資料4

兼松班
「血液製剤によるHIV/HCV重複感染者」に対する
肝移植適応作業部会

血液製剤によるHIV/HCV重複感染者　の肝移植適応について

研究代表者　：兼松隆之　＜長崎大学大学院　移植・消化器外科＞

分担研究者　：國土典宏　＜東京大学大学院肝胆膵外科　人工臓器・移植外科＞
白阪琢磨　＜大阪医療センター＞
中尾一彦　＜長崎大学大学院　消化器病態制御学＞
八橋　弘　＜国立病院機構 長崎医療センター 臨床研究センター＞
江口　晋　＜長崎大学大学院 移植・消化器外科＞

研究協力者：　市田隆文　＜順天堂大学医学部附属静岡病院　消化器内科＞
日本脳死肝移植適応評価委員長
大平勝美　＜はばたき福祉事業団＞
柿沼章子　＜はばたき福祉事業団＞
潟永博之　＜独立行政法人　国立国際医療研究センター ACC治療開発＞
立川夏夫　＜横浜市立市民病院　感染症内科＞

共同研究者　：菅原寧彦　＜東京大学大学院　肝胆膵外科　人工臓器・移植外科＞

厚生労働省　：平賀紀行　＜厚生労働省　健康局疾病対策課＞
秋月玲子　＜厚生労働省　医政局政策医療課＞
信沢正和　＜厚生労働省　医薬食品局総務課医薬品副作用被害対策室＞

2011 年 3月 22日 品川

血液製剤によるHIV/HCV重複感染患者における肝移植適応基準（案）

Modified Child-Pugh分類

1	2	3
アルブミン値 2.8未満	3.5超	2.8-3.5
ビリルビン値 3.0超	2.0未満	2.0-3.0
プロトロンビン時間 40%未満	70%超	40-70%
腹水 中程度以上	なし	軽度
脳症 昏睡III以上	なし	軽度I, II

＊門脈血栓ありの場合は1点付加、食道静脈瘤ありの場合は1点付加

M Child-Pugh A　5，6　点
M Child-Pugh B　7、8、9　点
M Child-Pugh C　10点以上

→ 肝移植適応リストへ

Ⅱ．研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

雑誌：

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Eguchi S, Takatsuki M, Hidaka M, Soyama A, Ichikawa T, Kanematsu T.	Perioperative synbiotic treatment to prevent infectious complications in patients after elective living donor liver transplantation: a prospective randomized study.	Am J Surg	201 (4)	498-502	2011
Eguchi S, Kanematsu T, Arii S, Omata M, Kudo M, Sakamoto M, Takayasu K, Makuuchi M, Matsuyama Y, Monden M ; for the Liver Cancer Study Group of Japan.	Recurrence-free survival more than 10 years after liver resection for hepatocellular carcinoma.	Br J Surg	98(4)	552-557	2011
Takatsuki M, Eguchi S, Yamanouchi K, Hidaka M, Soyama A, Kanematsu T.	Technical refinements of bile duct division in living donor liver surgery.	J Hepatobiliary Pancreat Sci.	18(2)	170-175	2011
Eguchi S, Soyama A, Hidaka M, Takatsuki M, Muraoka I, Tomonaga T, Kanematsu T.	Liver transplantation for patients with human immunodeficiency virus and hepatitis C virus coinfection with special reference to hemophiliac recipients in Japan.	Surg Today	41 (10)	1325-31	2011
Soyama A, Eguchi S, Yanaga K, Takatsuki M, Hidaka M, Kanematsu T.	Living donor liver transplantation with extensive caval thrombectomy for acute-on-chronic Budd-Chiari syndrome.	Surg Today	41 (7)	1026-1028	2011
Soyama A, Eguchi S, Takatsuki M, Hidaka M, Tomonaga T, Yamanouchi K, Miyazaki K, Inokuma T, Tajima Y, Kanematsu T.	Hemophagocytic syndrome after liver transplantation: report of two cases.	Surg Today.	41 (11)	1524-30	2011

Eguchi S, Takatsuki M, Soyama A, Hidaka M, Tomonaga T, Muraoka I, Kanematsu T.	Elective living donor liver transplantation by hybrid hand-assisted laparoscopic surgery and short upper midline laparotomy.	Surgery	150 (5)	1002-1005	2011
Eguchi S, Soyama A, Mergental H, AP.van den Berg , R Scheenstra, RJ Porte, MJH Slooff.	Honoring the contract with our patients: outcome after repeated re-transplantation of the liver.	Clin Transplant	25(2)	E211-218	2011
Eguchi S, Takatsuki M, Soyama A, Hidaka M, Muraoka I, Kanematsu T.	Is Preservation of Middle Hepatic Vein Tributaries during Right Hemi - Hepatectomy Beneficial for Live Donor Liver Transplantation?	Hepatogastroenterology.	59	115-116	2011
西田　聖剛、江口　晋、曽山　明彦、日高　匡章、高槻　光寿、高橋　正浩、Andreas G.Tzakis、兼松　隆之	マイアミ大学での HIV 陽性患者に対する肝移植	The journal of AIDS research	13	137-144	2011
江口　晋、高槻　光寿、曽山　明彦、村岡いづみ、原　貴信、兼松　隆之	後天性免疫不全症候群（ＡＩＤＳ）	外科	73 (12)	1282-1287	2011
Yanaga K, Eguchi S, Takatsuki M, Okudaira S, Tajima Y, Kanematsu T.	Two-staged living donor liver transplantation for fulminant hepatic failure.	Hepatogastroenterology	57	146-8	2010
Takatsuki M, Eguchi S, Yamanouchi K, Hidaka M, Soyama A, Miyazaki K, Tajima Y, Kanematsu T.	The outcome of methicillin-resistant Staphylococcus aureus infection after living donor liver transplantation in a Japanese center.	Journal of hepato-biliary-pancreatic sciences	17	839-43	2010
Eguchi S, Takatsuki M, Yamanouchi K, Kamohara Y, Tajima Y, Kanematsu T.	Regeneration of graft livers and limited contribution of extrahepatic cells after partial liver transplantation in humans.	Digestive diseases and sciences	55	820-825	2010
Eguchi S, Takatsuki M, Hidaka M, Soyama A, Tomonaga T, Muraoka I, Kanematsu T.	Predictor for histological microvascular invasion of hepatocellularcarcinoma: a lesson from229 consecutive cases of curative liver resection.	World journal of surgery	34:5	1034-1038	2010

Chiba K, Isoda M, Chiba M, Kanematsu T, Eguchi S.	Significance of PET/CT in determining actual TNM staging for Patients with various lung cancers.	International Surgery	95	197-204	2010
Nakamura H, Ichikawa T, Nakamura T, Kawakami A, Iwamoto N, Matsuzaki T, Miyaaki H, Yamasaki S, Ida H, Eguchi S, ayashi T, Nakao K, Kanematsu T.	Macrophage-dominant sialadenitis in human T-cell leukemia virus type I-associated myelopathy after living-donor liver transplantation.	Transplantation Proceedings	42	2797-2799	2010
Yamanouchi K, Eguchi S, Takatsuki M, Hidaka M, Kamohara Y, Miyazaki K, Hamasaki K, Tajima Y, Kanematsu T.	Management of fungal colonization and infection after living donor liver transplantation.	Hepato-gastroenterology	57	852-857	2010
曽山　明彦、江口　晋、濱崎　幸司、高槻　光寿、日高　匡章、村岡いづみ、小坂太一郎、朝長　哲生、兼松　隆之	生体肝右葉移植後の胆管吻合部難治性胆汁瘻の治療にT-tubeが奏功した１例	臨牀と研究	87(9)	148-149	2010
村岡いづみ、江口　晋、曽山　明彦、日高　匡章、山之内孝彰、高槻　光寿、兼松　隆之	生体肝移植後に非閉塞性腸管虚血症（Non－Occlusive Mesenteric Ischemia；NOMI）をきたした１例	臨牀と研究	87(9)	150-151	2010
Hidaka M, Eguchi S, Okudaira S, Takatsuki M, Tokai H, Soyama A, Nagayoshi S, Mochizuki S, Hamasaki K, Tajima Y, Kanematsu T.	Multicentric occurrence and spread of hepatocellular carcinoma in whole explanted end-stage liver.	Hepatology Research	39(2)	143-148	2009
Eguchi S, Kanematsu T.	What is the real contribution of extrahepatic cells to liver regeneration?	Surgery Today	39(1)	1, 1-4,	2009
Eguchi S, Hidaka M, Tomonaga T, Miyazaki K, Inokuma T, Takatsuki M, Okudaira S, Yamanouchi K, Miyaaki H, Ichikawa T, Tajima Y, Kanematsu T.	Actual therapeutic efficacy of pre-transplant treatment on hepatocellular carcinoma and its impact on survival after salvage living donor liver transplantation.	J Gastroenterol	44	624-629	2009

