and concomitant hepatocellular carcinoma were compared between the group receiving synbiotic therapy and the control group.

Subsequently, at 24 hours after LDLT, all patients received enteral nutrition with Elental (Ajinomoto Pharmaceutical Ltd, Tokyo, Japan), which is an elemental diet, through a tube jejunostomy made during liver transplantation. The initial infusion rate at 1 kcal/mL was 20 mL/h, and if tolerated the rate was increased 60 mL/h until sufficient oral intake was possible. The composition of Elental has been described elsewhere.[23]

Synbiotic therapy

All patients had started the oral administration of Yakult BL antiflatulent (Yakult Honsha, Tokyo, Japan), containing 20 mg of living *Lactobacillus casei* strain Shirota, 15 mg of living *Bifidobacterium breve* strain Yakult, and galactooligosaccharides 15 g/d (Oligomate 55; Yakult Honsha) 3 times per day from 2 days before elective LDLT, continued for 2 weeks after LDLT via either a tube jejunostomy or orally. Usually, both prebiotics and probiotics were taken with 10 mL of tap water. We selected this formula of synbiotics on the basis of a previous report on major hepatectomy.[16]

The rates of infectious complications and patient survival were recorded, and stool cultures were also performed.

Statistical analysis

All data are expressed as median values with ranges. Statistical analysis was performed using the Mann-Whitney U test for continuous values and the χ^2 test for categorical values. A statistically significant difference was defined as a P value $< .05$. StatView version 5.0 (Abacus Concepts, Berkeley, CA) was used for all statistical analyses.

Results

All patients tolerated synbiotic therapy throughout the study period. There was no difference in the patient characteristics between the groups (Table 1). Figure 1 shows the result of cultured bacteria in the feces. Generally, *Escherichia* spp, *Enterobacter* spp, and *Klebsiella* spp were regarded as normal bacterial flora in the stool. There was no significant pattern of the change of bacterial species between the groups. However after LDLT under immunosuppression, *Enterococcus* spp became evident in both groups in about 25% of the patients.

Table 2 that infectious complication occurred after LDLT in 6 of 25 of the patients in the control group (24%) and in 1 of 25 (4%) in group receiving synbiotic therapy ($P < .05$). In particular, the rate of urinary infection was higher without synbiotic therapy. The rate of intra-abdominal infection was not statistically different. *Enterococcus* spp and methicillin-resistant *Staphylococcus aureus* were the main bacteria related to the infection. The postoperative date of infection varied. Some infectious complication occurred after the termination of synbiotic therapy.

Table 3 shows that there was no significant difference between the groups in other complications after LDLT. In addition, there were no differences in the intensive care unit period, hospitalized period, and mortality rate between the groups.

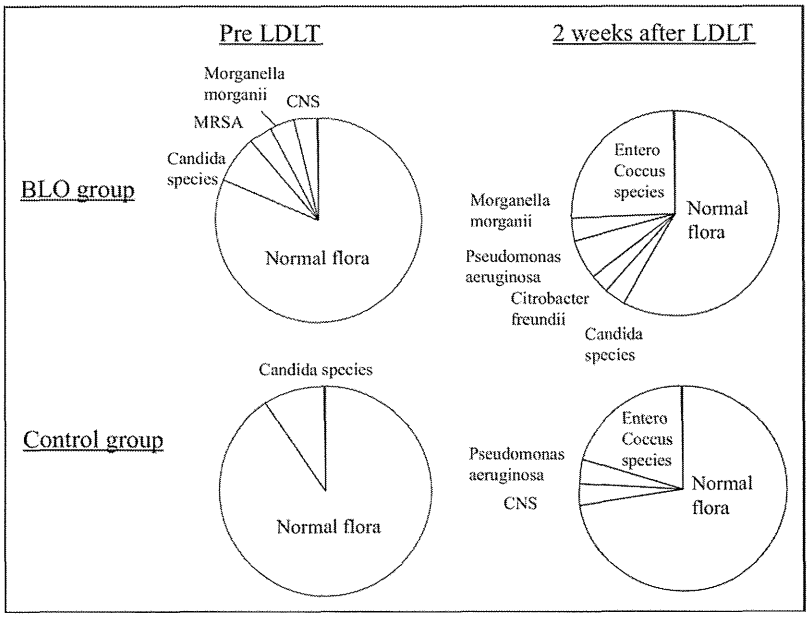

Figure 1 Bacterial profile in fecal culture. Cultured bacteria in the feces of the patients undergoing LDLT in each group. BLO = *Bifidobacterium breve*, *Lactobacillus casei*, and galactooligosaccharides; CNS = coagulase-negative staphylococci; MRSA = methicillin resistant *Staphylococcus aureus*.

