Acute liver failure and transplantation. Adult UCL experience

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Abbreviations

ELTR : European Liver Transplant Registry
Gr : group
ICP : intracranial pressure
LT : liver transplantation
(s)ALF : (sub)acute liver failure

Introduction

Acute liver failure (ALF) traditionally carried a 80% mortality. Introduction of cerebral monitoring and of prophylactic antiinfectious chemotherapy, in specialized liver units, led to an improvement of survival (1,2). It was however the introduction of liver transplantation (LT) that finally led to a therapeutical revolution, allowing nowadays to obtain 70 to 80% survival rates (1,2,3,4,5). We report the experience of the Cliniques Universitaires St-Luc in Brussels with LT in acute and subacute liver failure in a series of 47 adults.

Methods and material

During the period february 1984-march 31 1999 34 men and 13 women, having a median age of 36 years (range from 18.5 to 68.5), underwent LT because of acute (ALF) and subacute (SALF) liver failure.

ALF and SALF are defined in relation to the time interval between appearance of jaundice and onset of encephalopathy (6). In our center ALF and SALF respectively refer to intervals between 0 and 14 days and between 15 and 56 days (8 weeks). This distinction is based on the definitions given by Trey - Davidson (7) and Bernuau - Benhamou (8,9,10).

In accordance with the European Liver Transplant Registry (ELTR) five patients, with underlying liver disease, were included in the study group (autoimmune hepatitis (2 ×), Wilson's disease (2 ×) and failure after major hepatectomy for cancer in chronic hepatitis C) (Table I). As no patient in these series presented acetaminophen intoxication, indication for LT was based on the Clichy criteria only : presence of encephalopathy stage III and IV associated with factor V level less than 20 or 30% of normal in patients aged less than or over 30 years (8). When factor V level was not available prothrombin level of $< 20\%$ was selected instead as decisional parameter (Table II).

Cerebral status was followed combining clinical examination, non-invasive and invasive monitoring (Table III) (11,12). Invasive intracranial pressure (ICP) — monitoring was done only in selective cases (8 pat.) with stage IV encephalopathy in the presence of cerebral oedema (documented on CT scan) or in the presence of indirect clinical signs of intracranial hypertension as e.g. opistotonus, hypertensive crisis, bradycardia, etc ...

Liver implantation was done by either replacing or preserving the recipient's inferior vena cava (13).

Up to 1995 all patients had cyclosporine (Sandimmun® or Neoral® - Novartis - Basel - CH) based triple immunosuppression ; from 1996 onwards cyclosporine was replaced by tacrolimus (Prograft® - Fujisawa - Osaka - JPN) ;

Based on the important consequences of the use of prophylactic systemic and topical antiinfectious chemotherapy in ALF (1,14), patients were divided into two groups (Gr). Gr I included 11 patients, transplanted

Table I. — **Liver transplantation and acute liver failure : UCL adult experience (1984-1999) with 47 adults (10.6%)**

Fulminant	35 (74.5%)		
HAV	3	Toxic	1
HBV	14	Reye's syndrome	1
HCV	1	Haemorrhagic necrosis	1
NANBNC	10	Wilson	2*
HSV	1	Autoimmune	1*
Subfulminant	12 (25.5%)		
NANBNC	6	Right hepatectomy	1*
Toxic	4	Autoimmune	1*

* Patients having underlying chronic liver disease.

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Table II. — **Indications and contraindications of LT IN (sub)acute liver failure**

Indications			
Acute :	- neurological indices predominant		
	- biochemical indices :	- FV	
		- pH*	
Subacute :	- encephalopathy		
	- biochemical indices :	- bilirubin	
		- coagulation	
*Acetaminophen** :	- metabolic acidosis (< 7.3 pH)		[King's]
Viral infection :	- FV level (< 20-30% if age < 30 or > 30 yrs)		[Clichy]
Contraindications			
Neurological :	- bilaterally fixed pupils	> 1 hr	
	- CPP < 40 mmHg	> 2 hrs	
	- ICP > 35 mmHg	> 2 hrs (?)	
	- brain death		
	→ **in all other situations full neurological recovery possible !**		
Infections :	organ dysfunction due to sepsis		
Pulmonary :	ARDS (pa O_2/FiO_2 < 200)		

Table III. — **Evaluation of cerebral status in acute liver failure : multimodal monitoring**

Hour by hour evaluation of	
* *Clinical status* :	- encephalopathy
* *Cerebral perfusion* :	- intracranial pressure (ICP)
	- jugular vein bulb oxymetry (SjO_2)
	- transcranial Doppler-Ultrasound
* *Neurophysiology* :	- EEG
	- sensory evoked potentials

Table IV. — **Preoperative characteristics of 47 patients transplanted because of (sub)acute liver failure**

		Gr I (1984-88)	Gr II (1989-99)	p
N		11	36	
Median age (yrs)		33 ± 16	39 ± 14	NS
Systemic and topical antiinfections chemotherapy		no	yes	
Encephalopathy		2.6 ± 1.2	3.1 ± 0.8	NS
EEG		3 ± 1.3	3.4 ± 0.7	NS
Cerebral oedema		3	14	NS
Pre-LT	Infection	4	8	NS
	Pulmonary infection	1	3	NS
	Ventilation (d)	0.5 ± 0.5	1 ± 1	NS
	Organ support			
	pulmonary	6	23	NS
	renal	3	5	NS
	hepatic	—	2	/
F.V.	(%)*	25.8 ± 9.5	19 ± 9	0.05
Bilirubin	(mg/dl)*	23.3 ± 13.4	27.1 ± 11.1	NS
Creatinine	(mg/dl)*	1.9 ± 1.6	0.9 ± 0.3	< 0.05