Eguchi S, Hidaka M, Tomonaga T, Miyazaki K, Inokuma T, Takatsuki M, Okudaira S, Yamanouchi K, Miyaaki H, Ichikawa T, Tajima Y, Kanematsu T.	Actual therapeutic efficacy of pre-transplant treatment on hepatocellular carcinoma and its impact on survival after salvage living donor liver transplantation.	Journal of Gastroenterology	44	624-629	2009
Tokai H, Kawashita Y, Ito Y, Yamanouchi K, Takatsuki M, Eguchi S, Tajima Y, Kanematsu T.	Efficacy and limitation of bone marrow transplantation in the treatment of acute and subacute liver failure in rats.	Hepatology Research	39	1137-1143	2009
Eguchi S, Takatsuki M, Nakashima M, Kanematsu T.	Living -donor liver transplantation from second generation children for atomic bomb survivors.	Hepatology Research	39	1150-1152	2009
Hamada T, Eguchi S, Takatsuki M, Yamanouchi K, Sugiyama N, Kawashita Y, Okudaira S, Tajima Y, Ishii T, Kanematsu T.	Low-dose recombinant human hepatocyte growth factor enhances effect of hepatocyte transplantation in rats treated with retrorsine.	Hepato-gastroenterology	56	1466-1470	2009
Fujimoto M, Ichikawa T, Nakao K, Miyaaki H, Sibata H, Eguchi S, Takatsuki M, Nagaoka S, Yatsuhashi H, Kanematsu T, Eguchi K.	The significance of Enzyme Immunoassay for the assessment of hepatitis B virus core-related antigen folowing liver transplantation.	Internal medicine journal	48	1577-1583	2009
Eguchi S, Takatsuki M, Yamanouchi K, Hidaka M, Soyama A, Tomonaga T, Tajima Y, Kanematsu T.	Indocyanine Green Dye Excretion Bile Reflects Graft Function After Living Donor Liver Transplantation.	Transplantation	88	747-748	2009
Ichikawa T, Nakao K, Miyaaki H, Eguchi S, Takatuski M, Fujimito M, Akiyama M, Miuma S, Ozawa E, Shibata H, Takeshita S, Kanematsu T, Eguchi K.	Hepatitis C virus kinetics during the first phase of pegylated interferon-α-2b with ribavirin therapy in patients with living donor liver transplantation.	Hepatology Research	39	856-864	2009

Surg Today (2011) 41:1325–1331
DOI 10.1007/s00595-010-4556-x

SURGERY TODAY

Review Article

Liver Transplantation for Patients with Human Immunodeficiency Virus and Hepatitis C Virus Coinfection with Special Reference to Hemophiliac Recipients in Japan

SUSUMU EGUCHI[1], AKIHIKO SOYAMA[1,2], MASAAKI HIDAKA[1], MITSUHISA TAKATSUKI[1], IZUMI MURAOKA[1], TETSUO TOMONAGA[1], and TAKASHI KANEMATSU[1]

[1]Department of Surgery, Nagasaki University Graduate School of Biomedical Sciences, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan
[2]Japan Foundation for AIDS Prevention, Tokyo, Japan

Abstract
Liver transplantation for patients with hepatitis C virus (HCV) and human immunodeficiency virus (HIV) remains challenging. The advent of highly active antiretroviral therapy (HAART) for HIV has reduced mortality from opportunistic infection related to acquired immunodeficiency syndrome dramatically, while about 50% of patients die of end-stage liver cirrhosis resulting from HCV. In Japan, liver cirrhosis frequently develops after HCV–HIV coinfection resulting from previously transfused infected blood products for hemophilia. The problems of liver transplantation for those patients arise from the need to control calcineurin inhibitor with HAART drugs, the difficulty of using interferon after liver transplantation with HAART, and the need to control intraoperative coagulopathy associated with hemophilia. We review published reports of liver transplantation for these patients in the updated world literature.

Key words Liver transplantation · Hepatitis C virus · Human immunodeficiency virus · Coinfection · Highly active antiretroviral therapy

Introduction

According to a report compiled by the Japanese Ministry of Health, Labour and Welfare in October 2006, the number of HIV-infected patients in Japan was 8071 (6275 males and 1796 females), and this number has increased further since.[1] In 2008 there were 1557 new cases reported, including 1126 HIV-positive cases and 431 acquired immunodeficiency syndrome (AIDS) cases.[2] The possible routes of infection include sexual contact, through contaminated or unheated blood products, and mother-to-child transmission. When HIV infection is contracted through blood products, there is often coinfection with HCV.

Since 1995, there has been a major change in the cause of death of HIV-infected patients. It is believed that the major factor contributing to these trends is the improved HIV control achieved in recent years with highly active antiretroviral therapy (HAART).[3] HAART is defined as a combination of drugs from different classes of HIV therapy, comprising nucleoside reverse transcriptase inhibitors (NRTIs), and either non-nucleoside reverse transcriptase inhibitors (NNRTIs) or a protease inhibitor (PI). If the compliance is 95% or more, this therapy is successful in more than 50% of patients.[3–5]

This review focuses on liver transplantation in Japanese patients with HIV and HCV, especially those in whom the disease was caused by receiving contaminated blood products in the past and who may be candidates for liver transplantation.

Epidemiology of HIV–HCV Coinfection in Patients with Hemophilia in Japan

According to a survey by the Ministry of Health, Labour and Welfare in the 2008 fiscal year in Japan, 602 patients with hemophilia A (factor 8 deficiency) and 183 with hemophilia B (factor 9 deficiency) were alive with HIV infection (Table 1).[6] Among these, 524 with hemophilia A (87%) and 162 with hemophilia B (89%) also had HCV infections and liver disease (Table 2). Of the 524 persons with hemophilia A, 33 (6.3%) had cirrhosis, 5 (0.9%) had liver cancer, and 2 (0.4%) had liver failure. Two of these patients underwent a liver transplant procedure. It is highly possible that about 50 of the patients

Reprint requests to: S. Eguchi
Received: May 8, 2010 / Accepted: November 9, 2010
This article is a secondary publication, based on a review first reported in the *Japanese Journal of Transplantation* 2010;45(1): 46–53 with full references.

