厚生労働科学研究費補助金
「肝炎等克服緊急対策研究事業」

生体肝移植後のC型肝炎再発予防を目指した
ステロイド剤不使用による免疫抑制療法に関する研究

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総括研究報告書

生体肝移植後のＣ型肝炎再発予防を目指したステロイド剤不使用による
免疫抑制療法に関する研究

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研究要旨

京都大学移植外科で生体肝移植を受けたＣ型肝硬変患者112人の移植後肝炎の再発について検討したところ、肝生検によって診断された慢性肝炎の再発率は、移植後3年で81%であった。生体肝移植後肝炎再発防止を目指した新しい免疫抑制療法に関する無作為比較試験を開始し、これまで参加登録された34例には重篤な有害事象はなく、症例数のさらなる集積が望まれる。

A. 研究目的

　Ｃ型肝炎ウィルス(HCV)感染による肝硬変ならびに合併する肝細胞癌は、現在肝疾患のなかでも死亡原因となる最大の疾患であり、その治療法として肝移植に期待がかけられている。しかし、近年海外における肝移植医療において肝移植後のHCV肝炎再発が移植肝の予後を左右する重要な問題となっており、肝炎再発に関連するグラフト機能不全のために他の疾患に比べて5年以降の長期予後が有意に不良であることが示されている。

　肝移植後のHCV肝炎再発の特徴として、ウィルス量が肝移植後に急速に上昇しその値は移植前に比べて非常に高くなること、慢性肝炎から肝硬変への進展が早い、

すなわち肝の線維化速度が速いことなどが挙げられ、その原因として移植後免疫抑制療法の影響が考えられている。特に、ステロイド剤はHCVの増殖を促進すると言われ、移植後HCV肝炎再発防止のためにはこれまでのステロイドを中心とした免疫抑制療法の見直しが必要である。

　本邦でも成人生体肝移植の普及につれ、HCV関連肝硬変ならびに肝細胞癌患者に対する肝移植の実施数が増加している。本研究は、1）当施設で実施したＣ型肝炎への生体肝移植後の肝炎再発の実態を明らかにする、2）生体肝移植後肝炎再発防止を目指したステロイドフリーによる新しい免疫抑制療法を開発することを目的とする。

B. 研究方法

1）平成 11 年 3 月から平成 17 年 9 月までに、京都大学移植外科で生体肝移植を受けた C 型肝硬変患者 112 人を対象として、肝生検結果に基づく移植後 C 型肝炎の再発について検討した。

2）HCV 関連肝硬変患者の生体肝移植後肝炎再発防止を目指した新しい免疫抑制療法の開発を目的としてとして、多施設共同の前向きの無作為比較試験を開始している。その治療プロトコルは従来のタクロリムスとステロイド剤による免疫抑制療法を行う群（A 群）と、ステロイド剤を一切使用せずミコフェノール酸モフェチル（MMF）とタクロリムスを使う新しい免疫抑制療法を行う群（B 群）の 2 群に分けられ、両群を比較検討する。この臨床試験に関する倫理面への配慮については、本学および各研究参加施設の倫理委員会の審議を経てその指針を受けている。

C. 研究結果

1）112 例の移植後 5 年生存率は 72% で、他の疾患に対して生体肝移植を受けた成人 267 例の場合の 69% と同等であった。移植後 stage F1 以上の線維化を伴う慢性肝炎の再発は 58 例に認め、移植後 3 年累積再発率は 81% であった。さらに stage F2 以上の有意な線維化は 30 例に認めた。この有意な線維化進展のリスクファクターの検討では、レシピエントが女性、ドナーが男性などが挙げられた。これまで fibrosing cholestatic hepatitis 2 例を含む 5 例が肝硬変に進展し、2 例が死亡、1 例が再移植を受けている。

2）平成 16 年 2 月から実際に無作為比較試験を開始した。17 年 12 月までに 34 人が参加登録され、A 群または B 群に無作為に割り付けられプロトコルに基づく治療を受けている。この中には三重大学からの 3 例、熊本大学からの 4 例が含まれており、多施設共同研究として症例集積が進みつつある。これまで試験継続が不可能となる重篤な有害事象は認められておらず、研究計画における安全性は確認されたと考えられる。研究計画において中間解析は行わないことになっているため、肝炎再発予防における有効性の評価はまだ行われていない。

D. 考察

最近欧米での一部の施設において、脳死肝移植に比べて生体肝移植の方が移植後 C 型肝炎の再発の危険性が高いと報告された。しかし、今回の検討では 3 年再発率が 81% と脳死の報告と比べて同等の再発率であり、また 5 年生存率が 72% と遜色はなく、肝炎再発が生体肝移植後の予後に著明な影響を与えることはないと考えられた。

一方、生体肝移植後肝炎再発防止を目指したステロイドフリーによる新しい免疫抑制療法の開発に関する臨床試験はまだ開始したばかりであるが、これまで参

加登録された 34 例において安全性は確認されており、今後のプロトコル継続は可能であると判断された。

E. 結論
　生体肝移植後肝炎再発防止を目指したステロイドフリーによる新しい免疫抑制療法の開発に関する臨床試験は多施設共同の無作為比較試験として立ち上げられて2年が経過し、本施設以外の他の施設からも症例登録されるようになり、今後は登録症例数の増加と研究の推進が期待される。

