移植待機中の肝不全患者のうち，長期に高ビリルビン血症であったり，腹水のコントロールのために利尿剤を長期服用している症例は高率に腎障害を合併しており，抗真菌薬の投与に際しては，投与量，投与間隔の考慮が必要である。

移植後の診断

前記のような術前からの予防策に引き続き，術中には固有肝，胆汁，腸管（胆管・空腸吻合の場合）の培養検査を行いコロニーのチェックをしている。術後においては，週2回の各種培養検査とともにβ-D glucan，アスペルギルス抗原，クリプトコッカス抗原，カンジダ抗原などの生化学検査や38℃以上の熱が2日以上続く場合はCT検査をして感染源が存在するかどうか検索している。

真菌感染症，特に深在性真菌症の診断は肝移植においても非常に難しい問題の一つである。肝移植患者では術前からの監視培養により真菌のコロニーを把握しておくことは重要である。しかし，監視培養は真菌感染の有用な情報ではあるがコロナイゼーションと感染症発症との鑑別が難しいこともあり確定診断には，血液培養，組織診，眼底所見，気管支肺胞洗浄などと画像診断，臨床所見を加味した総合的な診断となることが多い。

本邦ではβ-D glucanの有用性が唱えられているが[4]，特異度の問題があり欧米ではまだ一般的な検査法とはなっていない。肝移植におけるβ-D glucan測定の有用性については現在日本移植外科真菌症研究会で調査中であるが，血液製剤，透析膜による偽陽性，移植直後（2週間ほど）の一過性の上昇などの特徴を理解した上で利用すると有用であると思われる。2003年2月に発表された臓器移植領域のガイドラインには，β-D glucan測定が補助診断として盛り込まれているが，確定診断となる基準にはなっていない[5]。しかし，β-D glucanが高値である肝移植症例に対しては，有熱症状などがなくとも抗真菌薬の投与を開始すべきと考える。また，PCR法による遺伝子診断はもう暫く臨床成績の集積が必要であると思われる[5]。ただ，アスペルギルス属については，PCR法によるスクリーニングを行い成果があったとする報告もある[6]。

移植後の治療

術中には，予防的投与としてFLCZまたはミカファンギン（ファンガード；MCFG）の点滴静注を行っている。カンジダ属に対する肝移植後の抗真菌薬予防投与は，術前の長期ステロイド，術前真菌感染の既往，抗菌薬の長期使用，長時間の移植手術，大量出血，血管合併症，糖尿病などがあるものについては積極的に行うべきと考えるが，危険因子がなく真菌感染を疑わせるものがない症例については，10日から2週間で中止している。FLCZ[7,8]やアムホテリシンB（ファンギゾン；AMPH-B)[9]の予防投与についての大規模試験の報告はあるが，危険因子の少ない肝移植患者に予防投与がどれほど有効であるかについては今後検討の余地がある。

アスペルギルス属による感染症は，肺移植に比べると肝移植では頻度が減少するが，カンジダ属の感染症に比べ致死率が非常に高いのが特徴である。施設によって差はあるが，数%から20%の頻度である[1]。アスペルギルス属に対する肝移植後の有効な抗真菌薬の予防投与の効果は報告されていないが，原疾患が劇症肝炎の患者にAMPH-BやITCZを予防的に投与する試みはされている。

クリプトコッカス属による感染症は，肝移植においてはアスペルギルス感染症に比べやや多い。カンジダ属と同じ酵母菌属であるた

めFLCZなどの予防投与は有効であると考えられるが，感染症としての頻度が低いためevidenceはない。

前記のような予防的抗真菌薬の投与にもかかわらず真菌感染症となった，または，疑われた症例に対しては，先制攻撃的治療，経験的治療，標的治療が必要となる。真菌感染症の発症は免疫抑制剤の量が多く，手術侵襲の影響が残っているため，術後1～2週間が要注意である。重症例では免疫抑制剤の減量を考慮しなくてはならない症例もある。感染部位と起炎菌が明らかになっている場合は，抗真菌薬による治療効果を厳重に監視しながら，効果の上がらない抗真菌薬は速やかに変更することも重要である。