Table 1. Coagulation disorders in Japan

	Hemophilia				
	A	B	VWD	VWD-related disease	Total
Total	4211	916	892	452	6471
Male	4185	908	406	246	5745
Female	29	8	486	206	726
HIV negative					
Total	3609	733	885	448	5675
Male	3583	725	404	245	4957
Female	26	8	481	203	718
HIV positive					
Total	602	183	7	4	796
Male	602	183	2	1	788
Female	0	0	5	3	8

Source: Official Report of the National Surveillance on Coagulation Disorders in Japan, 2008
HIV, human immunodeficiency virus; VWD, von Willebrand disease

Table 2. Stage of liver disease in patients with hemophilia and HIV infection (only reported surviving cases with HCV coinfection)

	No hepatitis	Acute hepatitis	Chronic hepatitis	Liver cirrhosis	HCC	Liver failure	Cured with IFN	Spontaneous cure	LT	Total
Hemophilia A	45	2	350	33	5	2	59	26	2	524
Hemophilia B	15	1	100	11	6	0	19	8	2	162
Total	60	3	450	44	11	2	78	34	4	686

Source: Official Report of the National Surveillance on Coagulation Disorders in Japan, 2008
HIV, human immunodeficiency virus; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; LT, liver transplantation; IFN, interferon

with cirrhosis may be candidates for liver transplantation in the future. In fact, this survey revealed that one-third of the deaths of HIV–HCV coinfected patients with blood-borne diseases were caused by liver disease.

A characteristic that should be taken into account when using imported blood products is that the proportion of patients with HCV genotype 1b is low, at 25% vs 70% in general for Japanese, and the proportion of patients with HCV genotype 3a is high, at 23%. Also, one study found that the proportion of patients with HIV–HCV coinfection with an HCV titer below the level of sensitivity of the assay was significantly lower than the proportion of such patients among non-HIV cases of HCV infection, at 44.0% vs 55.4%, respectively.[7] There have been a few reports from other countries on the problems associated with HCV and HIV infections in hemophiliac patients.[8,9]

Liver Transplantations in HIV–HCV Coinfected Patients

Indications for Liver Transplantation in Patients with HIV–HCV Coinfection

Regardless of the presence of hemophilia, the indications for and methods of liver transplantation are the same for patients with HIV–HCV coinfection. Therefore, information on liver transplantation for HIV–HCV coinfected patients without hemophilia is presented in this section. In fact, after successful liver transplantation, hemophilia can normally be cured. In principle, as for a non-HIV-infected patient, liver transplantation is indicated for patients with type C cirrhosis in liver failure and no expectation of a long-term prognosis.[10–14] Liver transplantation is also indicated for patients not yet in liver failure, but with severe liver damage caused by HAART, especially those with chronic hepatitis C, who need to suspend or stop HAART.[15–18] For patients receiving HAART, the indication needs to be considered in terms of both hepatic reserve and status of the HIV infection. Liver transplantation may also be indicated for hepatocellular carcinoma that develops during follow-up.[19] The conditions for liver transplantation are often defined as follows: AIDS symptoms have not surfaced; the CD4+ lymphocyte count is 200–250/μl or above; and as a result of HAART, the amount of HIV in the blood is below the level of sensitivity of the assay. However, there are cases of pancytopenia resulting from portal hypertension and, as such, some institutions believe that the criterion for liver transplantation resolved be a CD4+ lymphocyte count of 100/μl or more.[19–22] Therefore, an issue to be resolved is whether

the indication can be based solely on a CD4+ lymphocyte count. Although a ratio of CD4 to CD8 lymphocyte count of 14% or greater is also considered an indication, individual institutions still refer to their own criteria. A recent study found a significant correlation between the preoperative model for end-stage liver disease (MELD) score and the postoperative survival rates of HIV–HCV coinfected patients: this also warrants investigation.[23]

Results of Liver Transplantation for Patients with HIV–HCV Coinfection

Liver transplantation from deceased donors has been performed in HIV patients since the 1980s in the United States and Europe. Initially the results were poor, with survival rates of only about 47%,[24] but this has improved remarkably since the introduction of HAART (Table 3). According to a review article published in 2004, 51 HIV-positive patients received liver transplantation between 1996 and 2004 worldwide, with liver damage caused by HCV being the indication in 68%. Since 1997, liver transplantation has been performed in 29 HIV patients at the University of Pittsburgh: 26% of these patients were hemophiliac and 89% were HCV-positive.[25] According to a retrospective study by the United Network for Organ Sharing, involving 138 HIV-positive persons and 30520 HIV-negative persons and evaluating liver transplantation, from 1997 when HAART was introduced and thereafter, the prognosis of patients who were only HIV-positive was relatively good.[26] In this study, the prognosis of HIV–HCV coinfected patients was worse than that of patients who were positive only for HIV. A series of reports are listed in Table 3.[13,20,21,25–34] In reality, in addition to those listed there have been many sporadic reports, such as reviews, regarding expectations for liver transplantation, and assessments of indications.

A recent important study in France, on 14 patients, provided details on interferons, HAART therapy, and liver fibrosis.[33] In all patients, the preoperative amount of HIV in the blood was below the level of sensitivity, and the CD4+ T-cell counts ranged from 85 to 1015. As for calcineurin inhibitors, tacrolimus 0.5 mg per week was started in the 2nd week after surgery in principle; however, there were five cases (36%) of an overdose. HAART was recommenced in the 2nd week after surgery, resulting in the long-term administration of steroids. Liver biopsies in the 12th month after liver transplantation revealed one case of fibrosing cholestatic hepatitis (FCH), one case of fibrosis stage F3, two cases of F2, and five cases of F1. The prognosis after transplantation was thought to be encouraging, since there was only one death as a result of FCH in the series.

Living Donor Liver Transplantation for Patients with HIV–HCV Coinfection

The Koike Group of the Ministry of Health, Labour, and Welfare reported seven cases of living donor liver transplantation (LDLT) for HIV–HCV coinfected patients with hemophilia at The University of Tokyo, and one at Hiroshima University.[35,36] The HCV genotypes were 1a and 1b ($n = 1$), 1b and 3a ($n = 1$), 2a ($n = 1$), 2a and 2b ($n = 1$), and 3a and 1b ($n = 1$). The HVC-RNA levels ranged from 2.8 to 1410 kIU/ml, the HIV-RNA levels in two cases were 50 copies/ml or less, being below the sensitivity level, and the CD4+ T-cell counts ranged from 120 to 618/μl and were 250/μl or less in two cases. At the time of the report in 2005, four patients were alive. Small bowel bleeding (suspected cytomegalovirus enteritis) and graft dysfunction were cited as the causes of death of the nonsurviving patients. Interestingly, interferon therapy was given after surgery to the surviving patients, whereas it was suspended in the two patients who died. HAART therapy was not given to one patient on the grounds that the HIV virus disappeared as the interferon treatment progressed. The report stated that the administration of factor 8 products was never required after surgery for patient #1.

Living donor liver transplantation from a hemophilia carrier was reported in 2002,[37] and it seems that LDLT has been performed in up to 10 patients in Japan. As noted in the section on epidemiology, there are some 50 patients coinfected with HIV–HCV from blood products, in whom liver failure has developed. They, like other patients with chronic hepatitis, may be candidates for liver transplantation, so it is necessary to collect sufficient information.