Table 2 Infectious complications after LDLT

Variable	BLO group (n = 25)	Control group (n = 25)	*P*
Type of infection	1 catheter infection (POD 19)	3 sepsis (PODs 11, 10, and 9) 3 urinary tract infections (PODs 7, 8, and 5)	<.05
Bacteria cultured in blood	1 *Enterobacter asburiae* (POD 19)	2 MRSA (PODs 10 and 9) 1 MRSA + *Candida glabrata* (POD 11) 3 *Enterococcus faecium* (PODs 7, 8, and 5)	
Intra-abdominal infection	1 (4%) *Klebsiella oxytoca* + *Enterococcus faecium* (POD 19)	2 (8%) 1 *Enterobactor asburiae* (POD 19) 1 *Enterococcus faecium* (POD 14)	NS

BLO = *Bifidobacterium breve, Lactobacillus casei,* and galactooligosaccharides; MRSA = methicillin resistant *Staphylococcus aureus*; POD = postoperative day.

Comments

This prospective randomized study demonstrated that synbiotic therapy successfully reduced the rate of infectious complications after LDLT, which has a greater chance to induce temporary portal hypertension leading to bacterial translocation. The portal venous pressure after LDLT should have been elevated in the current series of patients, because the graft volume versus standard liver volume ratio was about 40%.[21] Therefore, synbiotic therapy may be potentially more effective in patients after LDLT than deceased-donor liver transplantation. In addition, LDLT is partial transplantation, in which liver regeneration should occur to support the patient's life. Infection itself was reported to reduce the magnitude of liver regeneration, so synbiotic therapy should be used for the patients undergoing LDLT.[24]

The patients in the present study received enteral nutrition, which has been shown to reduce the rate of infection from 29% to 14%.[25,26] This is probably why the rate of infection in this study was lower than in previous reports with synbiotic therapy. In addition, the rate of acute cellular rejection was not changed by synbiotic therapy. In a previous study, the rate of acute cellular rejection was reduced from 44% to 7% by enteral nutrition after whole-liver transplantation.[27] There was no difference in the rejection rate, even though there were more ABO-incompatible LDLT patients in the synbiotic group than in the control group.

Methicillin-resistant *S aureus* and *Enterococcus* spp were the principle bacteria causing sepsis, although gram-negative gut-derived bacteria are thought to be found in septic patients. Although there was no explanation for the gram-positive bacteria in this series, *Enterococcus* spp were frequently observed as the dominant bacteria after LDLT in the feces.[28] Immunosuppression and the duration of our antibiotic use might have cause *Enterococcus* sepsis in partial liver transplant recipients. In addition, the reduction of urinary tract infections was reported in a previous study, consistent with the current data, indicating that synbiotic therapy is likely to be responsible for the reduction of urinary tract infection.[29] Previous authors have speculated that in addition to their impact on bacterial translocation, probiotics act via several other mechanisms. For instance, they can reduce and eliminate potentially pathogenic microorganisms, reduce and eliminate various toxins and mutagens from the urine and feces, modulate innate and adaptive immune defense mechanisms, promote apoptosis, and release numerous nutrients, antioxidants, and growth factors from consumed fibers. These functions might all be important for the reduction of infections in surgical patients. However, a definite mechanism regarding the reduction of urinary tract infection awaits further investigation.[3,25,29,30]

In conclusion, infectious complications after LDLT were significantly decreased with synbiotic therapy. It is possible to achieve ecologic liver transplantation using synbiotic therapy while maintaining an intact environment in the body.

Table 3 Other complications

Variable	BLO (n = 25)	Control (n = 25)	*P*
Others	2 ACR 3 CMV 1 HAT 1 HPS 1 TMA 1 adrenal insufficiency	3 ACR 3 CMV 1 HAT 1 HPS 1 NOMI	NS
ICU period (days)	7 (4–35)	7 (2–48)	NS
Hospitalized period (days)	40 (16–132)	33 (16–97)	NS
Mortality	3	3	NS

Data are expressed as median (range) or as numbers.

ACR = acute cellular rejection; BLO = *Bifidobacterium breve, Lactobacillus casei,* and galactooligosaccharides; CMV = cytomegalovirus; HAT = hepatic arterial thrombus; HPS = hemophagocytic syndrome; ICU = intensive care unit; NOMI = nonocclusive mesenteric ischemia; TMA = thrombolytic microangiopathy.

