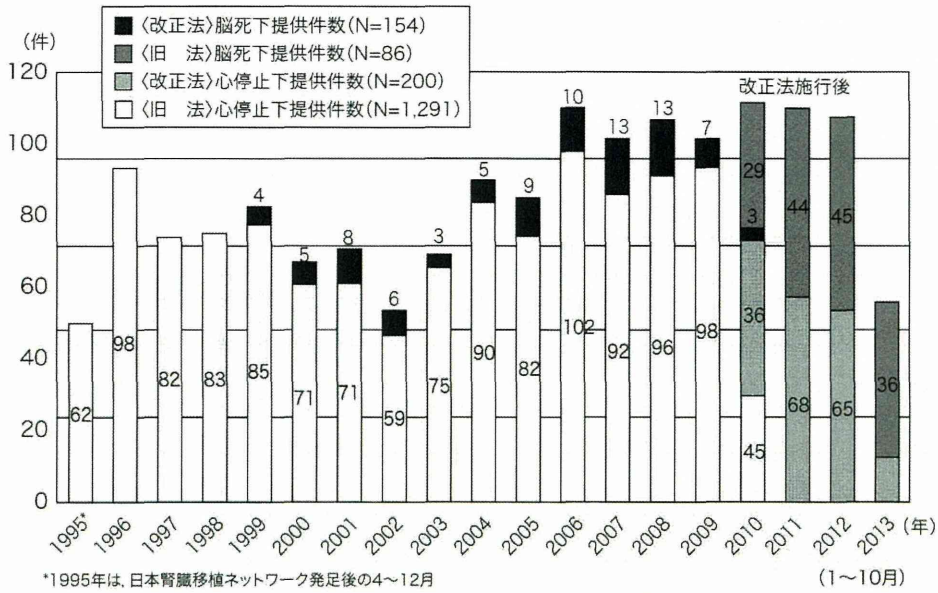

図2　臓器提供件数の年次推移

4 移植手術

手術は他の原因による劇症肝不全と基本的に差異はない．生体・脳死肝移植とも障害肝すべてを摘出しグラフトを移植する術式が選択されることが多い．一方，劇症肝不全の臨床経過を示す急激に荒廃した肝臓がなお旺盛な再生能を内包していることがある．このような症例では，障害肝を部分的に摘出しそのスペースにグラフトを移植する補助的同所性部分肝移植術(APOLT : Auxiliary Partial Orthotopic Liver Transplantation)を選択肢として考慮すべきである[16]．自己肝が十分に再生しグラフト肝の補助が不要になれば，免疫抑制剤を完全に中止できる利点があるためである．適応については，ヨーロッパの12施設30例のmulticenter reportが参考になる．すなわち，40歳以下の症例の78％，A・B型肝炎ウイルス・acetaminophenが原因である症例の82％，急性の臨床経過(黄疸から脳症までの期間が7日以下)を示した症例の87％に自己肝の完全な再生が認められたという[17]．さらに，障害肝の壊死パターンと自己肝再生能との緊密な関連や小児例における良好な自己肝再生能の報告もある[18,19]．自己肝とグラフト肝の間で起きる門脈血流不均衡や障害肝を残すことに起因するtoxic liver syndromeも考慮しなければならないが，原因薬物や年齢，病型，組織像などを勘案し，術式として常に念頭に置くべきである[20]．

5 術後管理

術後管理や免疫抑制療法についても他の劇症肝不全例と基本的な差異はない．唯一，原因薬物を用いるきっかけとなった原疾患にさらなる治療を要する場合，特別な配慮が必要となる．すなわち，当該薬剤に替わる治療薬が存在するか否か，その代替治療薬で十分な効果が得られるかなどを詳細に検討する必要がある(移植適応決定時も同様の検討が必要)．一例として，2013年に経験した抗結核薬による薬物性劇症肝不全に対し脳死肝移植

表3　薬物性劇症肝不全移植例(抗結核薬による劇症肝不全例)

	症例：64歳，女性
2012.8月	咳嗽出現
11.13	CT上左上肺野の浸潤影とガフキー5号にて活動性肺結核と診断
	2 month HRZE (INH，RFP，PZA，EB) + 4 month HR (INH，RFP)による治療開始
2013.4.18	黄疸，全身倦怠感あり．薬剤性劇症肝炎疑われ前医ICU入室
	血液濾過透析+血漿交換開始
4.19～21	ステロイドパルス療法施行
4.24	肝移植の適応に関し当科紹介(劇症肝炎急性型の診断)
4.27	脳死肝移植登録(10点待機) + 40歳長男をドナーとした生体肝移植の準備を開始
4.30	当院転院．
5.4	待機7日目脳死ドナー発生し脳死全肝移植を実施
5.23	術後19日目から抗結核薬(EB + LVFX + SM)の投与を再開
7.1	術後58日目に退院
	現在，結核の再燃なく肝機能にも異常を認めずに経過中

INH：イソニコチン酸ヒドラミド，RFP：リファンピシン，PZA：ピラジナミド，EB：エタンブトール
LVFX：レボフロキサシン，SM：ストレプトマイシン

を実施した症例を示す(表3)．2012年11月から活動性肺結核の診断でHRZE(INH＋RFP＋PZA＋EB)ならびにHR(INH＋RFP)療法が行われていた症例である．薬物開始5カ月目に黄疸が出現し急速に昏睡を発症．ステロイドパルスによるトランスアミナーゼの低下は得られず，当科紹介ののち脳死肝移植登録と生体肝移植の準備を開始した．移植適応決定は，紹介時に肺結核が非活動性であったこと，肝障害をきたした薬物を含まない治療で術後治療が可能と判断したことによる[21]．生体肝移植へのconvertを考慮していた登録7日目(血液浄化療法開始から16日目)に脳死ドナーが発生し，全肝移植を実施した(年齢からAPOLTは選択せず)．術後19日目から抗結核薬(EB＋LVFX＋SM)を再開し，術後58日に退院．現在，肺結核の再燃なく肝機能も良好に推移している．本症例は術前にD-LST非実施となっているが，INHもしくはRFPが原因薬剤と考えられた．

6 結語

現状では薬物性劇症肝不全に対する移植例も他の原因によるものと同様に対応されている．個々の薬剤性肝障害の病態解明など十分に検討されているとは言い難い．米国におけるLiverTox®のようなdata baseの構築が待たれる[22]．これにより劇症肝不全のなかでもウイルス性などとは異なった薬物性の特徴が明確となり，新しい患者カテゴリーとなるであろう．

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日消誌　2014：111：892—898

今月のテーマ　肝癌に対する肝臓移植の適応拡大と制限

肝癌移植症例におけるABO血液型不適合脱感作療法のインパクト

江川裕人[1)]　嶋村剛[2)]　藤堂省[3)]

要旨：本邦の生体肝移植の10%強が血液型不適合である．抗体関連拒絶を予防するため脱感作療法が工夫されてきたが，近年，リツキサン術前投与が広く行われるようになり，適合症例と遜色ないところまで成績が改善した．一方で，リツキサンの肝癌再発に対する影響はいまだ報告がない．今回，日本ABO血液型不適合移植研究会データベースと北海道大学全国集計肝癌肝移植データベースを融合させ，2009年末までに日本で実施された肝癌肝移植1106例（不適合66例）を解析した．リツキサン予防投与は再発を増強することなく生存率を適合症例と同等に改善した．リツキサン併施血液型不適合肝移植は，肝癌肝移植に対して有効な治療である．

索引用語：生体肝移植，血液型不適合，抗体関連拒絶，リツキシマブ，肝癌

はじめに

原則として血液型を一致させる脳死肝移植が主な欧米では，血液型不適合肝移植は，当初の重篤な合併症と不良な成績から緊急避難的手段とされてきた．本邦では脳死臓器提供がきわめて少ないことから生体肝移植が発達した．生体臓器提供者は選択範囲が近親者に限られるため，臓器提供の申し出があっても血液型が不適合となる頻度が高くなる．2011年の日本肝移植研究会登録ではわが国の肝移植において不適合移植は10%を超えている[1)]．血液型不適合移植の問題を解決するために，日本ABO血液型不適合移植研究会が組織され肝臓と腎臓で全国集計を行い経験を共有し，ともに戦略を練ってきた．