Problems with Liver Transplantation in HIV–HCV Coinfected Patients with Hemophilia

The Blood Concentration of the Calcineurin Inhibitor Used in Combination with HAART Is Increased

The risk of opportunistic infections caused by a delay in starting HAART and the appropriate time to start HAART has not been established. Moreover, early initiation of the therapy is associated with a high risk of drug-induced liver damage.[38,39] A new drug, Ralteglavir, does not interfere with the metabolism of the calcineurin inhibitor, and might reduce the chance of overshooting the trough level of the calcineurin inhibitor.[40]

Progression of HCV Recurrence Is Accelerated in These Patients Compared with Those Who Are Only HIV-Positive[41]

The HIV virus population dynamics manifest via the immune systems, which are targeted by antiviral drugs such as interferon and ribavirin as well as the HAART

Table 3. Reported series of liver transplantation for patients with HIV infection

First author, year, institution (Journal[Ref.])		*n*	Survival	Findings
Ragni, 2003, Pittsburgh	HIV only	24	3-Year 72.8%	Risk factor for mortality after LT
(J Infect Dis[27])	HIV+HCV	15	3-Year 56.9%	CD4+ <200/μl, HAART resume not possible HIV viral load >400 copies/ml
Neff, 2003, Pittsburgh	HIV positive	16	14/16	2 HAART discontinued due to liver damage
(Liver Transpl[28])				13/16 HIV negative before LT CD4+ <200/μl (6/16), <100/μl (2/16) ACR (6/16). FK trough level increased (6/16)
Fung, 2004, Review	HIV positive (total)	51	80%	68% HCV coinfection, 26% hemophilia
(Liver Transpl[25])	(Pittsburgh)	29	20/29	
Norris, 2004, London	HIV+HCV	7	2/7	4 HCV recurrence, died with sepsis
(Liver Transpl[29])	HIV only	7	7/7	HBV no recurrence
Moreno, 2005, Madrid	HIV+HCV	4	3/4	1 died with FCH 17 months after LT
(Liver Transpl[30])				CD4+ <100/μl (2/16) ACR (1/4), no opportunistic infection
Radecke, 2005, Essen	HIV+HCV	5	2/5	2 survived case on HAART
(Liver Int[31])				
Miró, 2007, Barcelona	HIV+HCV	Review	1-Year 50%–	Indication for LT: CD4+ >100/μl, HIV negative
(J HIV Ther[11])		($n > 200$)	55% (without LT)	
				SVR rate (post LT) 15%–20%
Schreibman, 2007, Miami	HIV positive	15	3-Year 73.3%	Infectious complication 26.7% vs 8.7% ($P = 0.006$)
(Transplantation[20])	HIV negative	857	3-Year 79.4%	Indication for LT: CD4+ >100/μl, HIV <200 copies/mm^3
Reiberger, 2008, Vienna	HIV+HCV (post)	31		HCV viral load increased on immunosuppression
(Eur J Clin Invest[32])	HIV+HCV (pre)	20		IFN effective if CD4+ preserved
	HCV only (pre)	25		SVR rate: HIV–HCV (post LT) 28%
	HIV+HCV (post LT) 50%, HCV only (post LT) 56%			
Mindikoglu, 2008, UNOS	HIV positive	138	2-Year 70%,	All after HAART era, HCV+ poor prognostic factor
(Transplantation[26])			3-year 66%	
	HIV+HCV	58	2-Year 52%	
	HIV negative	520	2-Year 81%, 3-year 77%	
Duclos-Vallée, 2008, France (THEVIC study group)	HIV+HCV	35	2-Year 73%, 5-year 51%	Pre LT MELD score most important factor for mortality
(Hepatology[21])	HCV only	44	2-Year 91%, 5-year 81%	HIV coinfection: fibrosis progression (>F2) quicker LT indication: CD4+ > 100/μl, HIV negative
Samri, 2009, France (multicenter)	HIV+HCV	14	2-Year 93%	LT indication: HIV negative, no AIDS
(J Hepatol[33])				FK and HAART resumed 2 weeks after LT, FK overdose 5/14 (36%) 1 FCH died. 1-year F2 2, F3 1, F4 (FCH) 2
Testillano, 2009, Bilbao	HIV+HCV	12	3-Year 62%	Patient survival, HCV recurrence, FCH not different ($P = 0.09$) from LT for patients without HIV
(Transplant Proc[34])	HCV only	59	3-Year 84%	

.HIV, human immunodeficiency virus; HCV, hepatitis C virus; HBV, hepatitis B virus; HAART, highly active antiretroviral therapy; FCH, fibrosing cholestatic hepatitis; LT, liver transplantation; ACR, acute cellular rejection; SVR, sustained virological response; IFN, interferon; UNOS, United Network for Organ Sharing; MELD, model for end-stage liver disease; FK, tacrolimus

drugs.[42–45] The best time to start interferon treatment and other post-transplantation measures to prevent HCV, optimal immunosuppressive regimens, and ways of monitoring drug blood levels are being studied, and further reports are expected.[46–51]

According to a review on the effects of interferon treatment after liver transplantation, the SVR rate ranges from 0% to 50%. This article reported that there had been many side effects in HIV-positive patients, especially caused by anemia and a low white blood cell

count, and that the continuation of treatment for such patients had been made possible by administration of the growth factor.[52]

Some Studies Refer to the Correlation Between T-Cell Counts and Acute Rejection

In practice, some studies showed the rate of acute cellular rejection to be similar, regardless of HIV positivity.[11,53] Induction therapy without steroids has also been attempted,[54] and the rate of opportunistic infection is reported to be similar after organ transplantation in HIV-positive patients.[20] Thus, the number of CD4+ lymphocytes present prior to liver transplantation is an important factor.

HAART Drugs Can Cause Hepatic Toxicity[55]

If HAART drugs induce liver failure, the best HAART drug to use after liver transplantation must be selected carefully. HAART drug toxicity can also induce complications with acute cellular rejection or other hepatic problems after liver transplantation. A liver biopsy may be needed to elucidate the real cause. Noncirrhotic portal hypertension has recently been reported in HIV-positive patients. HAART drugs may be related to those unresolved pathogeneses.[56]

The Control of Infection After Liver Transplantation for HIV–HCV Coinfection Is Based on the Count of CD4+ lymphocytes Obtained During the Perioperative Period

Therefore, the timing of recommencement of the HAART drug and the preoperative CD4+ lymphocytes counts are both important factors. According to previous reports, prophylaxis against bacterial and viral infections seems to be the same as for liver transplantation without HIV infection.[20]

The Presence of Hemophilia Makes It Difficult to Manage the Coagulation Time and Control Bleeding During the Intra- and Postoperative Period Before a Transplanted Liver Starts to Function

Moreover, when considering LDLT and when only carrier-donors exist, an assessment of the risks associated with the resection of the carrier-donor's liver would also be a problem.[37]

Conclusions

This review is an overview of liver transplantation performed to date for HIV–HCV coinfected persons. Although there have been no cadaveric liver transplantations for these patients in Japan,[57] conventional knowledge about cadaveric liver transplantation may be applicable in most cases, despite the unresolved problems. In light of the fact that most of these Japanese patients are the victims of contaminated blood products, we believe that the number of liver transplantations will increase, in the context of medical relief.[58]

Acknowledgment. This work was supported in part by a Grant-in-Aid for Research on HIV/AIDS from the Ministry of Health, Labour and Welfare of Japan.