F. 健康危険情報
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H. 知的財産権の出願・登録状況
なし

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Auxiliary Partial Orthotopic Living Donor Liver Transplantation: Kyoto University Experience

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Auxiliary partial orthotopic liver transplantation (APOLT) was initially indicated as a potentially reversible fulminant hepatic failure and non-cirrhotic metabolic liver disease to compensate for enzyme deficiency without complete removal of the native liver. We expand our indication of APOLT for small-for-size grafts to support the function of implanted grafts during the early post-operative period, and for ABO-incompatibility to sustain a patient's life if the patient has a graft failure.

We retrospectively reviewed 31 patients undergoing APOLT from living donor. The indication of APOLT was fulminant hepatic failure in 6, non-cirrhotic metabolic liver disease in 6, small-for-size grafts in 13 and ABO-incompatible cases in 6.

The cumulative survival rate for APOLT at 1 and 5 years was 57.9% and 50.6%, and 78.8% and 73.8% for standard LDLT. None of the patients who underwent transplantation with APOLT for fulminant hepatic failure had long-term patient survival. The incidence of acute cellular rejection was higher in APOLT (58.1%) than standard LDLT (35.0%). Biliary complication was higher and the need for retransplantation was greater in APOLT than standard LDLT (p < 0.01).

The results suggest that the indications of APOLT should be reconsidered in view of the risk for complications and retransplantation.

Key words: Auxiliary liver transplantation, living donor liver transplantation

Introduction

Liver transplantation from a living donor is increasingly accepted with excellent results, usually in coordination with a cadaveric organ transplant program (1). In countries where cadaveric donors are limited, however, living donor liver transplantation (LDLT) is often the only treatment of choice for patients with end-stage liver disease (ESLD). The LDLT program in Kyoto University began in June 1990, and under this program 970 transplants in 920 patients have been carried out in the period up to November 2003. Because of the growing waiting list and the establishment of acceptable results of pediatric LDLT, we have been compelled to expand our indication of LDLT from small children to older children, and even to adults.

Analysis of our studies revealed poor graft survival in older patients receiving small-for-size grafts (2). To treat patients with a graft-to-recipient weight ratio (GRWR) of less than 0.8%, auxiliary partial orthotopic liver transplantation (APOLT) was indicated from 1996 (3). The rationale of APOLT for a small-for-size graft is that the remnant native liver is expected to support the function of the implanted graft during the early post-operative period. The graft liver expands its function in proportion to volume growth. After the graft liver has grown sufficiently, it can be expected to meet the hepatic functional demands of the recipient.

APOLT was initially indicated for potentially reversible fulminant hepatic failure and non-cirrhotic metabolic liver disease (4,5). The double aim of APOLT for fulminant hepatic failure is full native liver regeneration and discontinuation of immunosuppressive therapy (6). The auxiliary graft should support the remnant native liver during regeneration.

The advantage claimed for APOLT in non-cirrhotic metabolic liver disease is that it can compensate for enzyme deficiencies without complete removal of the native liver, which may have to aid the recipient in case of potential graft failure. The remaining native liver could benefit in the future from potential success in gene treatment (7,8).

The other potential indication for APOLT is ABO-incompatible transplantation. Transplants of ABO-incompatible grafts are often unavoidable due to the

limited number of potential donor candidates in the LDLT program. In our LDLT program, 12% of patients had to have an ABO-incompatible graft. A high incidence of early graft failure with a high rate of biliary and vascular complications in ABO-incompatible liver transplantation was reported (9). The remnant native liver could sustain a patient's life if the anticipated graft failure occurred in an ABO-incompatible case.

APOLT from living donors was performed in 31 cases for the following indications: (i) fulminant hepatic failure; (ii) non-cirrhotic metabolic liver disease; (iii) small-for-size graft and (iv) ABO-incompatibility. However, the safety of using this technique in ESLD patients remains open to question. The objective of the present study was to investigate the long-term clinical outcome of the APOLT studies in the Kyoto University LDLT program.

Patients and Methods

Study population

Since APOLT was first indicated in March 1995 for a patient with ornithine transcarbamylase deficiency (OTCD), 31 cases of APOLT have been performed at Kyoto University Hospital. There were 13 male and 18 female patients with a median age of 23 years (range: 1.4–53.7 years) and a median weight of 53.4 kg (range: 11.3–108 kg). The indication for transplantation was fulminant hepatic failure in 6 patients (hepatitis B virus [HBV]-related in 1 and of unknown origin in 5); non-cirrhotic metabolic liver disease in 6 (citrullinemia in 3, OTCD in 2 and Crigler-Najjar syndrome type I in 1); biliary atresia in 7; primary biliary cirrhosis in 3; primary sclerosing cholangitis [PSC] in 2; Wilson's disease in 2; chronic hepatitis B in 2; autoimmune hepatitis in 1; Budd-Chiari syndrome in 1 and cryptogenic cirrhosis in 1. The follow-up period median was 83 months (range: 31–100 months).