I　抗体関連拒絶と脱感作療法

血液型不適合移植では血液型抗原に対する抗体による抗体関連拒絶（antibody mediated rejection；AMR）が問題となる[2)]．AMRは臨床的には，術後1〜2週間で発症し1カ月以内に肝壊死に陥る肝壊死型と，術後2〜3カ月で発症し胆管炎を繰り返して半年から数年かけて肝不全に陥る肝内胆管合併症型のどちらか一方あるいは混合型の経過をとる[2)3)]．AMRの機序は，移植臓器の血管内皮に発現している血液型抗原にレシピエントの抗体が結合し，補体反応が関与しながら惹起される血管内皮炎が元となって生じる循環障害による臓器障害である（Figure 1）．このような循環障害が著しい場合は一気に肝逸脱酵素が上昇し，CTで肝壊死が認められるようになる．一方，微小肝動脈のみが障害された場合は，当初は肝機能に異常がなくても1カ月後あたりから胆管炎を繰り返すようになり，肝移植後肝動脈血栓症や肝癌に対する肝動脈塞栓療法後にみられる虚血性胆管障害と同様の硬化性胆管炎の様相を呈してくる．

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Impact of desensitization for ABO-blood barrier on living donor liver transplantation for hepatocellular carcinoma
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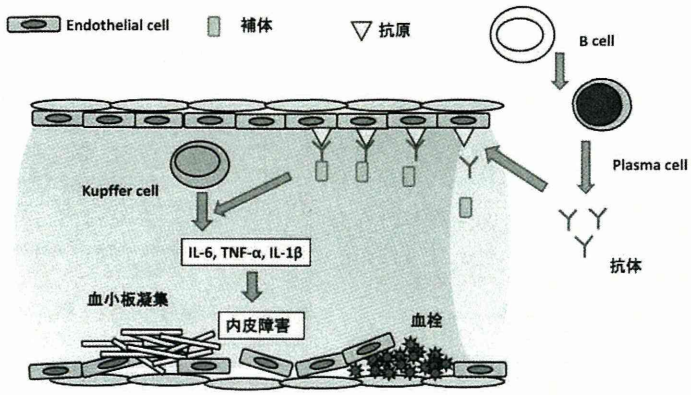


Figure 1. 血液型不適合肝移植における抗体関連拒絶の機序.

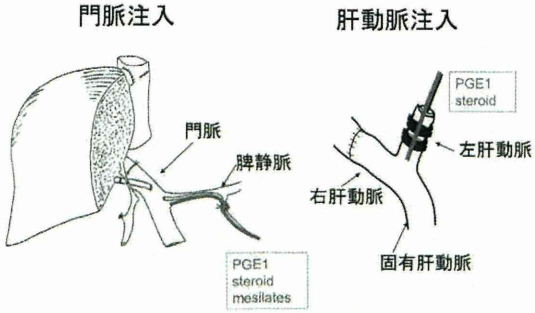


Figure 2. 肝持続注入療法：左：門脈注入療法．門脈本幹にカテーテル先端が来ないように注意する．右：肝動脈注入療法．固有肝動脈内腔にカテーテル先端が来ないように注意する．

このAMRを予防するためにさまざまな脱感作療法が工夫されてきた．まず抗ドナー血液型抗体を除去する目的で，交換輸血，血漿交換，血液濾過法などの血液浄化法が行われてきた．現在，血液型不適合肝移植に対する血漿交換は保険適応である．脾臓でB細胞が形質細胞に分化成熟することから移植後の新たな抗体産生を抑制するために乳幼児を除いて脾臓摘出が行われてきた．さらに通常の免疫抑制プロトコールに加え，エンドキサンやOKT3，予防的ステロイドパルスなどを用いて免疫抑制を強化する方法が試みられたが，若干の効果があるものの感染症で失う症例が多く，特に成人では2000年まで1年生存率は2割に満たなかった[2]．

このような状況の中で，2002年に慶應義塾大学より門脈持続注入療法の有効性が報告された[4]．肝持続注入療法は，門脈にカテーテルを留置し（Figure 2）[4]，プロスタグランディン（PG）E1，メシル酸ガベキサート，メチルプレドニゾロンの3剤を術中から持続的に投与する方法で，その機序は，血管内皮炎の局所的な抑制と考えられている．その効果は各施設で確認され，1年生存率も6割を超えるようになった[5]．一方，拒絶反応の際には門脈圧が上昇して門脈血流が逆流し門脈注入のみでは薬剤が肝内に送り込まれないことがある．そこで確実に薬剤を送り込むために，京都大学は門脈＋肝動脈持続注入療法を導入した[5]．その結果，胆管合併症がほぼなくなり肝壊死も軽減して死亡率が低下した．一方で，脾臓摘出と門脈カテーテル留置をした症例で門脈血栓が高頻度に認められた．そこで門脈血栓を防止するために，脾臓を温存し門脈にカテーテルを留置しない，肝動脈単独持続注入療法が2003年より行われるようになった[5][6]．

さらに2004年に，Bリンパ球抑制による抗体産生抑制を目的として抗CD20抗体（リツキシマブ：リツキサン®）が導入されるようになると，成績は著しく向上した[7][8]．骨髄で作られたB細胞前駆細胞は脾臓やリンパ節で成熟B細胞に分化し，最終的には抗体を産生する形質細胞に分化する．CD20はpre B細胞から成熟B細胞に発現し，形質細胞には認められない．リツキサンはB

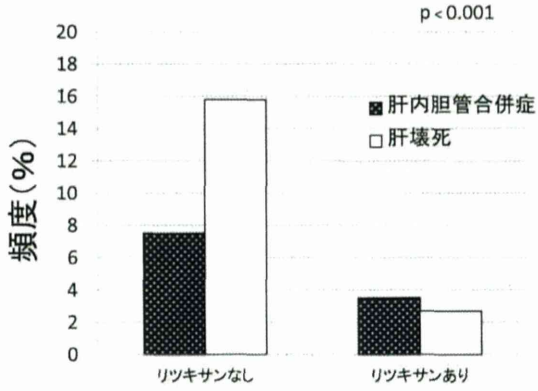


Figure 3. リツキサン予防投与と抗体関連拒絶頻度：肝壊死，肝内胆管合併症ともにリツキサン使用症例で有意に少ない．

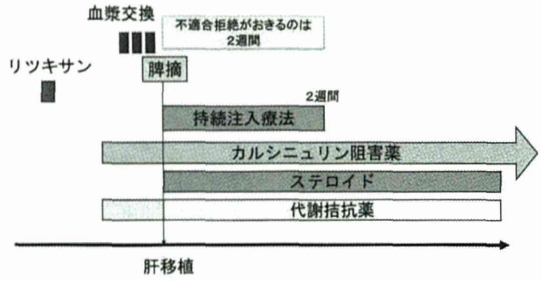


Figure 4. 脱感作療法：術前にリツキサンに1回，代謝拮抗薬（セルセプト，ミゾリビン）とカルシニュリン阻害薬を1週間前から開始する．抗体価が高ければ血液浄化療法を行う．術中に脾臓を摘出し，持続注入療法をする場合カテーテルを留置する．持続注入療法は通常2週間行う．ステロイド，カルシニュリン阻害薬，代謝拮抗薬は適合移植の場合と同量とする．

細胞表面に発現するCD20に特異的に結合した後，補体依存性細胞傷害作用および抗体依存性細胞介在性細胞傷害作用によりB細胞を破壊する．抗体を産生する形質細胞はCD20を発現しないため，リツキサンにより破壊されることはないが，形質細胞に分化する手前のB細胞を枯渇させることによって抗体産生能を低下させる機序が考えられている．リツキサンを術前に1回，成人で300～500mg投与すると，末梢Bリンパ球は3日ほどで低下する．2014年Egawaらの日本の全国集計報告では，成人で，リツキサン非投与症例（120例）のAMR発症率は26%であったのに対し，投与症例（258例）では6%であった[8]．特にAMRによる肝壊死は16%から3%に減少した(Figure 3)．生存率は，非投与症例で1年58%，5年48%に対し，投与症例でそれぞれ77%，70%に改善した[8]．リツキサンが導入された2004年を境として，血液型不適合移植の施行件数は増加し，2007年以降は年間40例程度となっている[8]．一方でリツキサン予防投与症例では，門脈持続注入療法も脾臓摘出も生存率の上乗せ効果が証明されなかった[8]．

Figure 4は現在の標準的な脱感作療法をすべて記入した図である．リツキサンが導入されるようになり持続注入療法を行わない施設が増加している[9]．脾臓摘出に関しては，術後に脾臓でBリンパ球が形質細胞に成熟化し抗体を産生する可能性がある一方で，リツキサンを使用すれば脾摘は不要であるという小規模の報告が散見される[10]．現在リツキサンの投与は保険適応外であるが，保険適応が認められれば，血液型不適合移植症例は今後さらに増加することが予測される．ただし，リツキサンを使用しても5%のAMRが発症している．このAMRに対するより効果的な治療法の確立が今後の課題である．