References

1. Annual report on patients with AIDS. Program entrusted by Ministry of Health, Labour and Welfare, Japan. 2005.
2. Annual report on patients with AIDS. Program entrusted by Ministry of Health, Labour and Welfare, Japan. 2008.
3. Valdez H, Chowdhry TK, Asaad R, Woolley IJ, Davis T, Davidson R, et al. Changing spectrum of mortality due to human immunodeficiency virus: analysis of 260 deaths during 1995–1999. Clin Infect Dis 2001;32:1487–93.
4. del Amo J, Hernández-Aguado I, Pérez-Hoyos S. Effect of antiviral therapy on liver-related mortality in patients with HIV and hepatitis C virus coinfection. Lancet 2003;362:1708–13.
5. Pineda JA, Romero-Gómez M, Díaz-García F, Giron-Gonzalez JA, Montero JL, Torre-Cisneros J, et al. HIV coinfection shortens the survival of patients with hepatitis C virus-related decompensated cirrhosis. Hepatology 2005;41:779–89.
6. Japan Foundation for AIDS Prevention. Official report of the national surveillance on coagulation disorders in Japan 2008.
7. Thomas DL. The challenge of hepatitis C in the HIV-infected person. Annu Rev Med 2008;59:473–85.
8. Rumi MG, De Filippi F, Santagostino E, Colombo M. Hepatitis C in haemophilia: lights and shadows. Haemophilia 2004;suppl 4:211–5.
9. Wilde JT. HIV and HCV coinfection in haemophilia. Haemophilia 2004;10:1–8.
10. Kumar R, Singla V, Kacharya S. Impact and management of hepatitis B and hepatitis C virus co-infection in HIV patients. Trop Gastroenterol 2008;29:136–47.
11. Miro JM, Aguero F, Laguno M, Tuset M, Cervera C, Moreno A, et al. Liver transplantation in HIV/hepatitis co-infection. Hospital Clinic OLT in HIV Working Group. J HIV Ther 2007;12:24–35.
12. Castells L, Escartín A, Bilbao I, Len O, Allende H, Vargas V, et al. Liver transplantation in HIV–HCV coinfected patients: a case-control study. Transplantation 2007;83:354–8.
13. Miró JM, Laguno M, Moreno A, Rimola A; Hospital Clinic OLT in HIV Working Group. Management of end stage liver disease (ESLD): what is the current role of orthotopic liver transplantation (OLT)? J Hepatol 2006;44(1 suppl):S140–5.
14. Ragni MV, Eghtesad B, Schlesinger KW, Dvorchik I, Fung JJ. Pretransplant survival is shorter in HIV-positive than HIV-negative subjects with end-stage liver disease. Liver Transpl 2005;11:1425–30.
15. Antoniades C, Macdonald C, Knisely A, Taylor C, Norris S. Mitochondrial toxicity associated with HAART following liver transplantation in an HIV-infected recipient. Liver Transpl 2004;10:699–702.
16. Bonacini M. Liver injury during highly active antiretroviral therapy: the effect of hepatitis C coinfection. Clin Infect Dis 2004;38 suppl 2:S104–8.
17. Duclos-Vallée JC, Vittecoq D, Teicher E, Feray C, Roque-Afonso AM, Lombes A, et al. Hepatitis C virus viral recurrence and liver mitochondrial damage after liver transplantation in HIV-HCV co-infected patients. Hepatology 2005;42:341–9.
18. Polard E, Camus C, Abault AY, Turlin B, Arvieux C, Messner M, et al. Retransplantation for acute liver failure due to combined

antiviral agents in an HIV-HCV coinfected liver transplant recipient. Transplantation 2005;80:1136–8.
19. Di Benedetto F, De Ruvo N, Berretta M, Masetti M, Montalti R, DiSandro S, et al. Hepatocellular carcinoma in HIV patients treated by liver transplantation. Eur J Surg Oncol 2008;34: 422–7.
20. Schreibman I, Gaynor JJ, Jayaweera D, Pyrsopoulos N, Weppler D, Tzakis A, et al. Outcomes after orthotopic liver transplantation in 15 HIV-infected patients. Transplantation 2007;84: 697–705.
21. Duclos-Vallée JC, Féray C, Sebagh M, Teicher E, Roque-Afonso A, Roche B, et al. THEVIC Study Group. Survival and recurrence of hepatitis C after liver transplantation in patients coinfected with human immunodeficiency virus and hepatitis C virus. Hepatology 2008;47:407–17.
22. Maida I, Núñez M, González-Lahoz J, Soriano V. Liver transplantation in HIV-HCV coinfected candidates: what is the most appropriate time for evaluation? AIDS Res Hum Retroviruses 2005;21:599–601.
23. Subramanian A, Sulkowski M, Barin B, Stablein D, Curry M, Nissen N, et al. MELD score is an important predictor of pretransplantation mortality in HIV-infected liver transplant candidates. Gastroenterology 2010;138:159–64.
24. Tzakis AG, Cooper MH, Dummer JS, Rangi M, Ward JW, Startzl TE. Transplantation in HIV+ patients. Transplantation 1990; 49:354–8.
25. Fung JJ, Eghtesad B, Patel-Tom K, DeVera M, Chapman H, Ragni M. Liver transplantation in patients with HIV infection. Liver Transpl 2004;10(10 suppl 2):S39–53.
26. Mindikoglu AL, Regev A, Magder LS. Impact of human immunodeficiency virus on survival after liver transplantation: analysis of United Network for Organ Sharing database. Transplantation 2008;85:359–68.
27. Ragni MV, Belle SH, Im KA, Neff G, Roland M, Stock P, et al. Survival of human immunodeficiency virus-infected liver transplant recipients. J Infect Dis 2003;188:1412–20.
28. Neff GW, Bonham A, Tzakis AG, Ragni M, Jayaweera D, Schiff ER, et al. Orthotopic liver transplantation in patients with human immunodeficiency virus and end-stage liver disease. Liver Transpl 2003;9:239–47.
29. Norris S, Taylor C, Muiesan P, Portmann BC, Knisely AS, Bowles M, et al. Outcomes of liver transplantation in HIV-infected individuals: the impact of HCV and HBV infection. Liver Transpl 2004;10:1271–8.
30. Moreno S, Fortún J, Quereda C, Moreno A, Perez-Elias MJ, Martin-Davila P, et al. Liver transplantation in HIV-infected recipients. Liver Transpl 2005;11:76–81.
31. Radecke K, Frühauf NR, Miller M, Ross B, Köditz R, Malagó M, et al. Outcome after orthotopic liver transplantation in five HIV-infected patients with virus hepatitis-induced cirrhosis. Liver Int 2005;25:101–8.
32. Reiberger T, Rasoul-Rockenschaub S, Rieger A, Ferenci P, Gangl A, Peck-Radosavljevic M. Efficacy of interferon in immunocompromised HCV patients after liver transplantation or with HIV co-infection. Eur J Clin Invest 2008;38:421–9.
33. Samri A, Roque-Afonso AM, Beran O, Tateo M, Teicher E, Feray C, et al. Preservation of immune function and anti-hepatitis C virus (HCV) immune responses after liver transplantation in HIV-HCV coinfected patients (ANRS-HC08 "THEVIC" trial). J Hepatol 2009;51:1000–9.
34. Testillano M, Fernandez JR, Suarez MJ, Gastaca M, Bustamante J, Pijoan JI, et al. Survival and hepatitis C virus recurrence after liver transplantation in HIV- and hepatitis C virus-coinfected patients: experience in a single center. Transpl Proc 2009;41: 1041–3.
35. Treatment guideline for patients with HIV-HCV co-infection. Project (Program) entrusted by Ministry of Health, Labour And Welfare, Japan (Study on hepatic diseases combined to HIV infection). 2005.
36. Sugawara Y, Ohkubo T, Makuuchi M, Kimura S, Tachikawa N. Living-donor liver transplantation in an HIV-positive patient with hemophilia. Transplantation 2002;74:1655–6.
37. Horita K, Matsunami H, Shimizu Y, Shimizu A, Kurimoto M, Suzuki K, et al. Treatment of a patient with hemophilia A and hepatitis C virus-related cirrhosis by living-related liver transplantation from an obligate carrier donor. Transplantation 2002;73: 1909–12.
38. Teicher E, Abbara C, Duclos-Vallee JC, Antonini T, Bonhomme-Faivre L, Desbois D, et al. Enfuvirtide: safe and effective antiretroviral agent for human immunodeficiency virus-infected patients shortly after liver transplantation. Liver Transpl 2009;15: 1336–42.
39. Graham CS, Baden LR, Yu E, Mrus JM, Carnie J, Heeren T, et al. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. Clin Infect Dis 2001;33:562–9.
40. Tricot L, Teicher E, Peytavin G, Zucman D, Conti F, Calmus Y, et al. Safety and efficacy of raltegravir in HIV-infected transplant patients cotreated with immunosuppressive drugs. Am J Transplant 2009;9:1946–52.
41. Benhamou Y, Bochet M, Di Martino V, Charlotte F, Azria F, Coutellier A, et al. Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus coinfected patients. The Multivirc Group. Hepatology 1999;30:1054–8.
42. Lavuer GM,Lucas M, Timm J, Ouchi K, Kim AY, Day CL, et al. Full-breadth analysis of CD8+ T-cell responses in acute hepatitis C virus infection and early therapy. J Virol 2005;79:12979–88.
43. Berenguer J, Alvarez-Pellicer J, Martín PM, Lopez-Aldeguer J, von-Wichmann MA, Quereda C, et al. Sustained virological response to interferon plus ribavirin reduces liver-related complications and mortality in patients coinfected with human immunodeficiency virus and hepatitis C virus. Hepatology 2009;50: 407–13.
44. Weis N, Lindhardt BO, Kronborg G, Hansen AB, Laursen AL, Christensen PB, et al. Impact of hepatitis C virus coinfection on response to highly active antiretroviral therapy and outcome in HIV-infected individuals: a nationwide cohort study. Clin Infect Dis 2006;42:1481–7.
45. Ciuffreda D, Comte D, Cavassini M, Giostra E, Buhler L, Perruchoud M, et al. Polyfunctional HCV-specific T-cell responses are associated with effective control of HCV replication. Eur J Immunol 2008;38:2665–77.
46. Reiberger T, Rasoul-Rockenschaub S, Rieger A, Ferenci P, Gangl A, Peck-Radosavljevic M. Efficacy of interferon in immunocompromised HCV patients after liver transplantation or with HIV co-infection. Eur J Clin Invest 2008;38:421–9.
47. Castells L, Esteban JI, Bilbao I, Vargas V, Allende H, Ribera E, et al. Early antiviral treatment of hepatitis C virus recurrence after liver transplantation in HIV-infected patients. Antivir Ther 2006;11:1061–70.
48. Moreno A, Bárcena R, García-Garzón S, Muriel A, Quereda C, Moreno L, et al. HCV clearance and treatment outcome in genotype 1 HCV-monoinfected, HIV-coinfected and liver transplanted patients on peg-IFN-alpha-2b/ribavirin. Hepatology 2005;43: 783–90.
49. Gruber SA, Doshi MD, Cincotta E, Brown KL, Singh A, Morawski K, et al. Preliminary experience with renal transplantation in HIV+ recipients: low acute rejection and infection rates. Transplantation 2008;86:269–74.
50. Rafecas A, Rufí G, Figueras J, Fabregat J, Xiol X, Ramos E, et al. Liver transplantation without steroid induction in HIV-infected patients. Liver Transpl 2004;10:1320–3.
51. Guaraldi G, Cocchi S, Codeluppi M, Di Benedetto F, Bonora S, Pecorari M, et al. Role of therapeutic drug monitoring in a patient with human immunodeficiency virus infection and end-stage liver disease undergoing orthotopic liver transplantation. Transplant Proc 2005;37:2609–10.