References

1. Backhed F, Ley RE, Sonnenburg JL, et al. Host-bacterial matualism in the human intestine. Science 2005;25:1915–20.

2. Bengmark S. Immunonutrition: role of biosurfactants, fiber and probiotic bacteria. Nutrition 1998;14:585–94.
3. Alverdy JC, Laughlin RS, Wu L. Influence of the critically ill state on host-pathogen interactions within the intestine: gut-derived sepsis redefined. Crit Care Med 2003;31:598–607.
4. Swartz MN. Hospital-acquired infections: diseases with increasingly limited therapies. Proc Natl Acad Sci U S A 1994;91:2420–7.
5. Bengmark S. Gut environment and immune function. Curr Opin Clin Nutr Metab Care 1999;2:83–5.
6. Liu Q, Duan ZP, Ha DK, et al. Synbiotic modulation of gut flora: effect on minimal hepatic encephalopathy in patients with cirrhosis. Hepatology 2004;39:1441–9.
7. Bengmark S, Andersson R, Mangiante G. Uninterrrupted perioperative enteral nutrition. Clin Nutr 2001;20:11–9.
8. Wacha H, Hau T, Dittmer R, et al. Risk factors associated with intraabdominal infections: a prospective multicenter study. Langenbecks Arch Surg 1999;384:24–32.
9. Shimizu K, Ogura H, Goto M, et al. Synbiotics decrease the incidence of septic complications in patients with severe SIRS: a preliminary report. Dig Dis Sci 2009;54:1071–8.
10. Pitsouni E, Alexiou V, Saridakis V, et al. Does the use of probiotics/synbiotics prevent postoperative infections in patients undergoing abdominal surgery? A meta-analysis of randomized controlled trials. Eur J Clin Pharmacol 2009;65:561–70.
11. Olah A, Belagyi T, Issekutz A, et al. Randomized clinical trial of specific lactobacillus and fibre supplement to early enteral nutrition in patients. Br J Surg 2002;89:1103–7.
12. Reid G, Jass J, Sebulsky MT, et al. Potential uses of probiotics in clinical practice. Clin Microbiol Rev 2003;16:658–72.
13. Seehofer D, Rayes N, Schiller R, et al. Probiotics partly reverse increased bacterial translocation after simultaneous liver resection and colonic anastomosis in rats. J Surg Res 2004;117:262–71.
14. Bengmark S. Bio-ecological control of perioperative and ITU morbidity. Langenbecks Arch Surg 2004;389:145–54.
15. Kinross J, von Roon AC, Penney N, et al. The gut microbiota as a target for improved surgical outcome and improved patient care. Curr Pharm Des 2009;15:1537–45.
16. Rayes N, Seehofer D, Neuhaus P. Prebiotics, probiotics, synbiotics in surgery—are they only trendy, truly effective or even dangerous? Langenbecks Arch Surg 2009;394:547–55.
17. Rayes N, Seehofer D, Theruvath T, et al. Effect of enteral nutrition and synbiotics on bacterial infection rates after pylorus-preserving pancreatoduodenectomy: a randomized, double-blind trial. Ann Surg 2007; 246:36–41.
18. Rayes N, Seehofer D, Theruvath T, et al. Supply of pre- and probiotics reduces bacterial infection rates after liver transplantation -a randomized, double-blind trial. Am J Transplant 2005;5:125–30.
19. Rayes N, Seehofer D, Hansen S, et al. Early enteral supply of lactobacillus and fiber versus selective bowel decontamination: a controlled trial in liver transplant recipients. Transplantation 2002;74:123–7.
20. Oláh A, Belágyi T, Pótó L, et al. Synbiotic control of inflammation and infection in severe acute pancreatitis: a prospective, randomized, double blind study. Hepatogastroenterology 2007;54:590–4.
21. Eguchi S, Yanaga K, Sugiyama N, et al. Portalvenous flow regulates regeneration of the liver in patients undergoing living-related partial liver transplantation. Liver Transplant 2003;9:547–51.
22. Eguchi S, Takatsuki M, Hidaka M, et al. Evolution and changes in living donor liver transplantation. A single center experience over 10 years. Surg Today 2008;38:785–800.
23. Takagi S, Utsunomiya K, Kuriyama S, et al. Effectiveness of an "half elemental diet" as maintenance therapy for Crohn's disease: a randomized-controlled trial. Aliment Pharmacil Ther 2006;24;1333–40.
24. Seehofer D, Stockmann M, Schirmeier A, et al. Intraabdominal bacterial infections significantly alter regeneration and function of the liver in a rat model of major hepatectomy. Langenbecks Arch Surg 2007;392:273–84.
25. Lidbeck A, Overvik E, Rafter J, et al. Effect of Lactobacillus acidophilus supplements on mutagen excretion in feces and urine in humans. Microb Ecol Health Dis 1992;5:59–67.
26. Moore FA, Feliciano DV, Andrassy RJ, et al. Early enteral feeding, compared with parenteral, reduces postoperative septic complications: the results of a meta-analysis. Ann Surg 1992:216:172–83.
27. Hasse J, Blue L, Liepa G, et al. Early enteral nutrition support in patients undergoing liver transplantation. JPEN J Parenter Enteral Nutr 1995;19:437.
28. de Jonge E, Schultz MJ, Spanjaard L, et al. Effects of selective decontamination of digestive tract on mortality and acquisition of resistant bacteria in intensive care: a randomised controlled trial. Lancet 2003;362:1011–6.
29. Reid G, Bruce AW, Taylor M. Instillation of Lactobacillus and stimulation of indigenous organisms to prevent recurrence of urinary tract infections. Microecol Ther 1995;23:32–45.
30. Gill HS, Rutherford KJ, Prasad J, et al. Enhancement of natural and acquired immunity by Lactobacillus rhamnosus (HN001), Lactobacillus acidophilus (HN017) and Bifidobacterium lactis (HNO19). Br J Nutr 2000;83:167–76.