Potential donors were evaluated by liver function tests, blood group, anatomical variation and graft size with computed tomography (CT) volumetry. All patients received grafts from family members. There were 14 male and 17 female donors with a median age of 43 years (range: 20–62 years) and a median weight of 57.3 kg (range: 39–81 kg). The indications for APOLT were: (i) fulminant hepatic failure in 6 patients; (ii) non-cirrhotic metabolic liver disease in 6 patients; (iii) small-for-size graft in 13 patients and (iv) ABO-incompatibility in 6 patients.

Surgical procedures

The operative procedure has been previously described (3,10). Native hepatectomy that varied in graft segment and volume, was performed prior to graft implantation. Graft types were left lateral segment in 8 cases, left lobe in 20 and right lobe in 3. The GRWR range was 0.45–2.08% (median 0.67%). The range of the operation time was 513–1379 min (median: 861 min), the range of the cold and warm ischemic time was 36–460 min (median: 157 min) and 32–77 min (median 48 min), respectively. Blood loss ranged 260–37650 g (median: 2645 g).

In one patient with biliary atresia, the left lateral segment of the native liver was prominently atrophic, and native hepatectomy was not necessary for graft implantation. The patient needed hepatic vein anastomosis with a new orifice of the inferior vena cava (11).

Part of the caudate lobe was resected in an initial 3 patients to shorten distance and to prevent kinking of the portal venous anastomosis. The stump

of the native hepatic vein and hepatic artery was used for anastomosis. Twenty-five cases (80.6%) had diversion of the native portal vein to prevent functional portal vein competition between the native and graft liver, meaning that interruption of portal flow to the native liver with all portal flow going through the graft (3,12). Hepatic artery reconstruction was performed using the microvascular technique in all cases without using vascular grafts. Biliary reconstruction was achieved using Roux-en-Y hepaticojejunostomy.

Immunosuppression

The immunosuppression protocol consisted of tacrolimus and low-dose steroids (13). Tacrolimus was begun 1 day prior to transplantation at a dose of 0.15 mg/kg/day divided into two doses, except for cases of hepatic encephalopathy and severe infection. The target for the post-transplantation whole blood trough concentration of tacrolimus was 10-12 ng/mL during the first 2 weeks and around 10 ng/mL thereafter. Steroids were started at graft reperfusion at a dose of 10 mg/kg, and then gradually reduced from 2 mg/kg/day to 0.3 mg/kg/day until the end of the first month. For patients receiving ABO-incompatible grafts, plasma exchange or double filtration plasmapheresis was performed to reduce anti-ABH antibody titers before transplantation. Post-operatively, prostaglandin E1, azathioprine and additional steroids were administered (14).

Rejection

Acute cellular rejection was diagnosed with liver biopsy. Histological diagnosis and grading of acute rejection were performed according to the criteria proposed by Demetris et al. (15). All the rejection episodes were treated with a steroid bolus injection. Diagnosis of chronic rejection was based on internationally accepted histological criteria (16). Graft failure was defined as patient death or allograft removal regardless of the reason.

Statistical analysis

Values are presented as mean ± standard deviation. Statistical analysis was performed with the generalized Wilcoxon test. Actuarial 1- and 5-year graft survival curves were calculated with the non-parametric Kaplan–Meier method and compared among groups with the Wilcoxon test. p-values of less than 0.01 were regarded as significant throughout the study.

The institutional review board approved the study and informed consent was obtained in all cases.

Results

APOLT was initiated between March 1995 and September 2001. In the same period we carried out 536 LDLTs. Thirty-one of 536 patients (5.8%) received APOLT (Table 5). None of the patients were lost to follow-up.

APOLT for fulminant hepatic failure (Table 1)

Six patients underwent APOLT for fulminant hepatic failure. Etiology of fulminant hepatic failure was HBV in 1 patient and of unknown origin in 5. The median interval between onset of jaundice and encephalopathy was 42 days (range: 9–140 days). Coma grade at transplantation was grade III in 2 patients and grade IV in 4 patients. All patients necessitated pre-operative plasma exchange and continuous veno-venous hemodiafiltration therapy for progressive encephalopathy, coagulopathy and combined kidney/pulmonary dysfunction.

Table 1: Characteristics of APOLT for fulminant hepatic failure

Case	Age (year)	Sex	Blood type	Graft type	GRWR	PVD	Outcome
1	1.8	M	Identical	Left lateral	2.08	−	Died* (POD55, sepsis)
2	1.5	M	Identical	Left lateral	2.00	−	Died[†] (POD141, sepsis)
3	19.5	M	Identical	Left lobe	0.62	+	Died (POD32, necrotizing enteritis)
4[‡]	43.3	F	Identical	Left lobe	0.51	+	Died (POD9, graft failure)
5	53.6	M	Compatible	Left lobe	0.61	+	Died (POD25, sepsis)
6	38.6	F	Identical	Right lobe	0.90	+	Died (POD43, sepsis)

GRWR = graft-to-recipient weight ratio (%); PVD = portal vein diversion; POD = post-operative day.
*Portal flow steal phenomenon.
[†]Retransplantation on day 34 from living donor for recurrent hepatitis.
[‡]HBV-related fulminant hepatic failure.
Retransplantation on day 29 from living donor for hepatic artery and portal vein thrombosis.

