Early, but not late treatment with human umbilical cord blood-derived mesenchymal stem cells attenuates cisplatin nephrotoxicity through immunomodulation in mice

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Background: Preemptive treatment with mesenchymal stem cells (MSCs) can attenuate cisplatin-induced acute kidney injury (AKI). However, it is uncertain whether MSC treatment after development of renal dysfunction prevents AKI progression, or if their immunomodulatory properties contribute to MSC therapy. In this study, human umbilical cord blood (hUCB)-derived MSCs were used to compare the effects and mechanisms of preemptive and late MSC therapy in a murine model.

Methods: After cisplatin injection into C57BL/6 mice, hUCB-MSCs were administered on day 1 (early preemptive treatment) or day 3 (late treatment). Outcomes (renal function, histopathology, intrarenal cytokines and intrarenal infiltrated immune cells analysed by flow cytometry) were examined on day 3 or day 6 after cisplatin injection.

Results: With early treatment, cisplatin nephrotoxicity was attenuated as evidenced by decreased blood urea nitrogen (BUN), reduced apoptosis (analysed by the percentages of cells expressing cleaved caspase-3), and tubular injury scores on day 3. Early treatment reduced intrarenal MCP-1 and IL-6 expression and increased IL-10 and VEGF expression. Flow cytometric analysis showed similar populations of infiltrated immune cells in both groups; however, regulatory T cells (Treg) infiltration was 2.5-fold higher in the early treatment group. The role of Tregs was further delineated by Treg depletion using anti-CD25 mAb treatment. After Treg depletion, early treatment with hUCB-MSCs could not show renoprotective effect demonstrating higher BUN level, increased apoptosis, and higher tubular injury score compared to isotype control group on day 3. The renoprotective effect of late treatment was compared with control and early treatment groups on day 6. Late treatment when BUN levels were 2-fold higher than baseline levels, showed no renoprotective effects. The population of intrarenal infiltrating immune cells (including Tregs) as well as intrarenal cytokine-expression levels (MCP-1, IL-6, TNF-α, IL-2, IL-10, and VEGF) was not changed by late treatment. Whereas, the renoprotective effect of early treatment sustained until day 6.

Conclusion: Our results suggest that early preemptive MSC treatment attenuates renal injury by Treg induction and immunomodulation, whereas late treatment after the development of renal dysfunction neither prevents AKI progression, nor alters the intrarenal inflammatory micromilieu.
Keywords: acute kidney injury, cisplatin nephrotoxicity, immunomodulation, mesenchymal stem cells, regulatory T cells