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Session Title : Immune Tolerance

Operational tolerance induced by a donor antigen specific immunomodulatory cell therapy in living donor liver transplantation

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Liver transplantation is a well-established treatment option for patients with end-stage liver disease. However,long-term results remain unsatisfactory because of adverse events associated with lifelong immunosuppression. To overcome this problem, different strategies have been attempted to induce operational tolerance, maintenance of normal graft function and histology without immunosuppressive therapy, but have achieved limited success. In living donor liver transplantation setting, we tried to induce operational tolerance by using an immunomodulatory cell-based cell therapy at Hokkaido University hospital. Adoptive transfer of an *ex vivo* generated donor antigen specific immunomodulatory cells was conducted in 10 consecutive patients early post-liver transplantation. Immunomodulatory cells were generated by using a 2-week coculture of recipient lymphocytes with irradiated donor cells in the presence of anti-CD80/CD86 monoclonal antibodies. Immunosuppressive agents were tapered from 6 months, reduced every 3 months, and completely discontinued at 18 months after transplantation. After the co-culture, the generated cells displayed cell-number-dependent donor-specific inhibition in the mixed lymphocyte reaction. Infusion of these cells caused no significant adverse events. Seven out of 10 patients have completed successful weaning and cessation of immunosuppressive agents. The other 3 recipients with autoimmune liver diseases developed mild rejection during weaning and resumed conventional low-dose immunotherapy. This tolerance induced patients have been immunosuppression free for more than 10 years without any signs of rejection on both laboratory or pathology. A cell therapy using an immunomodulatory cell-based cells is safe and effective for drug minimization and operational tolerance induction in liver transplant recipients. The clinical follow-ups of these patients, a brief description of the protocol and its theoretical background, and a possible explanation for the immunological findings will be presented.