Patient 1, in whom portal blood flow to the native liver was preserved, showed a portal flow steal phenomenon resulting in continuously poor portal blood flow to the graft. Native portal vein diversion at the time of transplantation was indicated in the latter four cases to prevent functional portal flow competition between the graft and remnant native liver (17). Acute cellular rejection that was confirmed by liver biopsy, was observed in 3 patients (patients 2, 4 and 5). Three technical complications occurred in 6 patients, biliary stricture in patient 1 and intra-abdominal bleeding in patients 5 and 6. Retransplantation was indicated in 2 patients: for recurrent hepatitis in patient 2 and for arterial/portal thrombosis in patient 6. All patients died within 5 months of APOLT, due to sepsis in four cases, necrotizing enteritis in one case and graft failure in one case. None of the patients showed sufficient native liver recovery, and none of them were able to withdraw from immunosuppressive therapy.

In the same period, 53 patients had a transplant with standard LDLT for fulminant hepatic failure. Etiology of fulminant hepatic failure was drug-induced in 1, HBV in 15 and of unknown origin in 37. The median age of recipients was 23.3 years (range: 0.1–68.9 years). Recipient and donor characteristics of APOLT or standard LDLT were comparable at the time of transplant. The cumulative 5-year graft and patient survival rates were 58.4% and 60.2% in the standard LDLT group, respectively. The graft survival was significantly lower after APOLT (p < 0.01).

APOLT for non-cirrhotic metabolic liver disease (Table 2)

Six patients had a transplant with APOLT for non-cirrhotic metabolic liver disease. Primary native portal vein diversion was indicated in the last four cases. We reported the case of patient 1 with OTCD who did not receive primary ligation of the native portal branch at the time of APOLT (18). After a severe rejection episode, the graft became smaller and the native liver showed compensatory hypertrophy. As a result of the delayed native portal vein diversion, at 26 months after APOLT the graft volume increased properly and was revealed to have acceptable metabolic function. In our previous study, the resistance of portal venous inflow in the graft liver was higher than in the native liver after APOLT (17), and the dominant portal venous flow to the native liver could be readily observed in the event of severe rejection. After the experience of the first two cases, we changed the standard procedure for APOLT of non-cirrhotic metabolic liver disease to indicate native portal vein diversion in all subsequent cases so that the graft liver received the entire portal venous flow. The native liver was supplied by arterial blood flow. In case 2, native partial hepatectomy was done to compensate the hypertrophy of the native liver after native portal vein diversion (12). No significant difference was found in pericellular or perivenular fibrosis in the native liver between the specimen at APOLT and at native hepatectomy. Despite the native portal vein diversion, steatosis of the native liver improved from 80% to 30% (19).

Table 2: Characteristics of APOLT for non-cirrhotic metabolic liver disease

Case	Age (year)	Sex	Original disease	Blood type	Graft type	GRWR	PVD	Outcome
1	3.0	F	OTCD*	Compatible	Left lateral	2.08	+[†]	Alive
2	5.8	F	OTCD*	Identical	Left lateral	1.34	+[‡]	Alive
3	52.7	F	Citrullinemia	Identical	Left lobe	0.84	+	Alive
4	5.5	M	Crigler-Najjar (type I)	Compatible	Left lateral	1.23	+	Alive
5	23.5	M	Citrullinemia	Identical	Left lobe	0.78	+	Alive
6	20.2	M	Citrullinemia	Compatible	Left lobe	1.21	+	Died (POD29, sepsis)

GRWR = graft-to-recipient weight ratio (%); PVD = portal vein diversion; POD = post-operative day; POM = post-operative month.
*Ornithine transcarbamylase deficiency.
[†]PVD for portal flow steal phenomenon (POM 26).
[‡]PVD for portal flow steal phenomenon (POM 14), and native hepatectomy for compensate hypertrophy (POM66).

Five patients had an episode of acute cellular rejection (patients 1, 2, 3, 4, 6). Patient 3 had biliary stricture and underwent rehepaticojejunostomy 3 years after transplant. Patient 5 had minor biliary leakage that was successfully managed with percutaneous aspiration drainage under ultrasound guidance. Patient 6 died from sepsis on postoperative day 29. The overall cumulative 5-year graft and patient survival rates were 83.3% and 83.3%, respectively.

Seventeen patients received standard LDLT for noncirrhotic metabolic liver disease in the same study period. Etiology of liver disease was tyrosinemia in four cases; OTCD in three; citrullinemia in three; glycogen storage disease in three; Crigler-Najjar type I in one; familial amyloidotic polyneuropathy in one; methylmalonic acidemia in one and propionic acidemia in one (20,21). The overall cumulative 1- and 5-year graft and patient survival rates were 70.6% and 62.7% and 70.6% and 62.7%, respectively. There was no significant difference in graft and patient survival between APOLT and standard LDLT for non-cirrhotic metabolic liver disease.