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 (J Infect Dis[27])	HIV only	24	3-Year 72.8%	Risk factor for mortality after LT
	HIV+HCV	15	3-Year 56.9%	CD4+ <200/μl, HAART resume not possible HIV viral load >400 copies/ml
Neff, 2003, Pittsburgh (Liver Transpl[28])	HIV positive	16	14/16	2 HAART discontinued due to liver damage 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 (Liver Transpl[30])	HIV+HCV	4	3/4	1 died with FCH 17 months after LT CD4+ <100/μl (2/16) ACR (1/4), no opportunistic infection
Radecke, 2005, Essen (Liver Int[31])	HIV+HCV	5	2/5	2 survived case on HAART
Miró, 2007, Barcelona (J HIV Ther[11])	HIV+HCV	Review ($n > 200$)	1-Year 50%–55% (without LT)	Indication for LT: CD4+ >100/μl, HIV negative SVR rate (post LT) 15%–20%
Schreibman, 2007, Miami (Transplantation[20])	HIV positive	15	3-Year 73.3%	Infectious complication 26.7% vs 8.7% ($P = 0.006$)
	HIV negative	857	3-Year 79.4%	Indication for LT: CD4+ >100/μl, HIV <200 copies/mm^3
Reiberger, 2008, Vienna (Eur J Clin Invest[32])	HIV+HCV (post)	31		HCV viral load increased on immunosuppression
	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 (Transplantation[26])	HIV positive	138	2-Year 70%, 3-year 66%	All after HAART era, HCV+ poor prognostic factor
	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) (J Hepatol[33])	HIV+HCV	14	2-Year 93%	LT indication: HIV negative, no AIDS 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 (Transplant Proc[34])	HIV+HCV	12	3-Year 62%	Patient survival, HCV recurrence, FCH not different ($P = 0.09$) from LT for patients without HIV
	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.

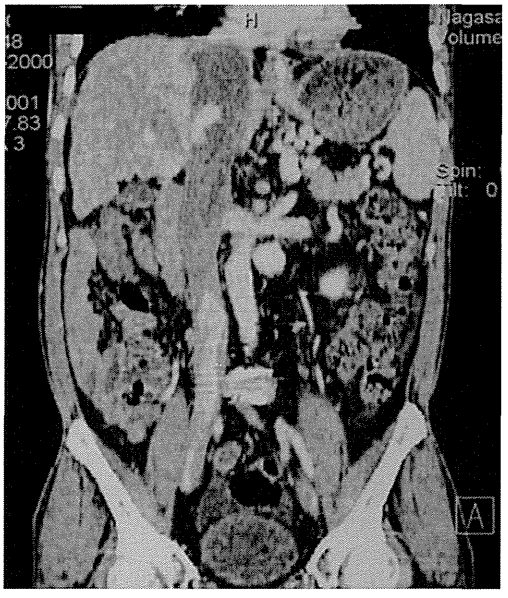

Fig. 1. Coronal view of preoperative abdominal computed tomography (CT) showed thrombosis of the inferior vena cava (IVC) extending from the suprahepatic IVC to below the left renal vein, a cirrhotic liver, and collateral vessels

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

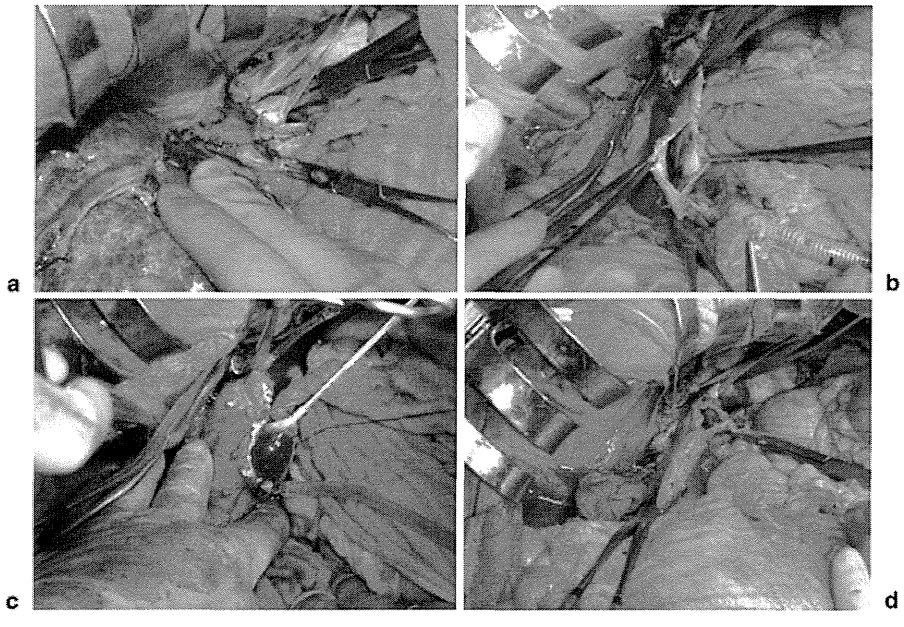

Fig. 2. Intraoperative photos showing cross-clamping of the IVC after opening the pericardium (**a**), opening of the IVC and subsequent thrombectomy with a Fogarty catheter (**b**, **c**), and cavoplasty performed to match the right hepatic vein of the graft (**d**)

