Liver cell transplantation - a new therapeutic option for children with urea cycle defect

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Abstract

Aims:

Urea Cycle Disorders (UCD) are inherited errors of metabolism with deficiencies of one of the six enzymes involved in the urea cycle. Patients suffering from UCDs cannot detoxify nitrogen and have a poor prognosis, especially if the onset of the disease occurs in the neonatal period. Mortality reaches about 85% after 10 years in these children, most of the survivors showing severe neurological impairment. The current therapeutic concepts include dietary restrictions and treatment with ammonia scavenger drugs, which are, however, often not sufficient to prevent UCD patients from recurrent hyperammonemic crisis. Early orthotopic liver transplantation (OLT) is a definite cure of the metabolic disease but a risky procedure in small children. Liver cell transplantation aims to provide an additional therapeutic option especially for the group of very young patients.

Methods:

Liver cell transplantation is applied to children with UCD in a clinical trial in Germany, after previous experience gained from individual therapeutic attempts. The children treated so far received 1-6 intraportal infusion of liver cell suspension after surgical catheter placement, with concomitant immunosuppression. The liver cells were isolated from donated organs (donor age, 5 days to 55 years) in a GMP compliant manufacturing procedure.

Results:

Intraportal liver cell infusion was well tolerated in all nine study patients and four cases of therapeutic attempts treated so far. The procedure was feasible even in neonates (n = 4) and no complications were noted during the infusions, which were carried out with ongoing control of peripheral oxygen saturation and portal blood circulation. In most patients the clinical situation stabilised after treatment over a period of up to 21 months or until OLT. Further efficacy evaluation using laboratory, biochemical, and immunohistological methods is currently still ongoing in order to quantify the engraftment of donor hepatocytes in the recipient’s liver.

Conclusions:

Intraportal liver cell transplantation is feasible and safe in children with UCD. In parallel to a broader clinical use of LCT based on clinical studies, research on suitable liver stem cells should be promoted to overcome the limited availability of adult hepatocytes, with concomitant improvement of repopulation.