APOLT for small-for-size graft (Table 3)

Thirteen patients underwent transplant with APOLT for a small-for-size graft. Small-for-size grafts can be defined by a recognizable clinical syndrome that results from the transplantation of too small a functional mass of liver for a designated recipient (22,23). The definition of a small-for-size graft in this study is an actual GRWR of less than 0.8% (2,3). The original liver disease was biliary atresia in 2 patients; liver cirrhosis in 2 (of which 1 was HBV-related); primary biliary cirrhosis in 3; primary sclerosing cholangitis in 2; Wilson's disease in 2; autoimmune hepatitis in 1 and Budd-Chiari syndrome in 1. The median GRWR was 0.62% (range: 0.45–0.75%). The decision was made preoperatively in this group of patients to use APOLT.

All patients had histologically proven fibrosis in the native liver, and a pre-operative Doppler study revealed that the blood supply depended on the hepatic artery being dominant rather than the portal vein. Native portal vein diversion was indicated in 10 patients. Six patients had an episode of acute cellular rejection (patients 3, 4, 5, 7, 8, 13) and one patient had chronic rejection (patient 13).

Four patients required relaparotomy for complications: intestinal perforation in patient 3; intra-abdominal bleeding in patients 4 and 9. Patient 7 with primary sclerosing cholangitis underwent native hepatectomy on post-operative day 35 after competent graft regeneration confirmed by CT volumetry and ^{99m}Tc-galactosyl serum albumin scintigraphy, which reflected the general function of the hepatocyte in the graft and native liver (24). The delayed native hepatectomy was intended to eliminate the potential risk of carcinogenecity of the remnant native liver. Interestingly, the explanted native liver showed no histological difference between the specimen at APOLT and at delayed native hepatectomy.

Two patients (patients 4 and 6) had hepatic vein stenosis that was treated by intervention. A metallic stent was inserted in patient 4 after several courses of balloon dilatation, but was thrombosed despite adequate anticoagulation therapy. Biliary complications were observed in 6 patients; biliary leakage in 3 (patients 1, 5 and 10) and stricture in 3 (patients 3, 7 and 8). Hypersplenism was observed in 2 patients (patients 3 and 6) who underwent splenectomy 7 years and 1 year after APOLT, respectively. Patient 6 developed de novo autoimmune hepatitis 2.5 years after APOLT (25).

Retransplantation was indicated in 2 patients due to hepatic vein thrombosis in patient 4 and chronic rejection in

Table 3: Characteristics of APOLT for small-for-size graft

Case	Age (year)	Sex	Original disease	Blood type	Graft type	GRWR	PVD	Outcome
1	23.2	F	Wilson's	Identical	Left lobe	0.72	−	Alive
2	47.1	M	LC (HBV)	Compatible	Left lobe	0.51	−	Died (POD35, sepsis)
3	22.9	F	Biliary atresia	Identical	Left lobe	0.48	+	Alive
4	24.1	M	Wilson's	Identical	Left lobe	0.62	−	Alive*
5	48.7	F	PBC	Compatible	Left lobe	0.62	+	Alive
6	15.9	F	Biliary atresia	Identical	Left lobe	0.54	+	Alive
7	20.6	F	PSC	Identical	Left lobe	0.49	+	Alive†
8	44.1	F	PBC	Identical	Left lobe	0.45	+	Alive
9	50.6	F	LC	Identical	Left lobe	0.67	+	Alive
10	30.0	F	PBC	Identical	Left lobe	0.59	+	Died (POD59, sepsis)
11	39.0	F	Budd-Chiari	Identical	Left lobe	0.69	+	Died (POD22, sepsis)
12	19.2	F	AIH	Identical	Right lobe	0.75	+	Alive
13	30.9	M	PSC	Identical	Right lobe	0.68	+	Died‡ (POD372, sepsis)

GRWR = graft-to-recipient weight ratio (%); PVD = portal vein diversion; POD = post-operative day; POM = post-operative month; LC = liver cirrhosis; PBC = primary biliary cirrhosis; PSC = primary sclerosing cholangitis; AIH = autoimmune hepatitis.
*Retransplantation from living donor for hepatic vein thrombosis (POM 33).
†Native hepatectomy after regeneration of graft (POD 35).
‡Retransplantation from living donor for chronic rejection (POM 6).

Table 4: Characteristics of APOLT for ABO-incompatible case

Case	Age (year)	Sex	Original disease	Graft type	GRWR	PVD	Outcome
1	19.6	M	Biliary atresia	Left lobe	0.55	+	Died (POD59, hepatic necrosis)
2	51.4	M	LC (HBV)	Left lobe	0.55	+	Died (POD32, sepsis)
3	13.8	F	Biliary atresia	Left lobe	0.62	+	Alive
4	4.5	F	Biliary atresia	Left lateral	1.37	+	Alive*
5	14.9	M	Biliary atresia	Left lateral	0.63	+	Alive
6	9.8	F	LC	Left lateral	1.16	+	Alive

GRWR = graft-to-recipient weight ratio (%); PVD = portal vein diversion; POD = post-operative day; POM = post-operative month.
*Retransplantation from cadaveric donor (split liver transplantation) for chronic rejection (POM 22).

patient 13. Patient death occurred in 4 of 13 patients, the main cause of death being sepsis. The overall cumulative 1- and 5-year graft survivals were 69.2% and 69.2%, respectively.