B細胞を抑制することの問題点について考えてみる．Egawaらによると，術後感染症の発症率は，リツキサン使用群では非使用群に比較して，細菌感染とウイルス感染は同等であったが，真菌感染は有意に低下した．これはリツキサン使用により闇雲に免疫抑制を強化することがなくなった，特にステロイド使用量が減少したことが関与していると推察される．悪性リンパ腫に使用する際の最も重篤な副作用はB型肝炎再活性化による劇症肝炎であるが，B型肝炎関連の肝移植ではあらかじめ核酸アナログとHBIGを使用するので問題にならない．C型肝炎に関連する免疫応答は，Tリンパ球でありかつ早期に抗ウイルス治療を導入するので問題にならない．そこで懸念されるのが肝癌の再発への影響である．

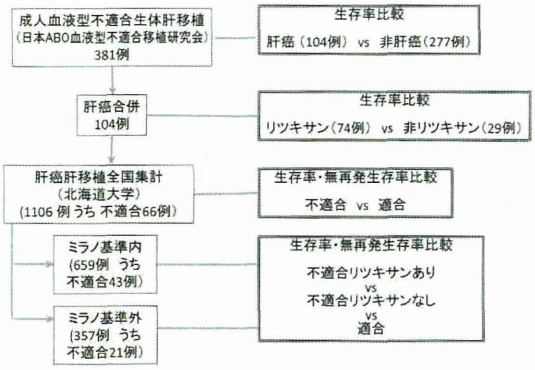


Figure 5. 本稿の解析の対象となった症例と解析内容.

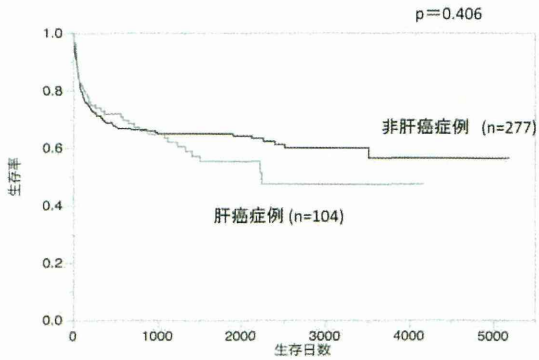


Figure 6. 成人不適合全症例における肝癌の有無が生存率に及ぼす影響：不適合移植症例の中で，肝癌症例（n＝104）と非肝癌症例（n＝277）の生存率に差はなかった（p＝0.406）.

II 肝癌移植症例における不適合移植のインパクト

1. 検討1 血液型不適合症例における肝癌合併およびリツキサンの影響

日本ABO血液型不適合移植研究会の2012年全国調査データベースを解析した（Figure 5）. 統計ソフトはJMP11を用いた. 年齢は21歳から70歳，中央値52歳. 性別は男性169例，女性212例. 観察期間は4～5193日. 2011年末までに血液型不適合肝移植を施行した381例のうち104例が肝癌合併症例であった. 不適合移植症例の中で，肝癌症例（n＝104）と非肝癌症例（n＝277）の生存率に差はなかった（Figure 6，p＝0.406）.

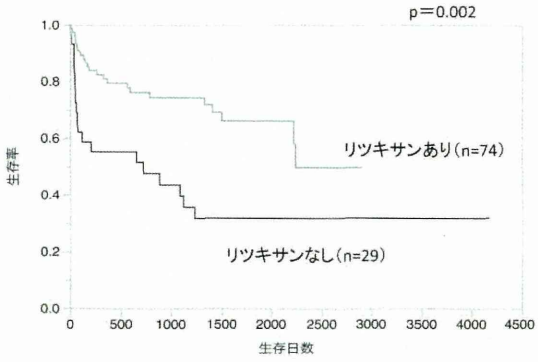


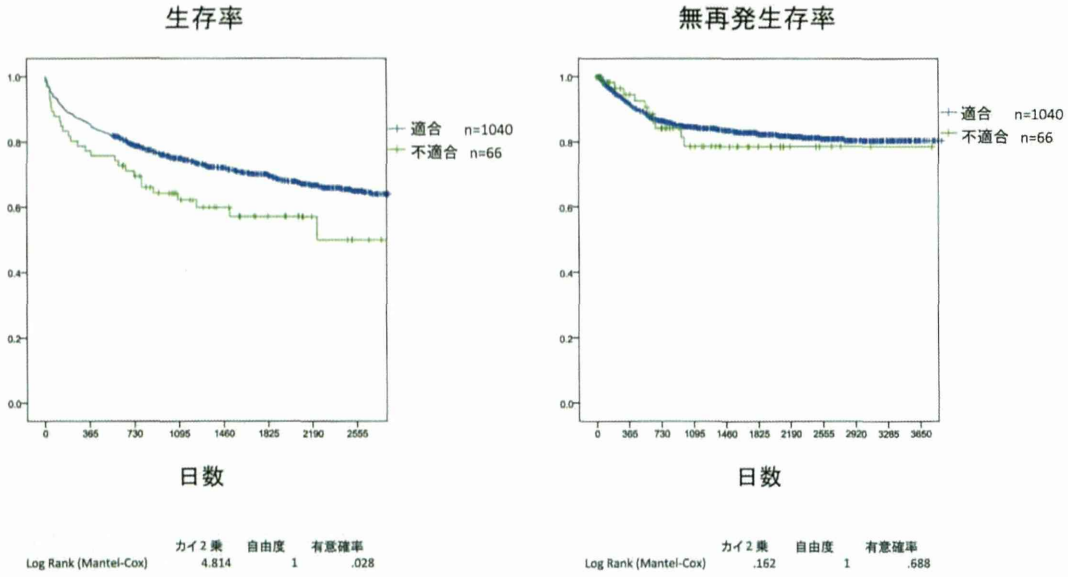
Figure 7. 成人肝癌不適合症例におけるリツキサン予防投与が生存率に及ぼす影響：肝癌症例の中でリツキサン使用症例（n＝74）と非使用症例（n＝29）を比較した. 1年生存率74%対29%（リツキサンあり対なし），5年生存率66%対32%で，有意にリツキサン使用症例で生存率が良好であった（p＝0.002）.

次に肝癌症例の中でリツキサン使用症例（n＝74）と非使用症例（n＝29）を比較した. 1年生存率74%対29%，5年生存率66%対32%で，有意にリツキサン使用症例で生存率が良好であった（p＝0.002）（Figure 7）.

2. 検討2 肝癌肝移植症例における血液型不適合移植およびリツキサンの影響

日本ABO血液型不適合移植研究会の2012年全国調査データベースは，不適合移植症例のみ登録され腫瘍因子や肝癌再発の情報は含まれていない. 一方，北海道大学が作成した全国集計肝癌肝移植データベースには血液型適合性と脱感作療法の情報が含まれていない. そこで両者を融合させ，2009年末までに日本で実施された肝癌に対する肝移植1106例（不適合66例）を本検討の対象とした. 統計ソフトはSPSSを用いた. 年齢は21歳から73歳，中央値56歳. 性別は男性798例，女性308例. 観察期間は1～4621日. リツキサン使用46例，非使用19例，不明1例. 術前画像ミラノ基準内659例，基準外367例，不明80例. 患者生存率と無再発生存率を，全症例で検討した後，ミラノ基準内と基準外に分けて検討した（Figure 5）.

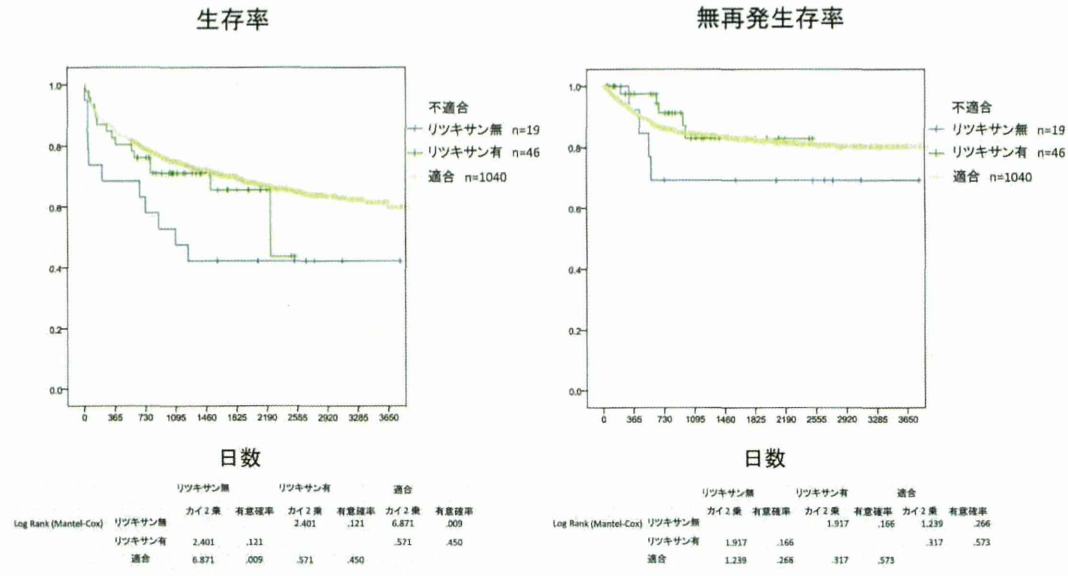
適合症例は不適合症例より生存率は有意に（p＜0.0258）良好であったが無再発生存率はほぼ