52. Fredrick RT, Hassanein TI. Role of growth factors in the treatment of patients with HIV/HCV coinfection and patients with recurrent hepatitis C following liver transplantation. J Clin Gastroenterol 2005;39(1 suppl):S14–22.
53. Gruber SA, Doshi MD, Cincotta E, Brown KL, Singh A, Morawski K, et al. Preliminary experience with renal transplantation in HIV+ recipients: low acute rejection and infection rates. Transplantation 2008;86:269–74.
54. Tan HP, Kaczorowski DJ, Basu A, Khan A, McCauley J, Marcos A, et al. Living-related donor renal transplantation in HIV+ recipients using alemtuzumab preconditioning and steroid-free tacrolimus monotherapy: a single center preliminary experience. Transplantation 2004;78:1683–8.
55. Turkova A, Ball C, Gilmour-White S, Rela M, Mieli-Vergani G. A paediatric case of acute liver failure associated with efavirenz-based highly active antiretroviral therapy and effective use of raltegravir in combination antiretroviral treatment after liver transplantation. J Antimicrob Chemother 2009;63:623–5.
56. Mendizabal M, Craviotto S, Chen T, Silva MO, Reddy KR. Noncirrhotic portal hypertension: another cause of liver disease in HIV patients. Ann Hepatol 2009;8:390–5.
57. Yoshimura N, Okajima H, Ushigome H, Sakamoto S, Fujiki M, Okamoto M. Current status of organ transplantation in Japan and worldwide. Surg Today 2010;40:514–25.
58. Joshi D, O'Grady J, Dieterich D, Gazzard B, Agarwal K. Increasing burden of liver disease in patients with HIV infection. Lancet 2011;377:1198–209.

Surg Today (2011) 41:1026–1028
DOI 10.1007/s00595-010-4376-z

SURGERY TODAY

How to Do It

Living Donor Liver Transplantation with Extensive Caval Thrombectomy for Acute-on-Chronic Budd–Chiari Syndrome

AKIHIKO SOYAMA[1], SUSUMU EGUCHI[1], KATSUHIKO YANAGA[2], MITSUHISA TAKATSUKI[1], MASAAKI HIDAKA[1], and TAKASHI KANEMATSU[1]

[1]Department of Surgery, Nagasaki University Graduate School of Biomedical Sciences, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan
[2]Department of Surgery, Jikei University School of Medicine, Tokyo, Japan

Abstract
The key consideration when performing living donor liver transplantation (LDLT) in patients with Budd–Chiari syndrome (BCS) is careful management of a stenotic or occluded inferior vena cava (IVC), because it is not possible to replace the recipient stenotic or occluded IVC with donor IVC as in cadaver donor transplantation. We describe how we performed LDLT with extensive thrombectomy in a patient with acute-on-chronic BCS with a totally thrombosed retrohepatic IVC. The operation was successful and the patient remains well, with follow-up images showing a patent IVC and hepatic veins. To our knowledge, LDLT for a BCS patient with severe extensive caval thrombus has never been reported before. We consider that the successful outcome of this patient clearly demonstrates the feasibility of our technique of extensive thrombectomy, without a vessel graft, to manage a stenotic or occluded IVC in LDLT in patients with BCS.

Key words Living donor liver transplantation · Budd–Chiari syndrome · Thrombectomy · Cavoplasty

Introduction

Liver transplantation is ultimately the treatment of choice for patients with Budd–Chiari syndrome (BCS), especially those with fulminant forms of BCS, those with established cirrhosis or frank fibrosis, and those with defined hepatic metabolic defects such as protein C or protein S deficiency.[1] The safety and efficacy of liver transplantation for patients with BCS has been confirmed by a multicenter study conducted in Europe and by a United States national registry analysis.[2,3]

In contrast to deceased donor liver transplantation, when the recipient stenotic or occluded inferior vena cava (IVC) can be replaced with the donor IVC, in living donor liver transplantation (LDLT) it cannot, so appropriate management of a stenotic or occluded IVC is imperative in LDLT in the patient with BCS. We recently performed successful LDLT with extensive thrombectomy in a patient with acute-on-chronic BCS with a totally thrombosed retrohepatic IVC.

Patient

A 63-year-old man was admitted with general fatigue and vomiting to a local hospital, where liver dysfunction was confirmed. He was transferred to our hospital when his liver function deteriorated severely, with the following laboratory findings: serum total bilirubin 5.6 mg/dl, aspartate aminotransaminase 3573 IU/l, and alanine aminotransferase 2034 IU/l. He also had grade 3 hepatic encephalopathy. Abdominal computed tomography (CT) showed occlusion of the middle and left hepatic veins with thrombus in the IVC, extending from below the renal vein to the suprahepatic IVC (Fig. 1), as well as moderate ascites, and a patent portal vein. As a result of intensive care including plasma exchange, the acute liver failure improved and the patient was referred as a candidate for LDLT, with a diagnosis of BCS.

Technique

The patient underwent LDLT 3 months after the onset of acute liver failure. He received a right lobe liver graft from his son. The intraoperative findings revealed a hard and irregular liver, with moderate ascites and signs of portal hypertension.