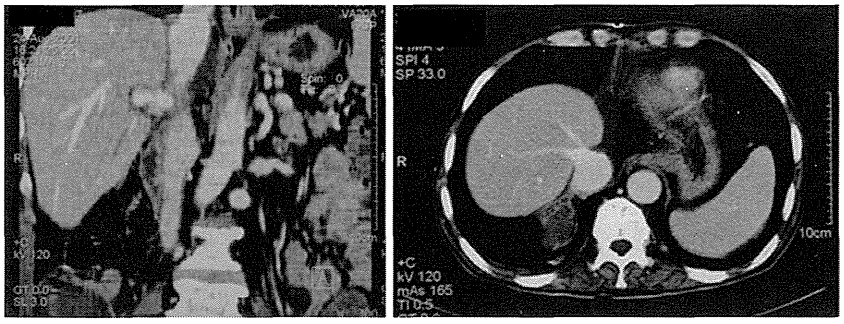

Fig. 3. Follow-up abdominal CT confirmed a patent IVC with no signs of recurrent thrombus

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.

Surgical Technique

Elective living donor liver transplantation by hybrid hand-assisted laparoscopic surgery and short upper midline laparotomy

Susumu Eguchi, MD, Mitsuhisa Takatsuki, MD, Akihiko Soyama, MD, Masaaki Hidaka, MD, Tetsuo Tomonaga, MD, Izumi Muraoka, MD, *and* **Takashi Kanematsu, MD,** *Nagasaki, Japan*

Background. *Although the technique of liver transplantation is well developed, the invasiveness of the operation can be decreased with laparoscopic procedures.*
Methods. *We performed elective living donor liver transplantation (LDLT) through a short midline incision combined with hand-assisted laparoscopic surgery (HALS). Nine selected patients with end stage liver disease underwent the procedure between July, 2010 and February, 2011 (median age 60, median Child-Pugh 9, median MELD score 14). Splenectomy was performed simultaneously in 7 cases. The liver (and spleen) were mobilized by a sealing device under a HALS procedure with an 8-cm upper midline incision, followed by explantation of the diseased liver (and spleen) through the upper midline incision which was extended to 12 to 15 cm. Partial liver grafts were implanted through the upper midline incision.*
Results. *The median duration of the operation was 741 minutes, the median time needed for anastomosis was 48 minutes, the median blood loss was 3,940 g, and the median liver weight was 866 g.*
Eight recipients are alive and have good graft function. A difficult implantation for one patient required an additional right transverse incision. When compared with 13 recent liver recipients who underwent LDLT with a regular Mercedes-Benz-type incision, no clinically relevant drawbacks of the HALS hybrid procedure were observed.
Conclusion. *We have shown the feasibility and safety of LDLT performed through a short midline incision without abdominal muscle disruption with the aid of HALS. (Surgery 2011;150:1002-5.)*

From the Department of Surgery, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

In an attempt to decrease the morbidity and invasiveness associated with liver surgery, several liver transplant teams have developed laparoscopic approaches to hepatectomy for living donors and patients with hepatic malignancies.[1-5] The surgical procedure performed on liver transplant recipients with portal hypertension is considered one of the most difficult abdominal operations because of the existence of collateral vessels. Nevertheless, selected patients have undergone a less invasive procedure with laparoscopic assistance, including patients with portal hypertension who underwent splenectomy.[6] We postulated that an elective liver transplant recipient procedure could be performed through an upper midline laparotomy after mobilization of the liver and spleen using hand-assisted laparoscopic surgery (HALS). We report a safe method for less invasive liver transplantation via a short midline incision without disruption of the abdominal musculature and nerves.[7]

Accepted for publication June 15, 2011.

Reprint requests: Susumu Eguchi, MD, Department of Surgery, Nagasaki University, Graduate School of Biomedical Sciences, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan. E-mail: sueguchi@nagasaki-u.ac.jp.

0039-6060/$ - see front matter

doi:10.1016/j.surg.2011.06.021

MATERIALS AND METHODS

Living donor liver transplantation (LDLT) through a midline incision using a hand-assisted laparoscopic procedure was planned in 9 patients between July 2010 and February 2011. Seven patients had liver cirrhosis due to hepatitis C, in

Table. Comparison of patient demographics and operative results

	HALS + upper midline (n = *9*)	*Mercedes-Benz-type incision* (n = *13*)	P *value*
Age	60 (44–69)	54 (27–72)	NS
Gender (Male:Female)	4:5	8:5	NS
Child-Pugh score	9 (6–14)	10 (5–15)	NS
MELD score	14 (7–43)	15 (7–35)	NS
Graft (RL:ELL)	1:8	6:7	NS
Operation duration (min)	741 (599–839)	812 (654–1,097)	$P < .05$
Anastomosis (min)	48 (37–55)	36 (32–65)	NS
Blood loss (g)	3,940 (1300–18,400)	3,350 (520–5,600)	NS
Explanted liver (g)	866 (596–1,270)	830 (399–1,250)	NS
Outcome	1 death	2 deaths	NS