	カイ2乗	自由度	有意確率
Log Rank (Mantel-Cox)	4.814	1	.028

	カイ2乗	自由度	有意確率
Log Rank (Mantel-Cox)	.162	1	.688

Figure 8. 血液型適合移植が生存率と無再発生存率に及ぼす影響：適合症例は不適合症例より生存率は有意に（p＜0.0258）良好であったが，無再発生存率はほぼ一致していた．

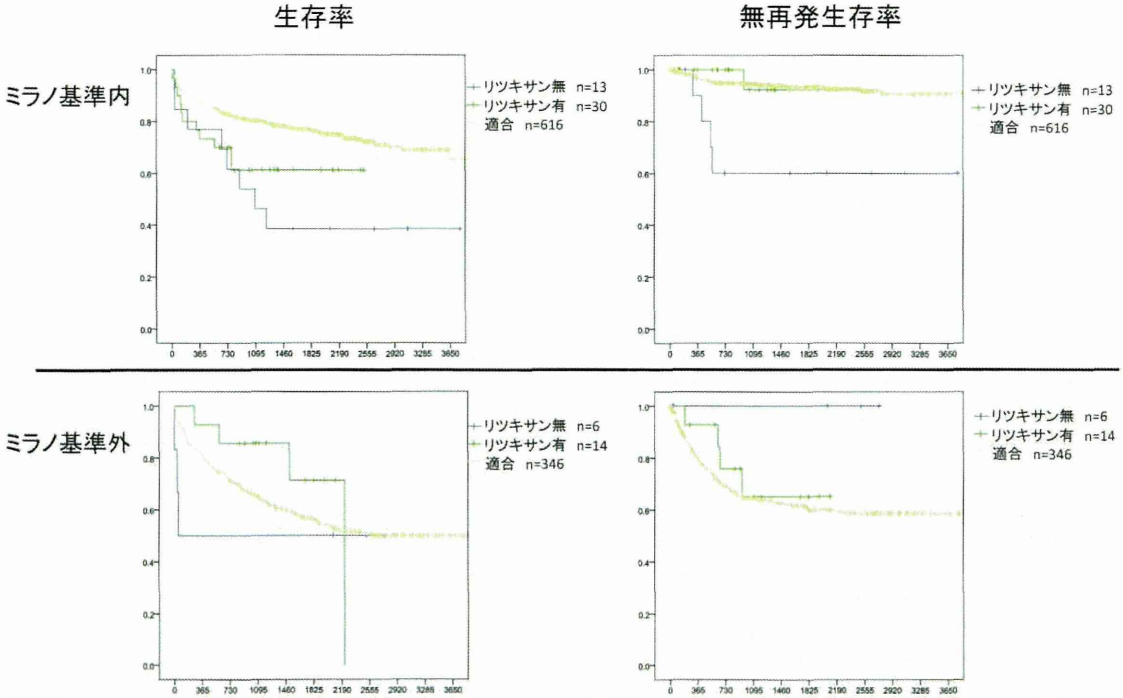


		リツキサン無		リツキサン有		適合	
		カイ2乗	有意確率	カイ2乗	有意確率	カイ2乗	有意確率
Log Rank (Mantel-Cox)	リツキサン無			2.401	.121	6.871	.009
	リツキサン有	2.401	.121			.571	.450
	適合	6.871	.009	.571	.450		

		リツキサン無		リツキサン有		適合	
		カイ2乗	有意確率	カイ2乗	有意確率	カイ2乗	有意確率
Log Rank (Mantel-Cox)	リツキサン無			1.917	.166	1.239	.266
	リツキサン有	1.917	.166			.317	.573
	適合	1.239	.266	.317	.573		

Figure 9. リツキサン使用が生存率と無再発生存率に及ぼす影響：適合症例はリツキサンあり不適合症例（46例）と生存率に差を認めなかったが，リツキサンなし不適合症例（19例）より有意に（p＝0.009）良好であった．無再発生存率は3群で差がなかった．

一致していた（Figure 8）．次に不適合症例をリツキサンあり（46例）となし（19例）に分け，適合症例と合わせて3群間で比較した（Figure 9）．適合症例はリツキサンあり不適合症例と生存率に差を認めなかったが，リツキサンなし不適合症例より有意に（p＝0.009）良好であった．無再



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			リツキサン無		リツキサン有		適合	
			カイ2乗	有意確率	カイ2乗	有意確率	カイ2乗	有意確率
Log Rank (Mantel-Cox)	基準内	リツキサン無			.901	.343	8.836	.003
		リツキサン有	.901	.343			4.624	.032
		適合	8.836	.003	4.624	.032		
	基準外	リツキサン無			.549	.459	.390	.532
		リツキサン有	.549	.459			.928	.336
		適合	.390	.532	.928	.336		

iMilanw0b1

			リツキサン無		リツキサン有		適合	
			カイ2乗	有意確率	カイ2乗	有意確率	カイ2乗	有意確率
Log Rank (Mantel-Cox)	基準内	リツキサン無			6.889	.009	15.235	.000
		リツキサン有	6.889	.009			.129	.719
		適合	15.235	.000	.129	.719		
	基準外	リツキサン無			1.211	.271	1.607	.205
		リツキサン有	1.211	.271			.376	.540
		適合	1.607	.205	.376	.540		

Figure 10. ミラノ基準とリツキサンの生存率と無再発生存率に及ぼす影響：術前画像診断におけるミラノ基準内と基準外に分けてそれぞれ，適合，リツキサンあり不適合，リツキサンなし不適合の3群間で生存率と無再発生存率を比較した．基準内では，患者生存率は，適合症例はリツキサンあり不適合症例（p＝0.032），リツキサンなし不適合症例（p＝0.003）のいずれの群よりも良好であった．無再発生存率は，適合症例とリツキサンあり不適合症例は一致し，リツキサンなし不適合症例より有意に（p<0.0001）良好であった．ミラノ基準外では患者生存率，無再発生存率ともに差を認めなかった．

発生存率は3群で差がなかった．次に，術前画像診断におけるミラノ基準内と基準外に分けてそれぞれ，適合，リツキサンあり不適合，リツキサンなし不適合の3群間で生存率と無再発生存率を比較した(Figure 10)．基準内では，患者生存率は，適合症例はリツキサンあり不適合症例（p＝0.032），リツキサンなし不適合症例（p＝0.003）のいずれの群よりも良好であった．無再発生存率は，適合症例とリツキサンあり不適合症例は一致し，リツキサンなし不適合症例より有意に（p<0.0001）良好であった．ミラノ基準外では患者生存率，無再発生存率ともに差を認めなかった．以上から，1）肝癌に対する肝移植では，不適合症例は患者生存率は適合症例より低値であるが，リツキサン使用により再発に影響することなく生存率は改善する，2）ミラノ基準内ではリツキサン非使用プロトコールの再発への関与が示唆される，と考えられた．

ま と め

生体肝移植が主たる現状では，リツキサン予防投与を併施する血液型不適合肝移植は，肝癌再発を増加させることのない有効な治療である．

本論文内容に関連する著者の利益相反
：なし

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ORIGINAL ARTICLE

Selection of Living Donor Liver Grafts for Patients Weighing 6kg or Less

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In the field of pediatric living donor liver transplantation (LDLT), physicians sometimes must reduce the volume of left lateral segment (LLS) grafts to prevent large-for-size syndrome. There are 2 established methods for decreasing the size of an LLS graft: the use of a segment 2 (S2) monosegment graft and the use of a reduced LLS graft. However, no procedure for selecting the proper graft type has been established. In this study, we conducted a retrospective investigation of LDLT and examined the strategy of graft selection for patients weighing ≤6 kg. LDLT was conducted 225 times between May 2001 and December 2012, and 15 of the procedures were performed in patients weighing ≤6 kg. We selected S2 monosegment grafts and reduced LLS grafts if the preoperative computed tomography (CT)–volumetry value of the LLS graft was >5% and 4% to 5% of the graft/recipient weight ratio, respectively. We used LLS grafts in 7 recipients, S2 monosegment grafts in 4 recipients, reduced S2 monosegment grafts in 3 recipients, and a reduced LLS graft in 1 recipient. The reduction rate of S2 monosegment grafts for use as LLS grafts was 48.3%. The overall recipient and graft survival rates were both 93.3%, and 1 patient died of a brain hemorrhage. Major surgical complications included hepatic artery thrombosis in 2 recipients, bilioenteric anastomotic strictures in 2 recipients, and portal vein thrombosis in 1 recipient. In conclusion, our graft selection strategy based on preoperative CT-volumetry is highly useful in patients weighing ≤6 kg. S2 monosegment grafts are effective and safe in very small infants particularly neonates. *Liver Transpl 21:233-238, 2015.* © 2014 AASLD.