2003年2月に出たガイドラインによると，先制攻撃的治療にはFLCZ 200～400mg/日，AMPH-B 0.2～0.5mg/kg/日，ミコナゾール（フロリード；MCZ）10mg/kg/日，経験的治療にはFLCZ 200～400mg/日，AMPH-B 0.2～0.5mg/kg/日，MCZ 10～15mg/kg/日などとなっており，標的治療にはMCFG 100～150mg/日も加わる[5]（表2）。当科においてもおおむねこのガイドラインと同様の治療を行ってきたが，AMPH-Bを投与することはまれである。

注意すべき点は，カンジダ属に比べアスペルギルス属に対しては，抗真菌薬の量が多く必要であることと，クリプトコッカス属に対してMCFGは無効であることである。また，ITCZは経口薬のみであるため，移植後早期の腸管運動が減弱している時期には使用しにくいということが挙げられる。ニューモシスティス・カリニ肺炎に対しては，スルファメトキサゾール・トリメトプリム（バクタ，バクトラミン；ST合剤）12錠／日，イセチオン酸ペンタミジン（ベナンバックス；Benambax）3～4mg/kgを投与している。当科では術後3ヵ月後に外来通院患者でカリニ肺炎を発症し，治癒した症例があった。また，アゾール系の抗真菌薬は肝臓でP-450により代謝されるため，免疫抑制剤のうちタクロリムス（プログラフ；FK506）やサイクロスポリンA（ネオーラル，サンディミュン；CsA）の血中濃度急上昇，腎毒性の増強などがあるため注意が必要である。

表2　真菌感染症に対する抗真菌薬の使い方

カンジダ症	
経験的治療：	フルコナゾール　200～400mg/日
（先制攻撃的治療）	ミコナゾール　10～15mg/kg/日
	アムホテリシンB　0.2～0.5mg/kg/日
標的治療：	フルコナゾール　200～400(800)mg/日
	ミコナゾール　15～20mg/kg/日
	ミカファンギン　100～150mg/日
	アムホテリシンB　0.5～1.0mg/kg/日
アスペルギルス症	
経験的治療：	アムホテリシンB　0.2～0.5mg/kg/日
（先制攻撃的治療）	イトラコナゾール　200～400mg/日
標的治療：	ミコナゾール　15～20mg/kg/日
	アムホテリシンB　1.0～1.5mg/kg/日＋
	フルシトシン　100mg/kg/日
	ミカファンギン　150～300mg/日
	イトラコナゾール　400～600mg/日

おわりに

臓器移植においては，全身状態の悪い患者が対象であることと免疫抑制剤を使用するということで深在性真菌症のリスクが高く，予後を左右する因子の一つになっている。10年，20年前を振り返ってみると，真菌症に対する診断，治療は進歩したが，さらなる移植後生存率の向上のためには，克服されるべき問題は多い。

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肝移植の現況と展望

Current Status and Prospect of Liver Transplantation

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1. はじめに

臓器移植法が成立し脳死肝移植の増加が期待されたがその数は伸び悩んでいる．一方，1989年にスタートした生体肝移植は年々増加し，末期肝不全患者を救命する手段として定着した感がある．適応も小児患者から成人例へと拡大され，年間の実施数では小児例を上回るようになっている．本講演では，これまでに術式や術後管理の面で改善してきたことや現時点での問題点,さらには今後の展望について自験例を中心に述べる．

2. 術　　式

A. ドナー

ドナーの手術は採取するグラフトの種類によって外側区域，左葉，右葉摘出の手術に大別できる．小児への移植では通常ドナーの外側区域や左葉をグラフトとして用いる．近年増加している成人への移植では尾状葉を付けた左葉や右葉をグラフトとして用いることが多い．グラフトの種類関わらずレシピエント手術の進行にあわせて調整するので手術時間はほぼ一定になっている．また出血量も1,000 mlを越えることはほとんど無く術前に準備した自己血を使用しない例も多い(表1)．ドナーからグラフトを採取した後の残肝容積は約35%以上あればよいと考える施設が多いが,先日わが国でもドナーの死亡例がでておりドナーの安全については今後さらに詳細に解析する必要がある．