Values are expressed as median (range).
HALS, Hand-assisted laparoscopic surgery; *MELD,* model for end-stage liver disease; *Anastomosis,* anastomosis for hepatic vein and portal vein reconstruction; *ELL,* extended left lobe graft with middle hepatic vein; *RL,* right lobe graft.

whom splenectomy was performed simultaneously. One patient required LDLT because of hepatitis B cirrhosis, and another for Caroli's disease. The Ethics Committee of Nagasaki University Hospital approved a laparoscopic approach for the living donors as well. After experience with the 3 living donor right hepatectomy procedures, we planned to introduce the procedure in the recipient operation as well. The laparoscopic procedure was described in detail to the recipients and they gave their written consent. Patient demographics are provided in the Table. This combined laparoscopic and upper midline laparotomy procedure was indicated only for elective LDLT without a previous history of upper abdominal surgery. Neither ascites nor the degree of portal hypertension was considered as an exclusion criterion. Splenectomy was performed for preemptive interferon therapy after the liver transplantation.

Operative technique. Patients were placed supine with arms adducted and a urinary catheter, and arterial and central venous lines were inserted. An 8-cm upper midline laparotomy was made followed by a 12-mm infra umbilical incision for the laparoscope. A Gelport (Applied Medical, Rancho Santa Margarita, CA) was used in at the 8-cm incision, and a 5-mm port was placed in the right and left lateral upper abdomen under pneumoperitoneum (CO_2 at 8 mmHg) (Fig, *A*). This configuration enabled the first assistant surgeon, who stood on the left side of the patient, to use the hand port for liver manipulation. The primary operator stood on the right side and used the right lateral 5-mm port for dissection. Using a laparoscopic sealing device (Enseal; Ethicon Endo-Surgery, Cincinnati, OH) and hand assist, the right lobe of the liver was mobilized until the inferior vena cava was exposed (Fig, *B*). For patients who needed splenectomy, the primary operator moved to the left side and used the left lateral 5-mm port to mobilize the spleen from the retroperitoneum, which was handled by the first assistant surgeon through a Gelport from the right side, using a sealing device. After those bilateral mobilizations, the midline incision was extended to 12–15 cm, and a wound protector was applied. The wound was retracted and opened with the Omnitract retractor. Under direct view, the short hepatic veins were divided and the right hepatic vein was encircled through a midline incision as well as by transection of the splenic hilum with an endovascular stapler. After hepatic hilum dissection, explantation of the liver was performed in our regular manner without veno-veno bypass (Fig, *C*).

Implantation of the left hepatic lobe with the middle hepatic vein was performed through the midline under cross-clamping on inferior vena cava using the standard procedure, followed by arterial and biliary reconstruction. Implantation of the right hepatic lobe was performed under partial clamping on inferior vena cava. After the procedure (Fig, *D*), 2 drains were placed through the 5-mm trochers, and the midline wound was closed.

In order to clarify the effect of our HALS hybrid procedure, data from 13 recent cases of the LDLT procedure involving a Mercedes-Benz-type incision after January 2010 were analyzed and compared (Table).

Statistical analysis. Univariate analysis was performed using the chi-square test for categorical factors and the Mann-Whitney test for numerical values. *P* values of less than .05 were considered to be statistically significant.

RESULTS

The Table shows the patient demographics and operation results for our hybrid procedure of LDLT in comparison with LDLT under regular Mercedes-Benz-type incision. Case 2 had massive

