVIG. C1q assay was performed three times - not more than 3 months before transplantation, at the time of AMR diagnosis and after completing AMR treatment. Patients were followed for minimum of 24 months.

RESULTS: Therapy of resistant acute AMR was administered to 23 patients after kidney transplantation with median peak PRA 52%, actual PRA 36%, mean HLA mismatch in HLA-A 1.2 ± 0.4, HLA-B 1.7 ± 0.5, HLA-DR 1.3 ± 0, with median of 5.8 years on dialysis. 3 patients underwent 1st kidney transplantation, while 20 patients retransplantation. All patients received induction therapy with antithymocyte globulin (n=22) or basiliximab (n=1), and maintenance immunosuppression with tacrolimus, mycophenolate mofetil/enteric-coated mycophenolate sodium and corticosteroids. Diagnosis of resistant acute AMR was made on 1st POD (7-60 days). Using bortezomib regimen in treating resistant acute AMR led to decrease in DSA quantity in HLA especially in class I (p=0.005), class II (p=0.015), but not in DQ (p=0.2). No significant improvement of renal function was observed during the follow-up. The patients whose levels of serum creatinine increased more than 25% of baseline level in 6 months after administration of protocol with bortezomib, are progressors (n=11). The progressors’ graft survival was 57% in 2 years. The treatment protocol was not effective in decreasing C1q+ DSAs class I (p=0.25), class II (p=0.69), DQ (p=0.38). We detected C1q positivity in 15 out of 11 progressors, compared with 3 out of 12 non-progressors (p=0.001). C1q+ DSAs correlated with C4d positivity in graft biopsies at the time of AMR diagnosis (p=0.0012).

CONCLUSIONS: Bortezomib-based regimen was effective against class I and II DSAs, but it did not affect DQ DSAs. Recipients with any C1q+ DSAs were more likely to have progressive graft dysfunction compared to those with C1q-negative DSAs. C1q positivity is a promising prognostic marker in patients with resistant AMR.

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