B. レシピエント

患者さんの固有肝を摘出した後でグラフトの脈管再建を行う．肝静脈，門脈の順に再建し門脈血流を再開した後，肝動脈吻合，胆管の再建を行う．

肝静脈の吻合は血流再開後にoutflow-blockがこないように吻合口を大きくすることが肝要で，そのために通常小児症例ではレシピエントの中，左肝静脈を一本に形成しグラフトの左肝静脈と端々吻合する．レシピエントの右，中，左肝静脈を一本にしてグラフト肝静脈と吻合する場合もある．

門脈はレシピエントの左右の門脈分岐部を開きパッチ状に形成してグラフトの門脈と端々吻合する．連続縫合を基本とするがレシピエントの門脈が細いときには半分を連続,残りを結節縫合とし狭窄を防いでいる．レシピエントの門脈が消失している例や狭窄で充分な流量がえられないと判断した例では，上腸間膜静脈と脾静脈との合流部にドナーから採取した静脈（大伏在静脈や卵巣静脈，下腸間膜静脈等）を間置してから門脈再建を行う．

動脈吻合は顕微鏡を用い，レシピエントの左右いずれかの肝動脈とグラフトの動脈を端々吻合する.通常，1～2 mmの動脈を10針ほどで結節縫合する．グラフトの動脈が二本ある場合でも，口径の大きい動脈の再

表1. 当科におけるドナー手術（74例）

術式(症例数)	手術時間 (時:分)	出血量 (ml)	他家血輸血 (症例)	移植肝重量 (g)	術後最高 T-Bil/AST	術後入院 期間（日）
S23 (30)	7:8	595	1	259	1.9/294	11
S234 (18)	8:59	769	0	278	2.3/306	12
S234MHV (12)	8:58	963	0	354	2.1/317	15
S5678 (14)	8:40	814	0	539	2.8/349	13

表2. 生体肝移植後に起こりやすい合併症

1. 出血
2. 血栓症
3. 急性拒絶反応
4. 感染症（細菌，ウイルス，真菌，原虫）
5. 胆道感染症（胆汁漏，吻合部狭窄）
6. 腹水貯留

建だけですむ事が多い．

胆道の再建は肝管空腸吻合が一般的である．成人例では総胆管と肝管を吻合する場合もある．いずれも8針程度で結節縫合し，内ステントや外ステントを留置する．術後に吻合部狭窄や閉塞を起こす例が約15～30%あるので何らかの改善が必要である．

3. 術後合併症と対策

表2に主たる合併症を列記する．

血栓症は肝動脈，門脈，肝静脈いずれの吻合部でも起こり，対処が遅れると致命的であるので早期発見が必要である．ドップラーエコーでの血流の変化は，肝機能の悪化に先行して起こるので早期発見に有用である．術後2週間は一日に3ないし4回の血流チェックを行い早期発見に努めている．血栓症が疑われた場合は血栓溶解療法や観血的な血栓除去術，再吻合，再移植を行う．

一般に肝臓は拒絶反応の起こりにくい臓器といわれている．また，近年の免疫抑制剤の発達は拒絶反応の制御を容易なものとしているが，それでも一般的な拒絶反応療法であるステロイドのパルス療法に抵抗性の拒絶反応がある頻度で起こっている．特に血液型が不適合である組み合わせ間の移植ではその頻度が高い．当科では7例のABO不適合移植中1例を抗体価の上昇に伴う超急性拒絶反応で亡くしている．最近，B細胞に対する抗CD20モノクローナル抗体を使用し，液性拒絶反応の予防や超急性拒絶反応からの回復例を2例経験した．血液型不適合移植での有効な治療法となるか，今後の検討が必要である．

術後は大半の症例で何らかの感染症を発症する．術前からの感染症が顕在化することも多いし耐性菌の出現率も高い．特に胆道閉鎖症の子供は，数回の手術で多くの耐性菌を内在していることが多いので注意が必要になる．適切な治療薬を選択することで細菌，真菌，ウイルス感染症のいずれも以前に比べて対処しやすくなってきている．ウイルス感染症の中では，CMVに対する特効薬が出現したので治療が容易になり，変わってEBウイルスが問題となっている．特に死亡率の高いPTLDが注目されている．