Forty patients received standard LDLT for a small-for-size graft during the same period in conjunction with APOLT. The median GRWR in the standard LDLT group was 0.73% (range: 0.60–0.79%). The GRWR was significantly lower for patients receiving APOLT versus those receiving standard LDLT ($p < 0.01$). The overall cumulative 1- and 5-year graft and patient survivals in the standard LDLT group were 65.0% and 65.0%, respectively. No significant difference was observed between the groups.

APOLT for cases of ABO-incompatibility (Table 4)

Six patients had a transplant with APOLT for ABO-incompatibility. Median recipient age was 14.4 years (range: 4.5–51.4 years). Acute cellular rejection was observed in 4 patients (patients 1, 4, 5 and 6). Patient 4 had chronic rejection.

Relaparotomy was indicated for 2 patients: ligation of the collateral vessel in patient 1 and intra-abdominal bleeding in patient 2. Patient 1 underwent ligation of the collateral vessel on post-operative day 9. After an episode of acute cellular rejection, graft portal venous flow decreased and the steal phenomenon of portal flow to the collateral vessel was confirmed by Doppler ultrasonography even though native portal vein diversion was indicated. The graft function did not recover and the native liver function was not sufficient to support the severe dysfunction of the graft. The patient died from hepatic necrosis on post-operative day 59. Three patients had biliary complications: bile leakage in patients 4 and 5, and biliary stricture in patient 6. Patient 4 underwent retransplantation with a cadaveric split graft in post-operative month 22 for chronic rejection. The overall cumulative 1- and 5-year graft survival rates were 66.7% and 44.4%, and the 1- and 5-year patient survival rates were 66.7% and 66.7%, respectively.

Thirty patients, all over 2 years old, underwent standard LDLT with an ABO-incompatible graft. Median recipient age was 30.1 years (range: 2.0–59.3 years). Acute cellular rejection was observed in 9 of 30 patients (30%). The overall cumulative 1- and 5-year graft and patient survival rates were 53.3% and 42.7%, respectively. There was no significant difference in graft and patient survival between APOLT and standard LDLT for ABO-incompatibility.

Profiles of APOLT and standard LDLT (Table 5)

Profiles of APOLT and standard LDLT performed in the same study period are shown in Table 5. The GRWR was significantly lower for patients receiving APOLT versus those who received standard LDLT.

The duration of the operation was significantly longer in the APOLT group (831.2 ± 222.0 min) than the standard LDLT group (690.8 ± 198.5 min).

Acute cellular rejection was detected in 18 of 31 (58.1%) cases of APOLT versus 177 of 505 (35.0%) cases of standard LDLT ($p = 0.02$). Chronic rejection was diagnosed in 2 of 31 (6.5%) cases of APOLT, versus 2 of 505 (0.4%) cases of standard LDLT ($p < 0.01$). The incidence of rejection was higher in the APOLT group.

There were no significant differences in vascular complications between APOLT and standard LDLT. Biliary leakage was observed in 6 of 31 (19.4%) cases of APOLT, versus 30 of 505 (6.0%) in standard LDLT ($p < 0.01$). Biliary stricture was observed in 7 of 31 (22.6%) cases of APOLT, versus 28 of 505 (5.5%) in standard LDLT ($p < 0.01$). Biliary complication was significantly higher in the APOLT group.

The need for retransplantation was significantly greater in the APOLT group (16.1% vs. 4.2% for standard LDLT group, $p < 0.01$). In-hospital deaths occurred in 13 of 31 patients (41.9%), 10 patient deaths (76.9%) were related to infectious complication. The median delay was 32 days (range: 9–184 days) after APOLT.

The 1- and 5-year cumulative grafts were lower after APOLT versus standard LDLT (57.9 and 50.6% vs. 78.8 and 73.8%, respectively), but the difference did not reach statistical significance ($p = 0.45$ and 0.18, respectively).

Table 5: Profiles of Auxiliary partial orthotopic liver transplantation and standard living donor liver transplantation