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Since Starzl et al.[1] first performed pediatric liver transplantation (LT) in 1967, there have been significant advances in surgical procedures, preservation technology, immunosuppressive management, and perioperative care; therefore, pediatric LT outcomes have significantly improved over the past 2 decades.[2] LT has become an established treatment for children with end-stage liver disease.

However, performing LT in very small infants remains a medical and surgical challenge because the procedure is associated with many problems, including size mismatches, vascular complications, and infections.[3-9] Among these problems, the most difficult issue is graft size mismatching in very small infants. To prevent large-for-size syndrome, transplant surgeons must reduce the size of left lateral segment (LLS) grafts. In principle, the graft/recipient weight ratio (GRWR) should be reduced to ≤4%.[10,11] In our experience, however, the median actual volume of LLS grafts (n = 152) used in our facility has been 234 g (range, 146-382 g). For recipients with a body weight of 6 kg, 4% of the GRWR is 240 g. Therefore,

Abbreviations: CPS1D, carbamoyl phosphate synthetase 1 deficiency; CT, computed tomography; GRWR, graft/recipient weight ratio; LDLT, living donor liver transplantation; LLS, left lateral segment; LT, liver transplantation; POD, postoperative day; S2, segment 2; S3, segment 3.

Potential conflict of interest: Nothing to report.

Naoya Yamada contributed to the study design, data acquisition, analysis and interpretation, and drafting of the manuscript. Taizen Urahashi, Yoshiyuki Ihara, Taiichi Wakiya, Noriki Okada, Yuta Hirata, Atsushi Miki, Yuji Kaneda, Hideki Sasanuma, and Yasunaru Sakuma contributed to the acquisition of data. Yukihiro Sanada, Yoshikazu Yasuda, and Koichi Mizuta contributed to the data analysis and interpretation and a critical revision of the manuscript for important intellectual content.

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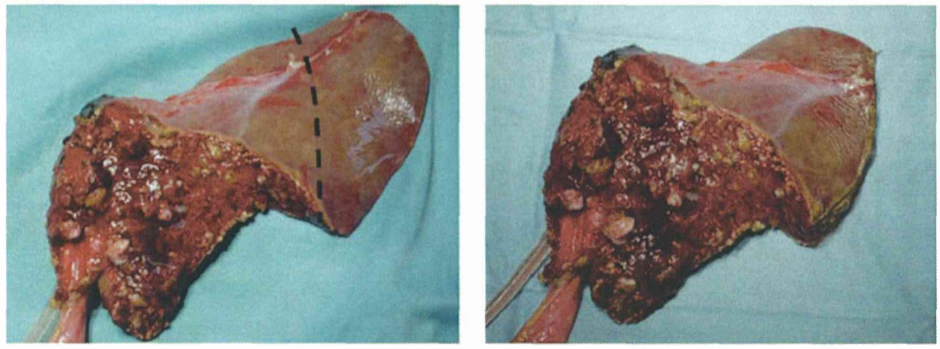

Figure 1. S2 monosegment graft and reduced S2 monosegment graft.

transplant surgeons must consider reducing the size of LLS grafts in recipients with a body weight ≤ 6 kg.

Kasahara et al.[12,13] introduced the technique of using reduced LLS grafts in small infants, and they reported good outcomes. On the other hand, we previously reported that segment 2 (S2) monosegment grafts were highly effective in small infants (particularly neonates; Fig. 1).[14] However, there is no consensus about how to distinguish between indications for S2 monosegment grafts and reduced LLS grafts, and selection procedures vary among institutes. We here present a retrospective analysis of our experience with performing living donor liver transplantation (LDLT) in patients weighing ≤6 kg, and we analyze the efficacy of our strategy for LDLT graft selection.

PATIENTS AND METHODS

Patients

A total of 219 pediatric patients underwent LDLT 225 times between May 2001 and December 2012 at Jichi Medical University Hospital (Tochigi, Japan). The median age and weight were 1.5 years (range, 0.04-19.5 years) and 9.9 kg (2.6-64.9 kg), respectively. The most common indication was biliary atresia (n = 166 or 73.8%). Among these cases, LDLT was 15 times performed in patients weighing ≤6 kg. The characteristics of these 15 patients are shown in Table 1. We retrospectively analyzed correlations between the graft type and the graft liver volume, graft survival rate, and 1-year incidence of complications (Clavien-Dindo score ≥ 2). Data were collected retrospectively from medical records. This protocol received a priori approval from the institutional review committee.

Preoperative Strategy for Graft Selection

We performed preoperative computed tomography (CT)–volumetry of the LLS for all donors. When the GRWR of the LLS graft according to preoperative CT-volumetry was ≤4%, we used the LLS graft. When the GRWR of the LLS graft was >4%, we planned a graft hepatectomy to reduce the GRWR of the LLS graft to <4%. We selected a reduced LLS graft when the predictive GRWR of the LLS graft was 4% to 5% and an S2 monosegment graft when the predictive GRWR of the LLS graft was >5%. If the actual GRWR of the graft was >4% on the back table, we performed a reduced hepatectomy. When we reduced the LLS graft on the back table, we first resected the lateral side of the LLS graft with the clamp-crush method, and we then resected the caudal side to make the graft ≤ 4% of the GRWR. When we reduced the S2 monosegment graft on the back table, we resected the lateral side of

TABLE 1. Summary of the Patient Data

Body weight, median (range), kg	5.1 (2.6-6.0)
Age, median (range), days	38 (13-266)
Sex, n (%)	
Male	2 (13.3)
Female	13 (86.7)
Original disease, n (%)	
Biliary atresia	8 (53.3)
Neonatal hemochromatosis	3 (20.0)
Fulminant hepatic failure	2 (13.3)
CPS1D	1 (6.7)
Idiopathic liver cirrhosis	1 (6.7)
Donor, n (%)	
Father	8 (53.3)
Mother	7 (46.7)
Blood type, n (%)	
Identical	6 (40.0)
Compatible	6 (40.0)
Incompatible	3 (20.0)
Graft type, n (%)	
LLS	7 (46.7)
S2 monosegment	4 (26.7)
Reduced S2 monosegment	3 (20.0)
Reduced LLS	1 (6.7)
Operation time, median (range), hours:minutes	13:37 (11:42-20:05)
Bleeding volume, median (range), mL	750 (200-2823)
Observation period, median (range), years	5.9 (0.1-12.2)

the S2 monosegment graft. We analyzed the graft selection procedure and the graft volume changes achieved with the reduction method for LDLT in patients weighing ≤6 kg.

Surgical Procedures for LDLT

The type of donor hepatectomy was determined according to the recipient body weight and the preoperative CT-volumetry value of the LLS graft. We performed left lateral segmentectomy for LLS grafts and in vivo segment 3 (S3) resection during left lateral segmentectomy for S2 monosegment grafts as previously reported.[14] The donor biliary anatomy was evaluated with either intraoperative repeated real-time cholangiography or preoperative magnetic resonance cholangiography. Donor graft hepatectomy was routinely performed with intraoperative ultrasonographic guidance. The allografts were preserved with University of Wisconsin solution (Viaspan). If necessary, graft hepatic vein venoplasty was performed on the back table. If the actual GRWR of the resected graft was >4%, an ex vivo partial reduction was performed from the distal side of the graft on the back table.

