Results of liver cell transplantation in urea cycle disorders

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The urea cycle is the final pathway for the metabolism of waste nitrogen in humans. As many inborn errors of metabolism, urea cycle disorders are based in the liver, but do not damage the liver itself. Indeed, an anomaly of this pathway leads to an accumulation of ammonia, with several deleterious effects to the brain including neurological damage and cognitive deficits. Management by strict diet protein restriction and use of ammonium scavengers are not always sufficient to control the disease and, eventually, the liver remains the target of curative treatment. Orthotopic liver transplantation (OLT) becomes then the ultimate solution to avoid repeated encephalopathic episodes and irreversible brain damage. Rapid transplantation is however limited by the organ shortage and the waiting time is long, during which irreversible brain damage may occur and jeopardize the long-term psychomotor development1 (2).

Liver cell transplantation (LCT) is an emerging therapy that has been shown to give short to medium-term metabolic effects in different diseases (3-4). This technique was proposed as a bridge to OLT in four children with urea cycle disorders, and as an alternative treatment in one because of liver transplant contra-indication (see table).

Four patients had an ornithine transcarbamylase deficiency (OTC), with antenatal diagnosis in two. The first child was transplanted over the first three and a half weeks of life leading to metabolic stabilization from day 20 to 315. On day 31, hyperammonemia reappeared suddenly suggesting that the hepatocytes had been rejected. Despite this setback, the patient was able to receive OLT at 6 months of age to correct the disorder. For the second neonate, blood ammonia was maintained within acceptable limits by combination of hepatocyte transplantation and medical management until 7 months, when the child received an auxiliary liver transplant6. The third and fourth patients were diagnosed after birth. The third one had undergone several hemodialysis for hyperammonemia resulting in severe limitation of vascular access, eliminating the possibility of liver transplantation7. Metabolic stabilization was obtained in this 5 years old boy after a single infusion of hepatocytes. Unfortunately, he developed an hyperammonemic coma after the liver biopsy performed 28 days after LCT. He received an additional LCT with cryopreserved cells, but remained comatose despite normalization of the metabolic status. He died of acute bronchopneumonia 43 days after the cell transplantation. The fourth child had experienced numerous attacks of hyperammonemia and was hospital bound. He received LCT between 14 and 18 months, while waiting for liver transplant (8). Ammonia levels decreased, urea synthesis appeared and the psychomotor development improved before OLT.

The fifth child had severe neonatal argininosuccinate lyase deficiency (ASL)9. Despite optimal medical management, she experienced several peaks of hyperam-

	Disease	Age at LCT	Viable cells	% fresh cells	Immuno-suppression	Follow-up	Outcome
1[5]	OTC	Day 1-23 37-51 113-116	 $4x10^9$ $3.3x10^9$ $1.7x10^9$	 20% 70% 100%	Tacrolimus (5-10ng/ml) + prednisolone	⇑ protein tolerance day20-30 complications Psychomotor OK	OLT at 6 months No specific
2[6]	OTC 1-26	Day	$1.9x10^9$	?	Tacrolimus (5 10ng/ml) + prednisolone	⇓ ammonia levels- ⇑ urea levels Normal diet Psychomotor OK	Auxiliary LT at 7 months No specific complications
3[7]	OTC	5 years	1x109	100%	?	⇓ ammonia levels Liver biopsies (+) for enzyme activity	Coma hyperNH4 at day 28 (after liver biopsy) Died at day 43
4[8]	OTC	Month 14-18	$2.4x10^9$	0%	Tacrolimus (6-8ng/ml) + prednisolone	⇓ ammonia levels ⇑ urea levels Psychomotor improvement	OLT at 20 months No specific complications
5[9]	ASL	Month 42-47	$3.4x10^9$	50%	Tacrolimus (6-8ng/ml) + prednisolone	⇓ ammonia levels Liver biopsies (+) for donor cells & enzyme activity Psychom catch-up	OLT at 61 months No specific complications

monemia with secondary psychomotor retardation. She was listed for liver transplantation at the age of 42 months and received hepatocyte transplantations over 5 months. Long-term metabolic stabilization was obtained up to 18 months after the first LCT, when she received a liver transplant. Presence of donor hepatocytes and enzyme activity were demonstrated in her liver. Psychomotor development improved significantly.

In conclusion, liver cell transplantation should be considered as a bridge to OLT in patients with severe urea cycle disorders. Long-term engraftment of donor cells with enzyme activity was demonstrated. Metabolic stabilization was obtained and allowed to decrease the risk of hyperammonemia and neurological sequellae during the waiting time for liver transplant. Additionally, with some further improvements of the technique, LCT could also become an alternative therapy for those diseases. This option would be less radical than liver transplant for patients whom have a normal liver besides the deficient enzyme, and would improve both their prognosis and quality of live.

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