術後数ヶ月から数年を経てから起きる胆道系の狭窄や閉塞は，現時点で最も移植医を悩ませている合併症である．拡張やステントの留置が可能であれば対処は容易であるが，再吻合が必要な場合，難渋することが多い．最初の吻合部に到達が不可能な場合は肝内の拡張した胆管を探し，その胆管と空腸の再吻合を試みることがある．胆管狭窄は患者にとっても主治医にとっても悩みの種であり，狭窄を起こさない吻合法の開発が危急の問題となっている．

4. 成人肝移植と適応の拡大

当初小児患者を対象に始まった生体肝移植は，近年成人例へと適応を広げ，一年間の実施数では小児例を上回るようになっている（図1）．成人肝移植ではレシピエントに必要なグラフト量を得るために尾状葉付き左葉グラフトや右葉グラフトが用いられる．いずれの場合も肝静脈の再建に工夫が必要となる．特に，ドナーの安全を考慮して中肝静脈をドナー側に残したグラフトでは，中肝静脈に注いでいるV5，V8の静脈断端が離断面に露出することになるので再建が必要になってくる．レシピエントから予め採取しておいた浅大腿静脈や大伏在静脈，卵巣静脈などを利用して再建する（表3）．

成人肝移植の普及と共に，ウイルス肝炎後の肝硬変やHCC合併例に対する移植が年々増加している．HCC患者への移植は，欧米ではミラノクライテリアに則って移植をすることが多い．わが国では生体肝移植

表3. 右葉グラフトにおけるV5V8の再建（11/14例）

症例	V5V8の再建方法	再建に用いた静脈
52	V8—レシピエントMHV	
61	V8—再建したMHV	卵巣静脈
62	V8—再建したMHV	浅大腿静脈
64	V8—再建したMHV	大伏在静脈
65	V5,8—再建したMHV	浅大腿静脈
66	V5,8—再建したMHV	浅大腿静脈
68	V5,8—再建したMHV	浅大腿静脈
69	V5,8—再建したMHV	浅大腿静脈
71	V5,8—再建したMHV	浅大腿静脈
72	V5—再建したMHV	浅大腿静脈
74	V5,8—再建したMHV	浅大腿静脈

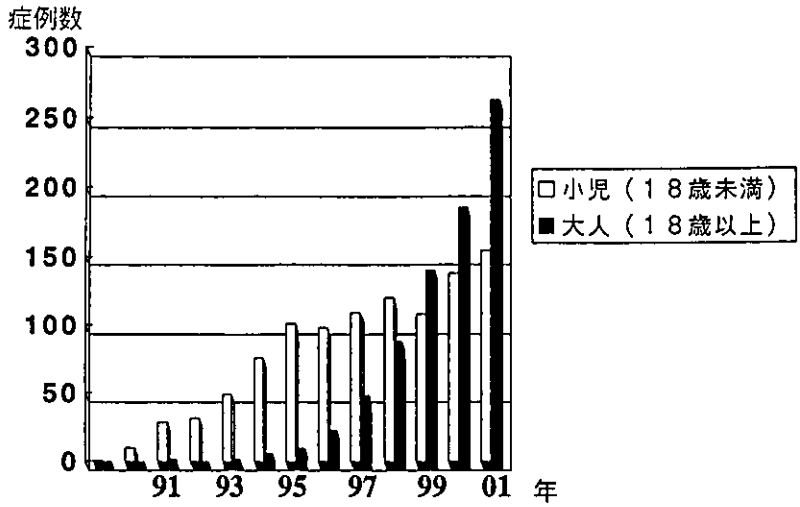

図1. 本邦における生体肝移植

が主流である特殊性もあり進行した例に対する移植が行われている．これまでの集計では，ミラノクライテリアに合致した症例の3年生存率は約80%で，ミラノクライテリアを越えて進行した症例の成績は3年生存が50%程度となっている．

5. おわりに

肝移植の普及で大きな障害になっているのは費用の問題である．特に，成人の生体肝移植は胆汁鬱滞性の疾患だけが保険適応で，わが国に多いＢ型肝炎，Ｃ型肝炎後の肝硬変やHCCに対する移植は適応外となっている．費用の面から移植を断念せざるを得ない患者さんも少なからずあり，医療の公平性の面からも早急な対応が求められている．(2004年から保険適応が拡大され，成人の劇症肝炎，肝硬変，HCCについても保険での移植が可能となった)．

生体肝移植がますます普及していく我が国ではあるが，ドナートなられた方々の中には何らかの合併症に悩む方もおられる．脳死からの臓器提供を増やす努力がこれまで以上に求められている．

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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

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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 post-operative 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 non-cirrhotic 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 pre-operatively 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.