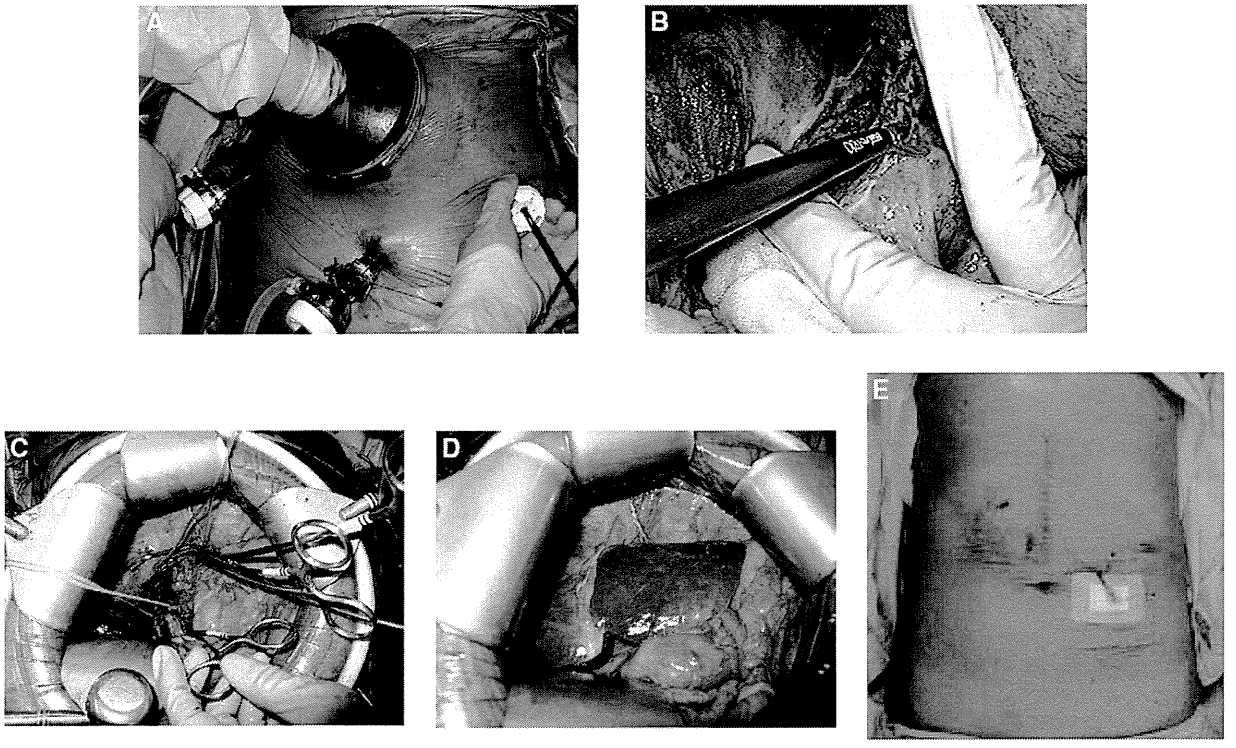

Fig. Case 2, 68 years old, female. (*A*) Hand-assisted port was applied for pneumoperitoneum. (*B*) Laparoscopic mobilization of the diseased liver. (*C*) Anhepatic phase though midline incision. (*D*) Implanted extended left liver lobe graft. (*E*) The abdominal wound 2 months after the operation. A biliary splint and tube jejunostomy was still placed and covered with white gauze.

3.5-L ascites that was evacuated through the laparotomy. A left lobe graft with the middle hepatic vein was implanted through the upper midline incision in 8 patients. The median duration of the operation was 741 minutes (range, 599–839) with a median blood loss of 3,940 ml (range, 1,300–18,400). The hepatic venous and portal venous reconstruction lasted a median of 48 minutes (range, 35–55). In case 2, the caudate lobe vein was also reconstructed. One case (Case 8) required an additional right transverse incision as it involved a difficult implantation. Eight recipients are alive and have excellent graft function. One death (Case 8) occurred due to thrombolytic microangiopathy on day 68. The wound in Case 2 was shown at 2 months after the LDLT (Fig, *E*).

When the results of the HALS hybrid procedure were compared with those of 13 recent LDLT recipients performed using a regular Mercedes-Benz-type incision, no clinically important limitations were observed with the HALS hybrid procedure (Table). In fact, the operative time was less in HALS hybrid cases (HALS: median 741 vs Mercedes-Benz: 812 minutes). Otherwise, there were no important differences between HALS hybrid cases and regular incision cases.

DISCUSSION

We showed the feasibility of LDLT through a midline incision without abdominal muscle disruption as occurs with the usual transverse incision combined with HALS. Because LDLT is performed usually in an elective manner, this procedure could be planned and prepared for.

Before this study, we had performed 130 LDLTs through the usual transverse Mercedes-Benz-type incisions.[8] Based on that experience, we presumed that it would be possible to perform explantation of the liver and spleen followed by implantation of the partial graft liver through a midline incision, because the liver hilum and inferior vena cava are usually located in the center of the upper abdomen. Also, because HALS has been used in the hepatectomy from the living donors, hepatic malignancy, and splenectomy, its use in the recipients seemed logical, because the magnified view under laparoscopy would allow us to obtain hemostasis using sealing devices.[9,10] Because the transverse incision is usually needed only for mobilization of the right liver lobe and spleen, the laparoscopic procedure would allow this mobilization, especially in patients with an increased body mass index.[11,12]

During liver transplantation for patients with hepatitis C, we perform splenectomy for postoperative interferon treatment with ribavirin, which is sometimes complicated by thrombocytepenia.[13] For this combined procedure with mobilization of the liver and spleen, as presented in 7 cases, the HALS procedure showed a marked benefit of visualization not possible with the usual open laparotomy. It made sense for us to perform the mobilization of the liver and spleen using HALS under the laparoscope, because after these procedures the liver transplantation could be performed through the short upper midline incision. Quick celiotomy and closure of the abdomen were also benefits of the upper midline incision.[14] Because no muscle disruption occurred, we believe that postoperative rehabilitation was facilitated. The additional duration of the laparoscopic procedure was offset by the rapid opening and closing of the abdominal incision.

In our series, for the hybrid procedure of HALS and a short midline laparotomy, we selected patients without a history of previous upper abdominal surgery. Although there was still a risk of massive bleeding from collateral vessels, the use of a sealing device with a magnified view allowed us to perform the laparoscopic mobilization. The median blood loss during LDLT was similar to what is reported in large LDLT series.[15] Although we have not had serious complications during the procedure, we would not hesitate to add a wide transverse incision if any difficulty occurred during the procedure, as occurred in our case 8.