For the recipient procedure, a Mercedes-Benz or transverse incision was created, and total hepatectomy was performed. In many infants after total hepatectomy, the recipient right, middle, and left hepatic veins were formed into a single orifice, which was then anastomosed in an end-to-end fashion to the graft left hepatic vein, whereas the portal vein was reconstructed between the recipient right or left portal vein branch patch and the graft left portal vein. Hepatic artery reconstruction was performed with microsurgical techniques. Biliary reconstruction was performed with Roux-en-Y hepaticojejunostomy. Intraoperative color Doppler ultrasonography was used to assess the blood flow velocity and pattern after vascular reconstruction and during abdominal wall closure. We judged whether to perform the primary abdominal closure during the operation mainly on the basis of the respiratory condition and the blood flow of the graft liver in these infant patients. In cases of graft compression, which could lead to graft blood flow insufficiency or respiratory insufficiency due to abdominal compartment syndrome, we did not perform primary abdominal closure.

Statistical Analysis

The data are expressed as medians and ranges or means and standard deviations on the basis of the presence or absence of a normal distribution. The significance of differences in the incidence of surgical complications between recipients weighing ≤6 kg and those weighing >6 kg was evaluated with the chi-square test. Recipient survival was calculated according to the Kaplan-Meier product-limited method, and differences in survival between the 2 groups were compared with the log-rank test. All statistical analyses were performed with the StatView software package (SAS Institute, Cary, NC), and differences with a P value < 0.05 were considered significant.

RESULTS

We used LLS grafts in 7 recipients (46.7%), S2 monosegment grafts in 4 recipients (26.7%), reduced S2 monosegment grafts in 3 recipients (20.0%) and a reduced LLS graft in 1 recipient (6.7%). The actual median graft volume and GRWR were 172 g (range, 93-222 g) and 3.6% (range, 3.0%-4.0%), respectively. The median recipient operative time and bleeding amount were 13 hours 37 minutes (range, 11 hours 42 minutes to 20 hours 5 minutes) and 750 mL (range, 200-2823 mL), respectively. In Table 2, we present the preoperative CT-volumetry values for the LLS grafts as well as the actual graft volumes and GRWRs after the volume reduction process. The mean reduction achieved with S2 monosegment grafts was 48.3%. Primary abdominal closure was possible in 13 patients (86.7%).

Recipient survival curves are shown in Fig. 2. One patient died of a brain hemorrhage on postoperative day (POD) 22. Except for this patient, all patients survived with properly functioning grafts. The 1- and 5-year recipient survival rates were both 93.3%. There were no significant differences with respect to the patients weighing more than 6 kg ($P = 0.67$).

The surgical outcomes and the surgical complications are shown in Table 3. One patient (6.7%) developed portal vein thrombosis and underwent thrombectomy on POD 3. Portal vein thrombosis occurred again 6 months after LDLT, and we performed stent placement via an endovascular intervention. Two patients (13.3%) developed hepatic artery thrombosis (POD 4 and POD 8, respectively), and both underwent balloon dilatation via an endovascular intervention. Two patients (13.3%) developed bilioenteric anastomotic strictures (POD 111 and POD 162, respectively), and both underwent percutaneous transhepatic biliary drainage and balloon dilatation (POD 251 and POD 253, respectively).

DISCUSSION

When one is performing LDLT in very small infants, it is important to select a size-matched graft and efficiently reduce the LLS graft. The techniques for reducing the volume of LLS grafts obtained from living donors are highly developed in Japan. Kasahara et al.[15] introduced the use of hyperreduced LLS grafts in which the caudal and lateral portions of the LLS are resected in situ. In this technique, the transection line is dependent on the anatomical variation of the hepatic vein system, not the portal vein system. The advantages of using a reduced LLS include the simplicity of the procedure using the energy device and the short amount of time required. The limitations of this technique include the fact that it is difficult to significantly reduce the volume and that a substantial amount of graft thickness remains.[16] As a result, the reduced graft volume is sometimes insufficient, and

TABLE 2. Characteristics of 15 Patients Weighing ≤6 kg

Case number	Body Weight (kg)	Original Disease	Preoperative Volumetry of LLS (g)	Donor LLS Volume (g)/GRWR (%)	Graft Type	Actual Graft Volume (g)/GRWR (%)	LLS Reduction Rate (%)	Abdominal Wall Closure
1	6.0	Biliary atresia	214	218/3.6	LLS	218/3.6	—	Primary
2	5.9	Biliary atresia	228	210/3.6	LLS	210/3.6	—	Primary
3	5.9	Biliary atresia	181	220/3.7	LLS	220/3.7	—	Primary
4	5.9	Biliary atresia	249	222/3.7	LLS	222/3.7	—	Primary
5	5.9	CPS1D	192	182/3.1	LLS	182/3.1	—	Primary
6	5.8	Biliary atresia	166	174/3.0	LLS	174/3.0	—	Primary
7	5.8	Biliary atresia	269	246/4.3	Reduced LLS	172/3.0	−30.2	Primary
8	5.1	Biliary atresia	196	218/4.3	LLS	218/4.3	—	Primary
9	4.8	Biliary atresia	363	359/7.5	Reduced S2	158/3.3	−56.0	Primary
10	3.4	Fulminant hepatic failure	—	221/6.5	S2	129/3.8	−41.5	Primary
11	3.1	Idiopathic liver cirrhosis	—	225/7.8	S2	124/4.0	−48.7	Secondary
12	2.9	Neonatal hemochromatosis	236	203/6.3	S2	107/3.6	−42.9	Secondary
13	2.8	Neonatal hemochromatosis	213	155/5.5	S2	93/3.3	−40.0	Primary
14	2.6	Fulminant hepatic failure	—	229/8.9	Reduced S2	98/3.8	−57.3	Primary
15	2.6	Neonatal hemochromatosis	233	248/9.6	Reduced S2	95/3.7	−61.5	Primary

NOTE: The graft type, the preoperative LLS graft volume, and the actual graft volume of each recipient are shown. Changes in the preoperative volumetry of the LLS graft and the actual graft volume and GRWR in association with the volume reduction process are shown. A 48.3% reduction rate for LLS grafts was achieved with S2 monosegment grafts.

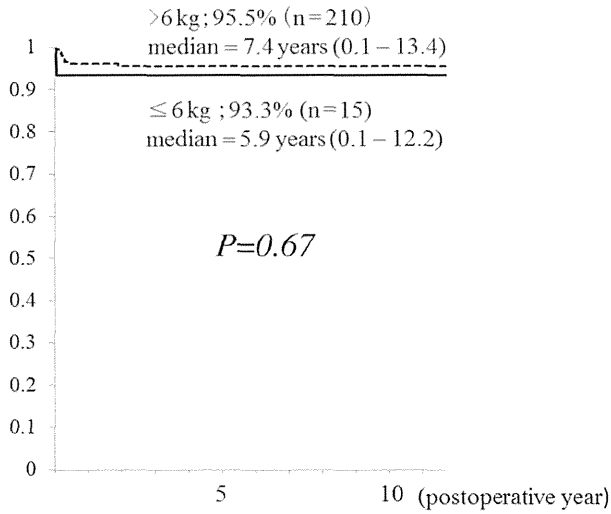

Figure 2. Recipient survival rates with respect to recipient weights for patients weighing >6 or ≤6 kg. No significant differences were seen.

performing primary abdominal closure is impossible; this creates consequent concerns regarding graft compression. The authors modified this technique to reduce the thickness; however, this procedure is complicated by a large graft resection membrane.[17]

In contrast, monosegment graft anatomic dissection is another established method used in small infants. S3 monosegment grafts were mainly used in the past,[18-20] and we previously reported the method and efficacy of using S2 monosegment grafts.[14]

As we previously reported, S2 monosegment grafts have some advantages in comparison with S3 monosegment grafts. The advantage of S2 monosegment grafts is that they enable the transplant surgeon to reduce around half of the graft volume and thin the graft shape. Therefore, S2 monosegment grafts are suitable for small infants with narrow abdominal cavities (particularly neonates), and they allow the use of primary abdominal closure without graft compression in some cases, even in neonatal LDLT.