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International Symposium

Impact of Enteral Nutrition in Adult-to-Adult Living Donor Liver Transplantation
: A Preliminary Study

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The Impact of enteral nutrition (EN) in living donor liver transplantation (LDLT) has not been well examined. We analyzed 83 consecutive adult-to-adult LDLT cases who had a preoperative MELD score of over 18points. There was no major complication related to the placement of EN tube. The better patient survival was found in the patients receiving EN (n=35) compared those who were not (n=48). Bilirubin clearance, prothrombin time, serum creatinine level and total lymphocyte count were better in EN group. Incidence of acute cellular rejection was lower in EN group. There was no difference about incidence of infectious and surgical complications. Our results demonstrated in adult-to-adult LDLT that EN was well tolerated and provided the better patient survival in more deteriorated patients.

Living donor liver transplantation, Enteral nutrition

Introduction

The living-donor liver transplant program first started in Japan in 1990, and remains the major form of liver transplantation because of the scarcity of the cadaveric donor pool[1]. Experience of, and technical improvements in pediatric living donor liver transplantation (LDLT) have led to the use of right lobe grafts in adult-to-adult LDLT[4]. Recently, the rapid increase in adult LDLT using right lobe grafts has dramatically changed the age and disease distribution. The overall 5-year survival of adult-to-adult LDLT in our center is 74.1% (n=200), and is comparable with those of cadaveric liver transplantation. However, the postoperative catch-up is not always satisfactory compared with cadaveric liver transplantation because of the 'small-for-size' graft. Major concems remain about the relatively 'small-for-size' syndrome in LDLT, such as the persistent hyperbilirubinemia, massive ascites, coagulopathy, and the possibility of inducing susceptibility to infection and kidney dysfunction associated with 'small-for-size' grafts[5].

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In nutrition care after liver transplantation, the superior status of enteral nutrition (EN) over total parenteral nutrition has been established in cadaveric liver transplantation, meaning that enteral feeding after liver transplantation is effective in maintaining the nutritional status and has potential benefits in terms of reduced complications[4,5,6]. However, all of these reports were based on the experience with cadaveric liver transplantation. It is expected that the positive impact of enteral nutrition might be significant with 'partial liver' more than with 'whole liver' transplantation. To support the nutrition status of patients, the maintenance of the relatively 'small-for-size' graft function and to obtain better patient survival following adult-to-adult LDLT, we initiated EN from October 2000. In the present study we evaluate the impact of EN in the patients who received adult-to-adult LDLT in Kyoto University Hospital.

Patients and Methods

Of 820 patients who underwent liver transplantation between June 1990 and October 2002, 200 patients received adult-to-adult LDLT at Kyoto University Hospital. Among the 200 patients, 83 patients (41.5%) had a preoperative MELD score of over 18 points, which stands as the model for end-stage liver disease[7]. Of these 83 patients, 13% received a blood type incompatible graft and 31% were kept in the ICU preoperatively. Thirty-five patients were managed posttransplantation with EN and 48 without EN. Table 1 shows the profile of the patients and operations involved in this study. There were no significant difference between the with and without EN groups as far as patient age, disease distributions and operation profiles were concerned. The follow-up period was shorter with the EN group ($p < 0.01$). None of the patients in the group without EN received nasogastric tube feeding.

The EN tube was placed after the completion of all transplant anastomoses. A site in the jejunum was selected which could be easily reached from the abdominal wall. The entry site in the proximal jejunum was 20 cm distal to the ligament of Treiz. A Witzel tunnel was created over the tube to avoid leakage.

Selective bowel decontamination including Kanamiycin sulfate, lactulose and polymyxin B by mouth was initiated 3 days before transplantation and enteral nutrition with ELENTALR® (Ajinomoto Pharma Co., LTD, Tokyo, Japan) was started on postoperative day 2. The formula contains nitrogen, carbohydrate and lipid, and is a special formula consisting only elemental components which are chemically well-defined and mostly absorbed in their original form, not being digested in the intestinal tract. It additionally contains free amino acids, carbohydrates, vitamins, mineral and 0.64g /100g fat.