Reprint requests to: S. Eguchi
Received: August 24, 2009 / Accepted: February 18, 2010

The preoperative abdominal CT showed a thrombosed IVC, so a portovenous bypass was established early in the procedure. The supradiaphragmatic IVC was cross-clamped after opening the pericardium. We introduced a Fogarty catheter through the opened and widened orifice of the right hepatic vein and common trunk of the left and middle hepatic veins. Since part of the thrombus was difficult to remove by using only a Fogarty catheter, we performed thrombectomy through a longitudinally opened IVC wall with segmental cross-clamp.

After removing the thrombus from the IVC, we performed cavoplasty to match the orifice of donor's hepatic vein without any patch or interposition graft. The right hepatic vein of the graft was anastomosed to the recipient's IVC in an end-to-side fashion (Fig. 2), and portal, arterial, and biliary anastomoses were completed in a standard fashion. Immediately after LDLT, intravenous heparin therapy was started, which was later changed to oral warfarin. The patient had an uneventful postoperative recovery and was discharged on postoperative day 28. Follow-up CT confirmed a patent IVC and hepatic veins (Fig. 3). The patient is now doing well without any signs of recurrence of BCS.

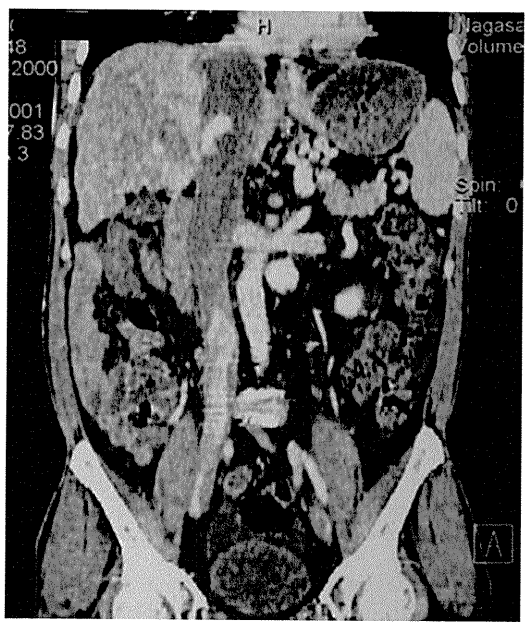

Fig. 1. Coronal view of preoperative abdominal computed tomography (CT) showed thrombosis of the inferior vena cava (IVC) extending from the suprahepatic IVC to below the left renal vein, a cirrhotic liver, and collateral vessels

Discussion

Yamada et al.[4] reported three cases of patients who underwent LDLT without replacement of a chronically occluded IVC because they had well-developed hemiazygos veins. As our patient did not have well-developed hemiazygos veins, the IVC had to be preserved as a return from the lower half of the body and as an outflow route from the liver.

As options to replace an occluded retrohepatic IVC in LDLT, Yan et al.[5] reported the usefulness of a cryopreserved vena cava graft, and Shimoda et al.[6] advocated an autologous vein graft. Although these

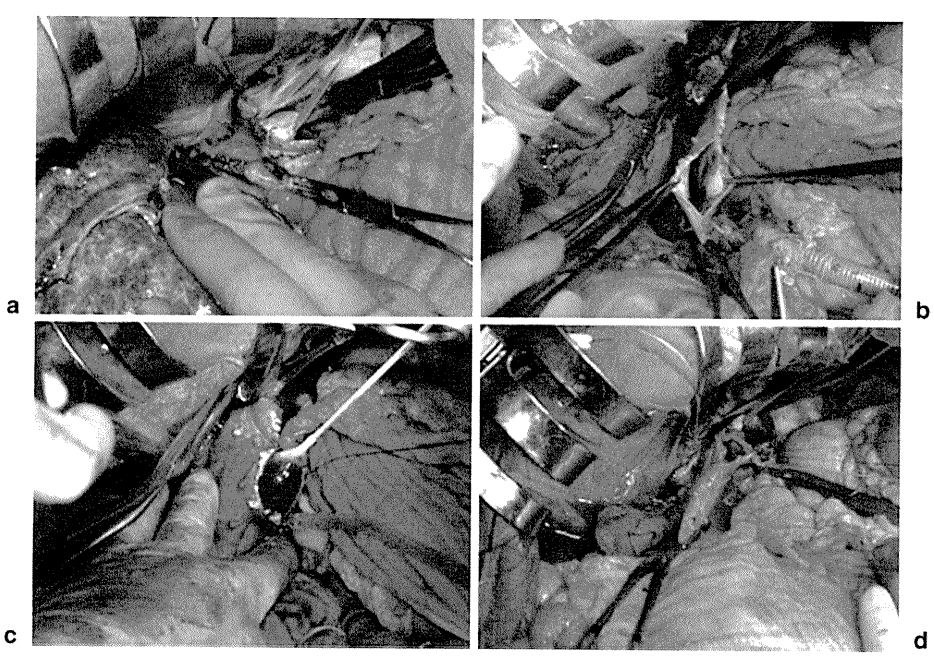

Fig. 2. Intraoperative photos showing cross-clamping of the IVC after opening the pericardium (**a**), opening of the IVC and subsequent thrombectomy with a Fogarty catheter (**b**, **c**), and cavoplasty performed to match the right hepatic vein of the graft (**d**)

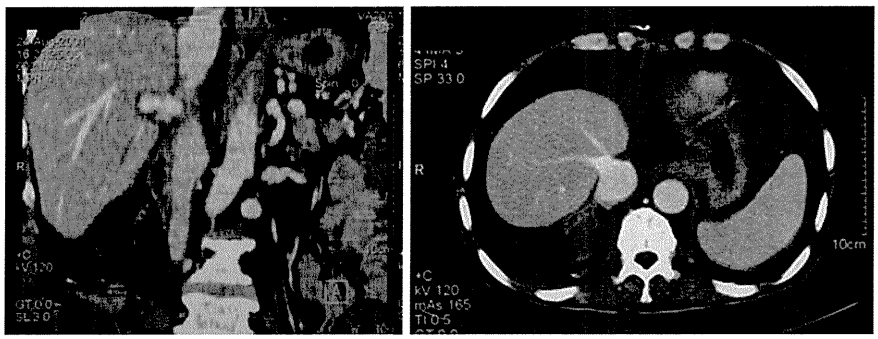

Fig. 3. Follow-up abdominal CT confirmed a patent IVC with no signs of recurrent thrombus

techniques have merit, appropriate cryopreserved grafts or autologous vessel grafts are not always available. Lee et al.[7] described replacing the diseased stenotic retrohepatic vena cava of the recipient with a large-caliber Dacron interposition graft, placed between the right atrium and the infrahepatic IVC. Although long-term outcomes should be evaluated, their technique might be feasible if the thrombotic obstruction of the suprahepatic IVC extends almost to the junction of the right atrium and the intrapericardiac IVC.[7]

The successful outcome of our patient confirms the feasibility of our technique, including extensive thrombectomy without a vessel graft, for managing a stenotic or occluded IVC in LDLT for the BCS patient. In slow-progressing BCS, the wall of inferior caval vein can become fibrotic if thrombosis exists there long term. Although our technique might be applicable for slow-progressing as well as acute BCS, it is important to check if the IVC has a fibrotic wall that could make the IVC stenotic even after thrombectomy.

To the best of our knowledge, this is the first report of LDLT in a BCS patient with such severe extensive caval thrombus. Thus, for patients with acute deteriorating BCS with IVC thrombosis, and for those without CT evidence of a well-developed long-standing hemiazygos vein, we consider LDLT with extensive thrombectomy to be a good treatment option.