Characteristics	APOLT (n = 31)	Standard LDLT (n = 505)	p-values
Male/female	13/18	213/292	0.87
Age (year)	25.8 ± 16.8 (1.5–53.6)	18.9 ± 20.4 (0.1–69.1)	0.06
Donor age (year)	43.5 ± 10.3 (20–62)	37.9 ± 10.8 (19–66)	<0.01
GRWR* (%)	0.87 ± 0.47 (0.45–2.08)	1.96 ± 1.27 (0.60–9.68)	<0.01
Cold ischemic time (min)	177.4 ± 111.2 (36–460)	116.7 ± 89.5 (14–943)	<0.01
Warm ischemic time (min)	49.4 ± 13.6 (32–77)	46.9 ± 13.8 (16–145)	0.32
Duration of operation (min)	831.2 ± 222.0 (513–1379)	690.8 ± 198.5 (329–1800)	<0.01
Blood loss/recipient boy weight (g/kg)	116.4 ± 140.4 (6.3–607.3)	119.7 ± 146.0 (8.3–1414.1)	0.89
Acute cellular rejection (%)	58.1	35	0.02
Chronic rejection (%)	6.5	0.4	<0.01
Surgical complications (%)			
Intestinal perforation	3.2	4.1	0.83
Intra-abdominal bleeding	16.1	9.4	0.62
Hepatic artery thrombosis	3.2	2.0	0.86
Portal vein thrombosis	3.2	1.4	0.95
Hepatic vein stenosis	6.5	1.4	0.16
Biliary leakage	19.4	6.0	<0.01
Biliary stricture	22.6	5.5	<0.01
Retransplantation (%)	16.1	4.2	<0.01
Graft survival (1-, 5-year survival, (%))			
For fulminant hepatic failure	0, 0	58.4, 58.4 (n = 53)	<0.01
For metabolic liver disease	83.3, 83.3	70.6, 62.7 (n = 17)	1.47
For small-for-size graft	69.2, 69.2	65.0, 65.0 (n = 40)	1.59
For ABO incompatible case	66.7, 44.4	53.3, 42.7 (n = 30)	0.53
Overall	57.9, 50.6	78.8, 73.8	0.45

GRWR = graft-to-recipient weight ratio (%).

Discussion

The most common indication for APOLT in western countries is fulminant hepatic failure (8). The first successful case of APOLT for fulminant hepatic failure, that is, full native liver regeneration and withdrawal of immunosuppressive therapy was reported in 1991 (26). The indication of APOLT for fulminant hepatic failure remains controversial because APOLT does not rule out potential regeneration of the native liver, resulting in unsatisfactory outcomes (6). In our series of APOLT for fulminant hepatic failure, none of the patients achieved long-term survival. The reasons for our poor results might be application of preemptive portal vein diversion and patient selection. The rationale of portal vein diversion is to prevent the portal flow steal phenomenon. We reported that the native liver has less resistant than the graft in fulminant hepatic failure (17), however, sufficient portal blood flow might be essential for native liver recovery and subsequent regeneration. An experimental study reported that the necessity of portal vein diversion in APOLT was dependent on the pathophysiology of the remnant native liver (27). The efficiency of portal vein diversion for fulminant hepatic failure, a paradox between the functional competition and the native liver recovery, remains unclear. Moreover, the optimal APOLT candidate for fulminant hepatic failure has not yet been clearly defined. A previous study suggests that native liver recovery is more likely to occur in those with a short interval between jaundice and encephalopathy (28). The median interval between onset of jaundice and encephalopathy was 42 days in our series. This delay might be one of the reasons for the poor outcome.

Bismuth et al. reported that the main advantage of APOLT for fulminant hepatic failure, that is, the potential for withdrawal of immunosuppressive therapy, was rarely achieved and that the indication of APOLT for fulminant hepatic failure should therefore be reconsidered because of the high degree of technical complications (6,10). We fully agree with this suggestion. While our experience of APOLT for fulminant hepatic failure is limited, based on the poor outcome, we also consider that APOLT should have a limited place in the treatment of fulminant hepatic failure. There might be a possibility, however, that APOLT could be used in toxic injury such as acetaminophen toxicity where recovery of the native liver is more likely than in idiopathic or viral fulminant hepatic failure (29–31).

In the case of non-cirrhotic metabolic liver disease, APOLT had a satisfactory outcome in our series with a 5-year graft survival of 83.3%. After the initial two cases of the portal flow steal phenomenon, we changed the standard procedure for APOLT of non-cirrhotic metabolic liver disease to indicate native portal vein diversion in all subsequent cases whereby the graft liver receives the entire portal venous flow. Concern remains about the dysfunction of the remnant native liver after portal vein diversion, which may

negate the support of a patient's life and the possibility of future gene therapy. However, it has been reported that occluded portal flow induces hepatocyte apoptosis rather than necrosis in the embolized lobe without changing the functional efficiency of the hepatocyte (32,33). Our previous report showed that ligation of the native portal vein had no detrimental effects on the native liver supplied by arterial flow only (17,34). The remnant native liver may sustain the recipient's life if the native portal vein is transected. APOLT with portal vein diversion is an effective technique to induce graft regeneration and to avoid functional portal flow competition in non-cirrhotic metabolic liver disease.

With regard to our experience of APOLT for small-for-size grafts, the patients had high surgical complications and unsatisfactory patient survival. Recent technical improvements in left lobe donation have led to the use of right lobe grafts in adult-to-adult LDLT to overcome problems encountered with small-for-size grafts (35). After a period of APOLT using left lobe grafts, which partially relieved the problems of small-for-size grafts, right lobe LDLT was systematically introduced from February 1998. The cumulative 1-year graft survival rate of right lobe LDLT was 76.8%, which was significantly higher than that of APOLT for small-for-size grafts ($p < 0.01$, n = 168). Moreover, in some cases, if the functional volume of the right lobe was not sufficient for recipients, right lobe with middle hepatic vein graft was indicated with special attention to donor safety. The overall cumulative 1-year graft survival rate of right lobe with middle hepatic vein graft was 82.2% (n = 28). Our current strategy is to consider the right lobe as the first choice followed by APOLT with a right lobe graft for small-for-size grafts.