Enteral nutrition was started at 480 kcal/day and increased to a maximum of 30 kcal/kg/day. Once oral intake was established, tapering off of the EN was started.

The operation was performed according to the standard right lobe LDLT procedure 2. A veno-venous bypass was not used as total clamping of the inferior vena cava could be avoided in all cases. Biliary reconstruction was basically achieved with duct-to-duct anastomosis, and 91.6 % of the group with EN and 89.6% of the group without EN received duct-to-duct biliary reconstruction ($p = NS$).

Immunosuppression consisted of tacrolimus and low dose steroids[8]. Tacrolimus administration was started from the day after transplantation. The target whole blood trough level of tacrolimus was 10-12 ng/ml for the first two weeks, approximately

Figure 1. Patients and operation profiles in adult-to-adult living donor liver transplantation (MELD* score >18)

	With EN**	Without EN**
Case number	35	48
Median follow-up (month)	9.0	31.0
Recipient age (years)	47.6±10.5	45.2±9.5
Donor age (years)	39.8±11.9	40.2±11.8
GRWR*** (%)	1.10±0.27	1.10±0.31
Cold ischemic time (min)	127±91.9	116±99.2
Warm ischemic time (min)	45.2±13.4	44.3±8.4
Original liver disease		
Liver cirrhosis (with HCC)	16 (7)	25 (5)
Fulminant hepatic failure	10	15
Cholestatic liver disease	5	4
Metabolic liver disease	1	1
Others	3	1

*; MELD: Model for end-stage liver disease 7)

**; EN: Enteral nutrition

***; GRWR: Graft-to-recipient weight ratio

10 ng/ml for the following two weeks and 5-10 ng/ml thereafter. Steroids treatment was initiated at the time of graft reperfusion at a dose of 10 mg/kg, then tapered from 1 mg/kg/day to 0.3mg /kg/day during the first month. Patients who received ABO-incompatible transplants had preoperative plasma exchange or double filtration plasmapheresis in order to reduce the anti-ABH antibody titer, and prostaglandin E1, cyclophosphamide and additional steroids were administered postoperatively from the portal vein or hepatic artery catheter[9].

Acute rejection was diagnosed on the basis of liver biopsy. All the rejection episodes were treated with a steroid bolus injection.

Values are presented as means±standard deviations. Statistical analysis was performed with the generalized Wilcoxon test. Actuarial 1- and 5-year graft survival curves were calculated with the non-parametric Kaplan-Mejer method and compared among the groups with the Wilcoxon test. P values less than 0.05 were regarded as significant throughout the study.

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

Results

There were 3 complications (8.6%) related to placement of the EN tube. Three patients had skin infection around the entry site of EN tube, which was easily managed with drainage.

No significant difference in the patient survival was seen between the group with EN (n=92, 75%) and the group without EN (n=108, 74.1%) after the overall adult-to-adult LDLT series (n=200) (p=0.18). However, if we compare those patients in a more advanced state of deterioration, whose preoperative MELD score was over 18 points, better patient survival was

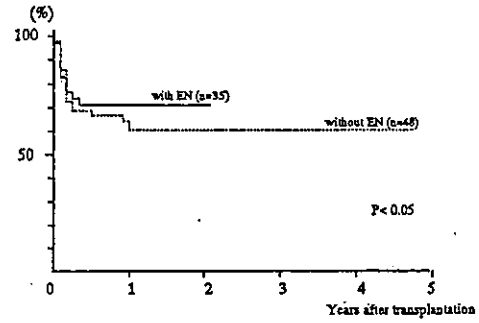

Figure 2. Patient survival in adult-to-adult living donor liver transplantation (MELD* score > 18) with or without enteral nutrition. Better patient survival was found in the patients receiving EN (71.0%) compared those who were not (60.4%) ($p < 0.05$).

found in the patients receiving EN (n = 35) compared those who were not (n = 48) (Figure 2. $p < 0.05$). Among these patients, 42% of the patients were classified as UNOS status 1 or classical 2A. Mean MELD score 28.5 ± 8.8 in the EN group and 28.1 ± 9.0 in the group without EN.