Because the S2 monosegment graft is the dorsolateral segment of the left hepatic lobe, it is more stable when it is implanted into the abdominal cavity. In addition, the use of S2 monosegment grafts is not associated with an increased risk of surgical complications in either recipients or donors in our experience. Furthermore, S2 monosegment grafts regenerate well within a few years after LDLT, as demonstrated previously.[21] On the other hand, because the transection surface of the monosegment graft is located ventrally, it is difficult to perform a periodic examination by Doppler ultrasonography and percutaneous liver biopsy. Furthermore, the long-term prognosis is unknown.[22-24] We think that if the donor's LLS is thick and the S2 volume is larger than the S3 volume, an S3 monosegment graft may be acceptable for neonatal LDLT. Because the transection surface of the S3 monosegment graft is dorsally located, there are some disadvantages: an unstable position for the graft liver and difficulty in treating bile leakage. We consider S2 to be the first choice for a monosegment graft, but S3 is acceptable in some cases. Transplant surgeons should preoperatively assess the monosegment graft

TABLE 3. Surgical Data and Complications

Complication	>6 kg (n = 210)	≤6 kg (n = 15)	*P* Value
Operation time, median (range), hours:minutes	15:02 (7:02-37:10)	13:37 (11:42-20:05)	0.44
Bleeding volume, median (range), mL/kg	70.7 (3.1-820.2)	141.5 (36.3-589.1)	0.018
Hepatic venous stenosis, n (%)	10 (4.8)	0 (0)	0.39
Portal vein thrombosis, n (%)	24 (11.4)	1 (6.7)*	0.57
Hepatic artery thrombosis, n (%)	15 (7.1)	2 (13.3)†	0.38
Bilioenteric anastomotic stricture, n (%)	33 (15.7)	2 (13.3)‡	0.81
Abdominal bleeding, n (%)	7 (3.3)	2 (13.3)§	0.50
Bile leakage, n (%)	7 (3.3)	0 (0)	0.47

NOTE: The incidence of surgical complications for pediatric LDLT in patients weighing ≤6 kg at our institution is shown. The incidence of complications was not significantly different from that observed for patients weighing >6 kg.
*Case 7.
†Cases 7 and 14.
‡Cases 7 and 9.
§Cases 6 and 11.

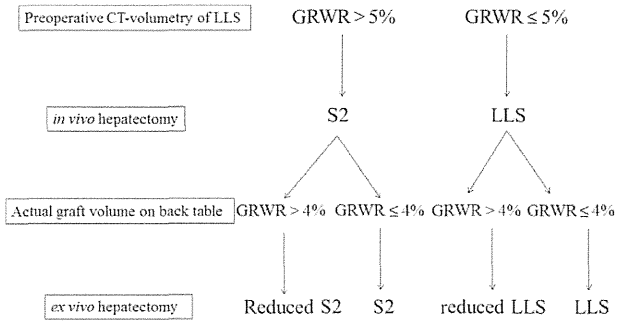

Figure 3. Strategy for graft selection among patients weighing ≤6 kg. We planned to keep the GRWR≦4% on the basis of the donor preoperative CT-volumetry value for the LLS graft. When the predictive GRWR of the LLS graft was ≦5%, we selected the LLS as the liver graft. When the predictive GRWR of the LLS graft was >5%, we selected the S2 monosegment as the liver graft. When the actual GRWR was >4%, we performed partial graft hepatectomy ex vivo to reduce the GRWR to ≦4%.

volume and anatomical variations of the portal and hepatic veins.

To make the graft volume satisfy the recipient's metabolic demands and fit the abdominal space, we must match the recipient's body weight and graft volume. We believe that graft CT-volumetry is important because the LLS graft volume of each donor is within the range of 146 to 382 g in our experience. We consider patients whose LLS graft GRWR is >5% to be candidates for S2 monosegment grafts because they require >20% LLS graft reduction. On the other hand, if the GRWR of the LLS graft is between 4% and 5%, it is suitable to use a reduced LLS graft because reducing the size of the LLS graft by only 20% is sufficient. In summary, we developed a perioperative strategy for graft selection in patients weighing ≤6 kg, as shown in Fig. 3. We planned to keep the GRWR≤4% according to the preoperative CT-volumetry values of the LLS grafts obtained from living donors. When the predictive GRWR of the LLS graft was ≤5%, we selected the LLS as the donor liver graft. When the predictive GRWR of the LLS graft was >5%, we selected the S2 monosegment as the liver graft. When the actual GRWR was >4%, we performed ex vivo partial hepatectomy on the back table. Using this strategy, we were able to obtain good results, especially with respect to the survival rate and primary abdominal closure; however, further studies of the long-term prognosis of these reduced grafts are needed.

In conclusion, our graft selection strategy based on the preoperative CT-volumetry value is highly useful in patients weighing ≤6 kg. The use of S2 monosegment grafts is effective and safe in very small infants and particularly in neonates.

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Living donor liver transplantation from an asymptomatic donor with mild coagulation factor IX deficiency: Report of a case

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Abstract: The use of donors with coagulation FIX deficiency is controversial, and there are no current protocols for peri-transplant management. We herein describe the first reported case of a pediatric LDLT from an asymptomatic donor with mild coagulation FIX deficiency. A 32-yr-old female was evaluated as a donor for her 12-month-old daughter with biliary atresia. The donor's pretransplant coagulation tests revealed asymptomatic mild coagulation FIX deficiency (FIX activity 60.8%). Freeze-dried human blood coagulation FIX concentrate was administered before the dissection of the liver and 12 h afterwards by bolus infusion (40 U/kg) and was continued on POD 1. The bleeding volume at LDLT was 590 mL. On POD 1, 3, 5, and 13, the coagulation FIX activity of the donor was 121.3%, 130.6%, 114.6%, and 50.2%, respectively. The donor's post-transplant course was uneventful, and the recipient is currently doing well at 18 months after LDLT. The FIX activity of the donor and recipient at nine months after LDLT was 39.2% and 58.0%, respectively. LDLT from donors with mild coagulation FIX deficiency could be performed effectively and safely using peri-transplant short-term coagulation FIX replacement and long-term monitoring of the plasma FIX level in the donor.

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Key words: coagulation factor IX deficiency – coagulation factor IX activity – freeze-dried human blood coagulation factor IX concentrate – living donor – living donor liver transplantation

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The use and safety of expanded-criteria donors have become accepted in clinical practice because of the scarcity of organs for transplantation. However, the use of grafts from donors with coagulation FIX deficiency has not been reported. There is a safety concern related to such donors because coagulation FIX deficiency exposes patients to greater risks of bleeding complications during the peri-transplant period; there is no consensus as to whether grafts from donors with coagulation FIX deficiency should be used.

Although the efficacy of FIX administration to patients with hemophilia undergoing surgical interventions has been shown (1) and some experiences of liver transplantation for hemophiliac patients with end-stage liver disease have been reported (2–13), there are no current protocols for the peri-transplant management of donors with coagulation FIX deficiency.

We describe the first reported case of pediatric LDLT from an asymptomatic donor with mild coagulation FIX deficiency.

Case report

Donor

A 32-yr-old woman was evaluated as a donor for her 12-month-old daughter with biliary atresia.

Abbreviations: Alb, albumin; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; FVIII, factor VIII; FIX, factor IX; FFP, fresh frozen plasma; Hb, hemoglobin; Hct, hematocrit; LDLT, living donor liver transplantation; Plt, platelet; POD, postoperative day; POM, postoperative month; PT-INR, prothrombin time-international normalized ratio; TB, total bilirubin.

Asymptomatic mild coagulation FIX deficiency was diagnosed during the pretransplant examination for LDLT based on the prolonged APTT. The blood test results were as follows: Hb 13.1 g/dL; Hct 39.2%; Plt 254 000/μL; Alb 4.2 g/dL; TB 0.89 mg/dL; AST 16 mU/mL; ALT 11 mU/mL; PT-INR 1.02; APTT 37.0 s; FVIII activity 91.4%; FIX activity 60.8%; von Willbrand factor >134.0%.

Pretransplant liver volumetry, as measured using Synapse Vincent (FUJIFILM Medical Co., Ltd., Tokyo, Japan), showed that the donor's whole liver volume was 1001 mL and that the left lateral segment volume was 180 mL. Therefore, the post-transplant predictive FIX activity of the donor was calculated as 49.9% (60.8% × 821/1001), assuming that the remnant liver would elaborate FIX.

The donor underwent left lateral segmentectomy for ABO-identical LDLT. The length of the operation was four h 47 min, and the volume of the bleeding was 590 mL. No transfusion was administered during the operation. The donor's post-transplant predictive FIX activity was calculated as 52.9% (60.8% × 854/1001) for the left lateral segment graft (147 g).

Freeze-dried human blood coagulation FIX concentrate (Novact M, Kaketsuken, Kumamoto, Japan) was administered before the dissection of the liver and 12 h afterwards by bolus infusion (40 U/kg) and was continued on POD 1 to obtain a steady-state plasma level above 60.0%. Early discontinuation of FIX concentrate was possible because of good remnant liver function and an absence of bleeding episodes. On POD 1, 3, 5, and 13, the donor's FIX activity was 121.3%, 130.6%, 114.6%, and 50.2%, respectively (Fig. 1). The post-transplant course was uneventful, and the donor was discharged from the hospital on POD 18.

She is currently doing well at one yr after LDLT, and her FIX activity was 39.2% at the most recent examination (Fig. 1).