* mean values ± SD

Table V. — **Intra- and postoperative characteristics of 47 patients transplanted because of (sub)acute liver failure**

		Gr I (1984-88)	Gr II (1989-99)	p
Delay admission-LT (d)		2.9 ± 2.8	2.2 ± 1.5	NS
Total ischaemia (min)		409 ± 118	570 ± 162	< 0.01
Transfusion (L)		12.2 ± 6.4	2.6 ± 2.4	< 0.001
Perioperative bleeding		6	6	< 0.05
Post-LT	Infection	7	5	< 0.01
	Pulm. infection	4	3	< 0.05
Re-OLT (< 7 d)		1	3	NS

between 1984 and 1988, which did not have antiinfectious therapy ; Gr II included 36 patients, transplanted between 1989 and december 1999, having systemic and topical antiinfectious chemotherapy. Topical therapy consisted of selective bowel decontamination administered during the whole pre- and posttransplant hospitalization.

Pre- and intraoperative characteristics of both patient groups are shown in table IV. Infection included pulmonary infection and/or blood culture positivity.

Their were only two significant differences between the two groups nl higher creatinemia level in Gr I and lower factor V level in Gr II. Blood lactate level, NH_3 and fibrinogen were not significantly different.

Two Gr II patients had temporary pretransplant hepatic xenoassistance using the Hepat Assist device® (Circe Biomedical - Lexington - USA) (15).

Early and late mortality were defined as events occurring within or after 3 posttransplant months.

Results

Actuarial 5 years survival of the whole patient group was 73.3%.

Early posttransplant survival improved significantly in Gr II patients (91.7% - 33/36 pat. vs 54% - 5/11 pat. in Gr I - $p > 0.01$).

Intraoperative blood product use and posttransplant infection rates were significantly lowered in group II (Table V).

Three Gr I patients died of infectious complications occurring in the setting of haemorraghic transplant procedure whilst three Gr II patients died of cerebral problems. One patient became brain death just after LT, one patient had brainstem herniation at start of haemodialysis on post-LT day 5 and one patient had cerebral bleeding around the ICP-monitoring device. This patient needed re-LT because of primary graft non-function ; it was probable that the bleeding was triggered by the first allograft non-function.

During late follow-up only one patient died of specific allograft related problem (chronic rejection) (Table VI).

Discussion

Liver transplantation has revolutionized the management and outcome of acute liver failure (1,3). Referral of these patients to specialized liver units led to an improved medical treatment including monitoring of cerebral perfusion and of intracranial pressure and also of, adapted, prophylactic antifungal and antibacterial chemotherapy.

Such specialized liver units, as Clichy in Paris and King's College in London, were able to develop reliable criteria for indication of LT (1,9,10) (Table II).

Our experience shows that excellent results can nowadays be obtained (92% early survival during the last decade) when adhering to strict pre-, intra- and posttransplant management schemes. Adequate antiinfectious chemotherapy, multimodal cerebral monitoring and non haemorraghic surgery are the cornerstones for successful LT in this highly vulnerable patient group.

In view of the obtained results in recent literature (Table VII) value and place of auxiliary LT (16) and of bioartificial liver devices should be interpreted with caution (15).

In order to optimize survival chances, patients presenting with (sub)acute liver failure should be referred as soon as possible to a liver unit offering all therapeutical aspects of disease treatment, including liver transplantation.

Table VI. — **Early and late mortality after liver transplantation for (sub)acute liver failure**

		Gr I (1984-88)	Gr II (1989-99)	p
Early (< 3 mo) mortality		45.5% (5/11 pat)	8.3% (3/36 pat)	< 0.001
* sepsis		3	/	
sepsis-bleeding		1	/	
sepsis-recurrent disease		1	/	
* cerebral bleeding (ICP-PNF)		/	1	
oedema post-OLT		/	1	
oedema at haemodialysis		/	1	
Late (> 3 mo) mortality		9% (1/11 pat)	11.1% (4/36 pat)	
* Chronic rejection	(12 mo)	1		
* Intestinal volvulus	(16 mo)	1		
* HCV cirrhosis	(31 mo)	1		
* Tuberculosis	(67 mo)	1		
* Myocard. infarction	(120 mo)	1		
Survival				
* Early	(< 3 mo)	54.4%	91.7%	< 0.01
* Long-term	(> 3 mo)	45.5%	81.6%	
* Overall		72.3%		

Table VII. — **Acute liver failure — Results of transplantation**

Iwatsuki	1989	Pittsburgh	42	59%
Schafer	1989	Nebraska	24	58%
Gallinger	1989	Toronto	18	72%
Castells	1993	Barcelona	28	79%
Munoz	1993	Philadelphia	18	65%
Ascher	1993	San Francisco	35	92%
Wall	1995	Ontario	28	59%
Gonzalez	1995	Madrid	26	62.7%
Daas	1995	Mayo	19	63.1%
Bismuth	1995	Paris	128	68.1%
Mirza	1995	Birmingham	145	63%
Williams	1995	London	109	62%
UCL	1999	Brussels	47	72.3%
ELTR (Europe)	1996	Sub/fulminant	100/1258	55/60%
UNOS (USA)	1991		605	61%
EURALT	1995	APOLT / APHLT*	35 / 11	69

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