References

1. Klein AS, Molmenti EP. Surgical treatment of Budd–Chiari syndrome. Liver Transpl 2003;9:891–6.
2. Mentha G, Giostra E, Majno PE, Bechstein WO, Neuhaus P, O'Grady J, et al. Liver transplantation for Budd–Chiari syndrome: A European study on 248 patients from 51 centres. J Hepatol 2006;44:520–8.
3. Segev DL, Nguyen GC, Locke JE, Simpkins CE, Montgomery RA, Maley WR, et al. Twenty years of liver transplantation for Budd–Chiari syndrome: a national registry analysis. Liver Transpl 2007;13:1285–94.
4. Yamada T, Tanaka K, Ogura Y, Ko S, Nakajima Y, Takada Y, et al. Surgical techniques and long-term outcomes of living donor liver transplantation for Budd–Chiari syndrome. Am J Transplant 2006;6:2463–9.
5. Yan L, Li B, Zeng Y, Wen T, Zhao J, Wang W, et al. Living donor liver transplantation for Budd–Chiari syndrome using cryopreserved vena cava graft in retrohepatic vena cava reconstruction. Liver Transpl 2006;12:1017–9.
6. Shimoda M, Marubashi S, Dono K, Miyamoto A, Takeda Y, Nagano H, et al. Utilization of autologous vein graft for replacement of the inferior vena cava in living-donor liver transplantation for obliterative hepatocavopathy. Transpl Int 2007;20:804–7.
7. Lee SG, Hwang S, Kim KH, Ahn CS, Moon DB, Ha TY, et al. Toward 300 liver transplants a year. Surg Today 2009;39:367–73.

Ⅲ. 研究成果の刊行物・別刷

■ 総　説

HIV-HCV 重複感染患者に対する肝移植

江口　晋[1]，日高匡章[1,2]，高槻光寿[1]，曽山明彦[1]，
朝長哲生[1]，小坂太一郎[1]，村岡いづみ[1]，兼松隆之[1]

Liver transplantation for patients with HIV and HCV co-infection —current status of the world—

[1]*Department of Surgery, Nagasaki University Graduate School of Biomedical Sciences,*
[2]*Japan Foundation for AIDS Prevention*

Susumu EGUCHI[1], Masaaki HIDAKA[1,2], Mitsuhisa TAKATSUKI[1], Akihiko SOYAMA[1], Tetsuo TOMONAGA[1], Taichiro KOSAKA[1], Izumi MURAOKA[1], Takashi KANEMATSU[1]

【Summary】

Liver transplantation for patients with hepatitis C virus (HCV) and human immunodeficiency virus (HIV) is still challenging. With the progress of highly active anti-retroviral therapy (HAART) for HIV, mortality due to opportunistic infection resulting from AIDS has dramatically reduced, while half those patients have died of end-stage liver cirrhosis due to HCV. Especially, in Japan patients with HCV-HIV coinfection have become cirrhotic due to previous use of infected blood products for hemophilia. The problems of liver transplantation for those cases are: 1) difficulty to control calcineurin inhibitor with HAART drugs; 2)the optimal timing to initiate HAART after liver transplantation has not been established; 3)difficulty to use interferon after liver transplantation in patients on HAART; and 4)control of coagulopathy due to hemophilia etc. In this article, we review recent reports of liver transplantation in patients with HCV-HIV coinfection the world literature.

Keywords: liver transplantation, human immunodeficiency virus (HIV), hepatitis C virus (HCV), coinfection

I. はじめに

東アジアでのHIV感染者は依然増加しており，わが国でも若年層を中心に増加が続いている。厚生労働省からの報告によると2006年10月における国内感染者数は，累計で8,071人（男性6,275人，女性1,796人）で，AIDS発症者数はうち3,949人（男性3,445人，女性504人）といわれている[1]。感染経路としては，①性行為，②汚染血液・非加熱製剤の使用，③母子感染が考えられるが，②の血液製剤によるHIV感染はHCVの重複感染を伴うことが多い。実際，1995年以降，HIV感染例の死亡数は減少するとともに，死因に大きな変化がみられた。米国での1997～2000年に死亡した135人のHIV患者のうち，AIDS関連死（日和見感染による死亡）は約50%，残りの約半数のうち，約90%は肝疾患関連であり，多くはHCV感染症による死亡であった[2]。その他の諸国でも同様な問題が指摘されてきている[3-5]。

これは昨今のhighly active anti-retroviral therapy（HAART）によるHIVのコントロールの改善が主因であると考えられる。HAARTでは，①核酸系逆転写酵素阻害薬（NRTIs），②非核酸系逆転写酵素阻害薬（NNRTIs），③プロテアーゼ阻害薬（PI）を用い①+②or③の組み合わせで行い，服薬率が95%以下の場合，半数以上が治療不成功といわれている[6]。

米国でもHIV感染患者の25~30%がHCVを重複感染しているとされ，特に退役軍人では40%とさらに高値と報告されている[7,8]。合計では約30万人がHIV-

[1]長崎大学大学院移植・消化器外科，[2]日本エイズ予防財団
（2009・10・6受領；2009・12・18受理）

HCV 重複感染と推計されているが，75–90% は薬物濫用によるものと考えられている[9]。本稿では，本邦での肝移植適応となる可能性のある血友病など血液疾患に対する過去の汚染血液製剤使用による HIV-HCV 重複感染者に対する肝移植を念頭に進める。

II. HIV-HCV 重複感染症の疫学

実際本邦には肝移植が必要となる血液製剤による HIV-HCV 重複感染者はどれくらい存在するのであろうか。2008 年版の厚生労働省の調査[10]では血友病患者で HIV 感染生存例は，血友病 A（第 8 因子欠損）：602 人，血友病 B（第 9 因子欠損）：183 人であった（**表 1**）。この中で HCV 感染があり，肝疾患の病期が報告されているものは，血友病 A：524 人（87%），血友病 B：162 人（89%）であった。血友病 A の 524 人では肝硬変 33 人（6.3%），肝癌 5 人（0.9%），肝不全 2 人（0.4%）で，肝臓移植を受けた患者も 2 人存在した（**表 2**）。また，血友病 B の 162 人では肝硬変 11 人（6.8%），肝癌 6 人（3.7%），肝不全 0 人で，肝臓移植を受けた患者も 2 人（1.2%）存在した。現在，既に肝硬変の症例約 50 人程度が，今後の移植適応となってくる可能性が高い。実際，本報告では血液疾患による HIV-HCV 重複感染患者での死因の 1/3 は肝疾患であると報告されている[10]。

これらの患者は，輸入血液製剤を介するための特徴として，HCV 遺伝子型 1b 型が 25%（日本人では通常 70%）と少なく，3a 型が 23% と多い。また，HIV-HCV 重複感染例では HCV が測定感度以下となっている割合が 44.0% と，HIV 非感染例 HCV 例の 55.4% よりも有意に低かった[7]。海外でも血友病患者での HCV や HIV 感染に伴う諸問題の報告も散見される[11-13]。

表 1　日本における血液凝固異常症総数

	血友病		VWD	類縁疾患	総数
	A	B			
総　数	4,211	916	892	452	6,471
男性	4,185	908	406	246	5,745
女性	29	8	486	206	726
HIV 非感染					
総　数	3,609	733	885	448	5,675
男性	3,583	725	404	245	4,957
女性	26	8	481	203	718
HIV 感染					
総　数	602	183	7	4	796
男性	602	183	2	1	788
女性	0	0	5	3	8

（平成 20 年度エイズ予防財団血液凝固異常全国調査）

HIV：human immunodeficiency virus，VWD：von Willebrand disease

表 2　HIV 感染を伴う血液凝固異常症における肝疾患の病期

	肝炎なし	急性肝炎	慢性肝炎	肝硬変	肝癌	肝不全	IFN 治療により治癒	自然治癒	肝臓移植	合計
血友病 A	45	2	350	33	5	2	59	26	2	524
血友病 B	15	1	100	11	6	0	19	8	2	162
計	60	3	450	44	11	2	78	34	4	686

（平成 20 年度エイズ予防財団血液凝固異常全国調査）

生存症例中で HCV 感染があり，肝疾患の病期が報告されているもののみ

HIV：human immunodeficiency virus，HCV：hepatitis C virus