The graft survival in children younger than 2 years old receiving an ABO-incompatible graft is similar to those receiving compatible grafts. The survival is gradually affected with age by specific complications associated with blood type mismatching such as focal hepatic necrosis due to microcirculatory disturbance and multiple non-anastomotic biliary strictures attributable to arteriole insufficiency (36). In our LDLT program, an ABO-incompatible graft was unavoidable in 12% of the recipients. Despite the application of pre-operative plasma exchange, splenectomy and enhanced immunosuppression, the 5-year graft survival was less than 50% in an adult population. The application of APOLT to ABO-incompatible cases improved graft survival; however, graft survival was not satisfactory. Recently, an intra-portal infusion protocol was introduced (37), and improved patient survival was observed in ABO-incompatible cases. We modified the protocol from intra-portal to intra-hepatic arterial infusion from December 2001. Although it is still a tentative trial, intra-hepatic arterial infusion protocol dramatically improved survival with 1-year graft survival of 85% (data not shown). After the introduction of a novel immunosuppression protocol, APOLT is not adopted for ABO-incompatible cases. Further study of hepatic artery

infusion therapy is now underway in order to transcend the ABO-barrier.

The higher rejection episodes in APOLT series are a consequence that requires further investigation. Immunological differences in the responses to orthotopic and auxiliary allografts were reported in an experimental study, given the increased expression of class II MHC antigen on hepatocytes in auxiliary liver transplantation, and the increase in the rejection response to the auxiliary grafts (38). Auxiliary liver allografts were also demonstrated to be more susceptible to rejection than non-auxiliary allografts (39). Further histopathological studies into the mechanisms of susceptibility to rejection in APOLT cases are currently underway.

Unlike standard LDLT, the incidence of biliary complications and the need for retransplantation were shown to be higher in APOLT cases. According to our present study, we conclude that APOLT should have a restricted indication in the treatment of fulminant hepatic failure, small-for-size grafts and ABO-incompatibility. Conceptual changes were made in the treatment of small-for-size grafts, through the introduction of LDLT using right lobe with or without middle hepatic vein graft, and in the treatment of ABO-incompatible cases, through the use of a novel intra-hepatic arterial immunosuppression protocol. Non-cirrhotic metabolic liver disease may be a suitable indication for APOLT.

Acknowledgment

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ORIGINAL ARTICLE

Using a radial artery as an interpositional vascular graft in a living-donor liver transplantation for hepatocellular carcinoma

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Summary

With increasing numbers of living-donor liver transplantations (LDLTs) for hepatocellular carcinoma (HCC), cases with some arterial troubles are encountered; because most HCC cases waiting for LDLT have undergone interventional treatments. In these patients, the reconstruction of the graft artery needs to be planned preoperatively. We report a 52-year-old male, with hepatitis C-related liver cirrhosis and advanced HCC, who for 4 years repeatedly underwent continuous intraarterial chemotherapy through an implanted reservoir port. A suitable artery was not available for arterial reconstruction and the patient underwent LDLT using an autologous radial artery conduit based on the infrarenal aorta. Postoperatively, the patient is well with normal liver function and efficient arterial flow. Autologous radial artery can be safely and successfully used as an aortic-based arterial conduit when HCC patients waiting for LDLT have undergone long-term repeated intraarterial chemotherapy.

Introduction

For living-donor liver transplantation (LDLT), successful hepatic artery reconstruction is essential and interpositional vascular grafts are needed in the case of an inadequate or thrombotic hepatic artery. There are several reports regarding vascular grafts in liver transplantation: including of the saphenous vein [1], iliac artery [2], inferior epigastric artery [3] and the cadaveric iliac artery [4]. On the contrary, with increasing numbers of LDLTs for hepatocellular carcinoma (HCC) [5], cases with some arterial troubles are being encountered more often because most HCC cases waiting for LDLT have undergone interventional treatments such as transcatheter arterial embolization (TAE), transcatheter arterial chemoembolization (TACE) and intraarterial chemotherapy through the implanted reservoir. In these patients, the reconstruction

of the graft artery has to be planned preoperatively. We undertook LDLT using the radial artery as an interpositional vascular graft between the graft artery and the infrarenal aorta for an HCC patient who previously had repeated interventional treatments. Although it has routinely been used for coronary artery bypass grafting [6], there are few reports on its utility for the reconstruction of the hepatic artery in LDLT. Here, we report its versatility as an arterial conduit in LDLT.

Case report

A 52-year-old male was found positive for the hepatitis C antibody during a routine health examination in 1991. He was treated with interferon twice and has been followed ever since then because the initial treatment was not effective. In November 1999, three nodular HCC