Biochemical findings

Serum asparate aminotransferase (AST), total bilirubin, prothorombin time (PT), serum creatinine, total cholesterol, cholinesterase, serum albumin and total lymphocyte count (TLC) were collected preoperatively and for the first 4 postoperative week.

There was no significant difference in AST levels between the two groups. Serum bilirubin clearance was much delayed and persistent hyperbilirubinemia was observed in the group without EN at POD 10 and later ($p < 0.05$). The difference in prothrombin time was not prominent, but some delayed recovery was observed also in the group without EN. Interestingly, the serum creatinine level was significantly lower in the enteral nutrition group ($p < 0.01$). Whether this was really caused by prevention of a catabolic state cannot be answered by the present study. Twenty-three percent of patients in the EN group, and 15% of those in the no EN group received continuous hemofiltration therapy in perioperative period. Total cholesterol and cholinesterase levels were better in the latter half of the first month in the EN group, although the difference was not statistically significant. The albumin lebel was better in the group without EN, which might reflect frequent use of intravenous albumin for correction of ascites and pleural effusion in the immediate post-transplant period. Regarding the total lymphocyte count (TLC), better TLC recovery was found in the EN group, although without statistical significance (Figure 3).

Infectious complications

Incidence of bacteremia during the first month post-transplant, which is defined as postperative blood culture positive, was higher in the EN group (31.4%) than in the group without EN (18.8%). However, the incidence of Gram negative bacteremia was lower in the EN group (36.4%) than in the group without EN (44.4%). The common Gram negative bacteremia was caused by *Pseudomonas aeruginosa, Serratia, and Xanthorophomonas maltophilia*. Gram positive bacteremia was mainly caused by the Staphylococcus species. The incidence of EBV infection was higher in EN group (8.6% for the EN, and 0% for the group without EN), and CMV infection was also high in the EN group (40.0% for the EN, and 14.6% for the group without EN), but the differences were not statistically significant.

Acute cellular rejection

The incidence of acute cellular rejection (ACR) was lower in the EN group (22.9% vs. 45.8%, $p < 0.05$), however the onset of ACR did not differ with each group. As we did not measure immune

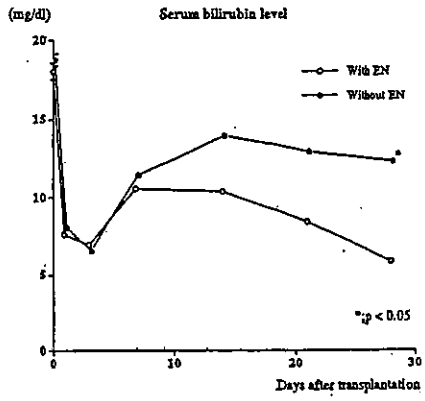

Figure 3A. Changes in serum bilirubin level

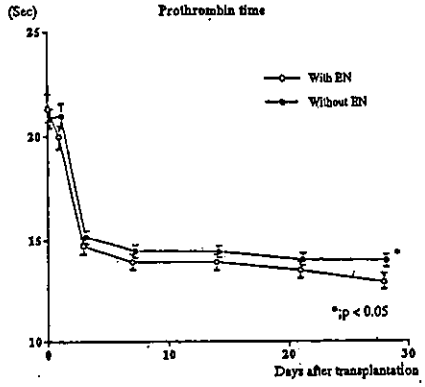

Figure 3B. Changes in Prothrombin time

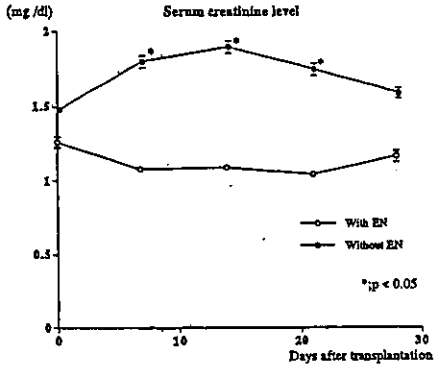

Figure 3C. Changes in serum creatinine level

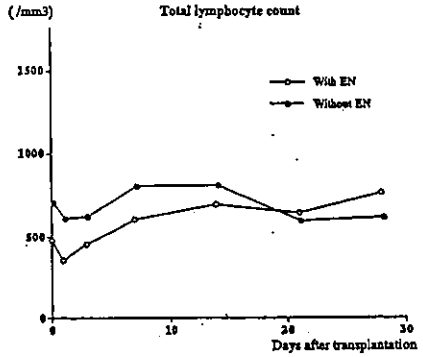

Figure 3D. Changes in total lymphocyte count

and inflammatory responses in this study group, further study is necessary to make a definite conclusion about EN and ACR.