Recipient

A 12-month-old female infant with biliary atresia underwent LDLT because of intractable cholangitis and portal hypertension. Her body height and weight were 75.0 cm and 8.3 kg, and the standard liver volume was 288 mL. The blood test results were as follows: Hg 11.0 g/dL; Hct 35.5%; Plt 182 000/μL; Alb 3.4 g/dL; TB 1.25 mg/dL; AST 191 mU/mL; ALT 96 mU/mL; PT-INR 0.97; APTT 31.9 s; FVIII activity 179.8%; FIX activity 45.0%; von Willbrand factor >201.0%. Because the donor's predicted left lateral segment volume was 180 mL, the recipient's post-transplant predictive FIX activity was calculated as 38.0% (60.8% × 180/288), assuming that the graft liver would elaborate FIX.

The recipient underwent ABO-identical LDLT using a left lateral segment graft. The length of the operation was nine h 15 min, and the bleeding volume was 537 mL. A total of 292 mL of red blood cells concentrate and 128 mL of FFP were infused during the LDLT. The recipient's post-transplant predicted FIX activity was calculated as 31.0% (60.8% × 147/288) for the left lateral segment graft (147 g).

Freeze-dried human blood coagulation FIX concentrate was administered by a bolus infusion (100 U/kg) only at the time of the anesthesia induction to obtain a steady-state plasma level above 60%. The early post-transplant course was favorable, with a good allograft function and an

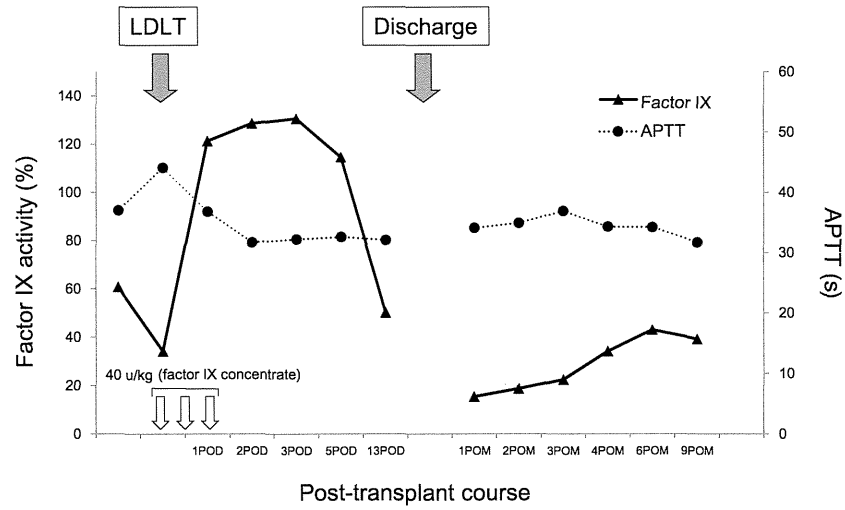

Fig. 1. The post-transplant course of a donor with mild coagulation FIX deficiency.

absence of bleeding episodes after single administration of FIX concentrate. On POD 1, 3, 5, 7, 13, 20, and 30, the recipient's FIX activity was 38.3%, 65.7%, 42.6%, 47.4%, 91.6%, 86.3%, and 59.6%, respectively (Fig. 2). The post-transplant course was uneventful, and the recipient was discharged from hospital on POD 34.

She is currently doing well at one yr after the LDLT, and her FIX activity was 58.0% at the most recent examination (Fig. 2).

Discussion

The anticipated problems associated with a hepatectomy for patients with hemophilia and coagulation factor deficiency include the peri-operative management of coagulopathy because the post-hepatectomy state exposes patients to greater risks of bleeding complications during the peri-operative period. Although the safety of factor replacement treatment during peri-operative surgical procedures has been reported (1), factor administration should be minimized as much as possible. Various regimens have been utilized, including bolus infusion and continuous infusion therapy, ranging from a few days to a few weeks to maintain a normal level of coagulation FIX activity (54–160%) (1–13). In this case, the bolus infusion of FIX concentrate might have been more appropriate and effective than a continuous infusion. Although normal levels of FIX activity were not achieved after the hepatectomy, we concluded that there was no further need for FIX replacement on POD 1 because there were no bleeding episodes. For donors with mild coagulation FIX deficiency, FIX concentrate should be administered at the time of anesthesia induction and at the end of the LDLT by bolus infusion (40 U/kg) and then continued for a few days after the LDLT by bolus infusion (40 U/kg), based on whether bleeding episodes occur during the monitoring of the plasma FIX level.

Regarding the suitability of a donor with coagulation FIX deficiency, we predicted the post-transplant FIX activity by pretransplant liver volumetry using Synapse Vincent. The pretransplant liver volumetry showed that the donor's whole liver volume was 1001 mL and the left lateral segment volume was 180 mL. The predicted post-transplant FIX activity of the donor and recipient was calculated as 49.9% (60.8% × 821/1001) and 38.0% (60.8% × 180/288), respectively. We considered the donor suitable because her predicted post-transplant FIX activity, as well as that of the recipient, would not fall within the category of moderate or severe coagulation factor deficiency (<5%). The post-transplant FIX activity could be predicted by pretransplant liver volumetry to some extent. We consider that pretransplant liver volumetry is important for an indication of donor suitability.

During the post-transplant course, the donor showed a gradual decrease in FIX activity until POM 1; thereafter, it increased gradually until POM 6 (Fig. 1). The recipient showed a gradual decrease in FIX activity until POM 2, which increased gradually until POM 3 (Fig. 2). The actual post-transplant FIX activity (43.0%) of the donor was lower than the predictive value (52.9%); it was 20% lower than the predictive FIX activity. The actual post-transplant FIX activity (61.6%) of the recipient was higher than the predicted value (31.0%) and >200% of the predictive FIX activity. The regeneration of the remnant liver and the graft liver might be associated with the recovery of FIX activity, and the

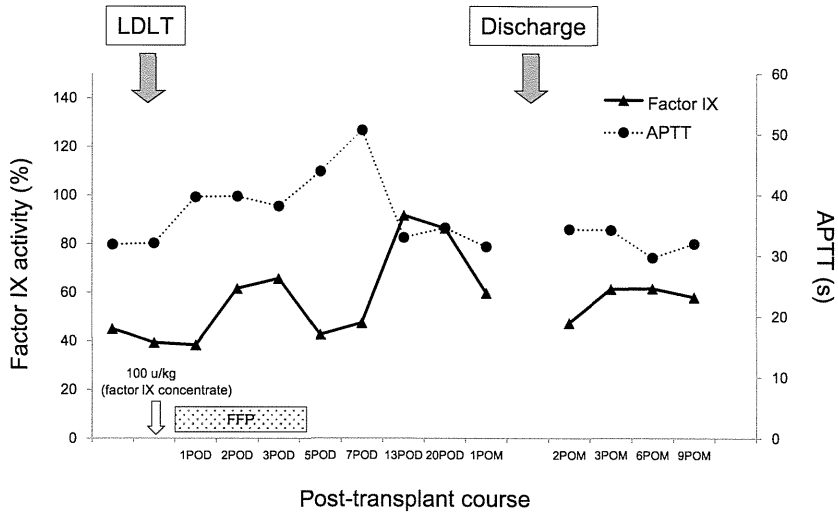

Fig. 2. The post-transplant course of the recipient transplanted with the graft with mild FIX deficiency.

rate of liver regeneration in the recipient might be higher than that of the donor. In this recipient, the monitoring of FIX activity might have been become a good indicator of the graft liver function.

The efficacy of coagulant factor administration to adult patients with hemophilia undergoing surgical interventions has been shown (1). There is no established consensus on the optimal factor levels or the duration of replacement treatment for pediatric patients with hemophilia. Recently, the management of invasive procedures in pediatric patients has been reported (14–16). We consider the target plasma FIX level to be 80–100% in surgical interventions and 60–80% in invasive procedures (e.g., liver biopsy, etc.), based on previous reports. Transplant surgeons should measure and monitor the plasma FIX level before surgical interventions or invasive procedures.

In conclusions, LDLT from donors with mild coagulation FIX deficiency could be performed effectively and safely by peri-transplant short-term FIX replacement and long-term monitoring of the plasma FIX level in the donor. The accumulation of further cases and the long-term observation of this case are needed to confirm our findings.

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Conflict of interests

None.

Authors' contributions

YS: Study design, acquisition of data, analysis and interpretation of data, and drafting of the manuscript; HS, YS, KM, NK, YK, AM, TF, AS, MH, YH, NY, NO, YI, and TU: Acquisition of data, and analysis and interpretation of data; SM, JM, KM, and YY: Analysis and interpretation of data, and critical revision of the manuscript for important intellectual content.

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