Surgical complications

There was no difference concerning the surgical complications between the two groups, such as bleeding (20.0%, EN ; 18.8%, no EN), perforation (5.7% vs. 4.2%), biliary leakage (8.6% vs. 10.4%), and HAT (5.7% vs. 2.0%) in each group. Shorter hospital stay was seen in the EN group (45.7±26.8 days in the EN, and 56.2±39.3 days in the group without EN), but the difference was not statistically significant.

Discussion

The patients after liver transplantation are at high risk for malnutrition related complications. Most patients who undergo liver transplantation, however, do not need nutrition assistance to meet their metabolic demands, aside from oral dietary supplementation[10]. The actual percentage of liver transplant recipients who might benefit from EN is a difficult number to obtain and will somewhat depend on the referral base[11]. Also the selection criteria for EN are difficult to determine who the most appropriate liver transplantation candidates might be.

Based on the initial experience of 100 adult-to-adult LDLT cases in Kyoto University hospital, 17% of the patients had perioperative infectious complications. It was reported that EN was well tolerated and decreased the rate of postoperative infections in liver transplant recipients[12]. In the present study, we investigated the impact of EN in more deteriorated patients whose MELD score was over 18 points, because of their delayed oral intake.

With this study, however, EN did not provide the same benefit as previously reported in cadaveric liver transplantation, such as bacterial and viral infections and surgical complications[4,5,12]. With regard to adult-to-adult LDLT, the patients had a potential risk of small-for-size graft which sometimes induces poor outcomes[3]. Our recent study demonstrated that infectious complications after LDLT are associated with decreased reticuloendothelial function and gut oxygen extraction, and consequent overgrowth of intestinal bacteria because of the potentially small-for-size graft, and the pathogenesis of infection in small-for-size grafts is related to a functional factor of the graft rather than pretransplant factors[13]. Further study is now going on whether EN can support the graft regeneration in partial liver transplantation using CT volumetry and cytokine expression (eg. TNF-α, INF, TGF-β).

Interesting results from among the biochemical findings were the better bilirubin clearance and serum creatinine level in the EN group. Bile duct epithelium is exposed to ischemia-reperfusion injury in liver transplantation, and bile stasis easily destroys the bile duct epithelium[14]. It was reported that EN could reduce bile stasis[15]. An increase in renal plasma flow and glomerular filtration rate have also been reported using EN, and the protection of renal function was partly related to maintenance of renal blood flow[16]. To prevent bile stasis and support renal insufficiency, the application of EN might be effective in LDLT patients.

The incidence of ACR was lower in the EN group in the present study. There have been several report about mucosal immunity related to nutrition. EN activates mucosal immunity, which induces Th2 cytokine production such as IL4 and IL10[17]. The Th2 cytokine expression of intraendothelial lymphocyte was suppressed, and Th1 cytokines were activated under the use of total parental nutrition[18-20]. As we did not measure immune and inflammatory responses in this study group, further study is necessary to make a definite conclusion about EN and ACR. Postoperative EN was accomplished successfully in LDLT. EN was well tolerated and resulted in better patient survival in patients whose condition had deteriorated further. With our study, EN did not provide the same benefit as previously reported in cadaveric liver transplantation, such as Bacterial/Viral infections and surgical complications.

However, EN can reduce hospital stay.

We conclude that after introduction of EN in adult-to-adult LDLT, the patient survival was improved. It could be recommended that EN should be indicated for the patients with MELD score greater than 18. The incidence of infections was not significantly reduced according to our conventional EN. Recently, the effectiveness of a fiber diet containing immunonutrition was reported[12]. To clarify the efficacy of EN in the LDLT program, further study is now going on as to whether EN can support small-for-size graft function.

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