REFERENCES

1. Cherqui D, Soubrane O, Husson E, Barshasz E, Vignaux O, Ghimouz M, et al. Laparoscopic living donor hepatectomy for liver transplantation in children. Lancet 2002;359:392-6.
2. Koffron AJ, Kung R, Baker T, Fryer J, Clark L, Abecassis M. Laparoscopic-assisted right lobe donor hepatectomy. Am J Transplant 2006;6:2522-5.
3. Kim SH, Cho SY, Lee KW, Park SJ, Han SS. Upper midline incision for living donor right hepatectomy. Liver Transpl 2009;15:193-8.
4. Nitta H, Sasaki A, Fujita T, Itabashi H, Hoshikawa K, Takahara T, et al. Laparoscopy-assisted major liver resections employing a hanging technique: the original procedure. Ann Surg 2010;251:450-3.
5. Nguyen KT, Gamblin TC, Geller DA. World review of laparoscopic liver resection-2,804 patients. Ann Surg 2009;250: 831-41.
6. Tomikawa M, Akahoshi T, Sugimachi K, Ikeda Y, Yoshida K, Tanabe Y, et al. Laparoscopic splenectomy may be a superior supportive intervention for cirrhotic patients with hypersplenism. J Gastroenterol Hepatol 2010;25:397-402.
7. Jain A, Nemitz P, Sharma R, et al. Incidence of abdominal wall numbness post-liver transplantation and its complications. Liver Transpl 2009;15:1488-92.
8. Eguchi S, Takatsuki M, Hidaka M, Tajima Y, Kanematsu T. Evolution and changes in living donor liver transplantation. A single center experience over 10 years. Surg Today 2008; 38:785-800.
9. Soubrane O, Cherqui D, Scatton O, Stenard F, Bernard D, Branchereau S, et al. Laparoscopic left lateral sectionectomy in living donors: safety and reproducibility of the technique in a single center. Ann Surg 2006;244:815-20.
10. Kurosaki I, Yamamoto S, Kitami C, Yokoyama N, Nakatsuka H, Kobayashi T, et al. Video-assisted living donor hemihepatectomy through a 12-cm incision for adult-to-adult liver transplantation. Surgery 2006;139:695-703.
11. Koffron AJ, Kung RD, Auffenberg GB, Abecassis MM. Laparoscopic liver surgery for everyone: the hybrid method. Surgery 2007;142:463-8.
12. Wakabayashi G, Nitta H, Takahara T, Shimazu M, Kitajima M, Sasaki A. Standardization of basic skills for laparoscopic liver surgery towards laparoscopic donor hepatectomy. J Hepatobiliary Pancreat Surg 2009;16:439-44.
13. Eguchi S, Takatsuki M, Soyama A, Hidaka M, Tokai H, Hamasaki K, et al. Intentional conversion from tacrolimus to cyclosporine for HCV-positive patients on preemptive interferon therapy after living donor liver transplantation. Ann Transplant 2007;12:11-5.
14. Nguyen KT, Marsh JW, Tsung A, Steel JL, Gamblin TC, Geller DA. Comparative benefits of laparoscopic versus open hepatic resection: a critical appraisal. Arch Surg 2011;146: 348-56.
15. Morioka D, Egawa H, Kasahara M, Ito T, Haga H, Takada Y, et al. Outcomes of adult-to-adult living donor liver transplantation: a single institution's experience with 335 consecutive cases. Ann Surg 2007;245:315-25.

原　著

マイアミ大学でのHIV陽性患者に対する肝移植

西田　聖剛[1]，江口　晋[2]，曽山　明彦[2,3]，日高　匡章[2]，高槻　光寿[2]，
高橋　正浩[1]，Andreas G. Tzakis[1]，兼松　隆之[2]
[1] マイアミ大学移植外科，[2] 長崎大学大学院移植・消化器外科，[3] エイズ予防財団

目的：肝移植先進国でのHIV陽性患者に対する肝移植成績を明らかにする。
患者と方法：1999年より2010年1月までに米国マイアミ大学で26人に対して29回の肝移植を施行した。HIV感染経路は，血液製剤2例，輸血1例，静注薬使用7例，同性間性感染の男性13例，異性間性感染3例であった。移植時年齢は以下中央値（範囲）45歳（36～62），男性23例，女性3例，2002年以降24例のMELD（model for end-stage liver disease）スコア22（1～43），HIV以外にHBV感染10例，HCV感染12例，HBV/HCV共感染2例であり，肝細胞癌合併5例，CD4陽性T細胞実数は155/μL（23～1,045）であった。
結果：脳死ドナー年齢46歳（18～65），移植手術は冷阻血時間436分（256～1,946），温阻血時間33分（25～57）で，輸血量は12U（0～45），FFP 17U（0～97），PC18U（0～98）であった（米国1Uは日本2Uに相当）。移植後入院期間は12日（1～107）で，overallの患者生存は3年69.1%，5年61.4%，死亡例12例の死因は敗血症4，HCV再燃3，再発肝細胞癌1，移植後リンパ増殖性疾患1，進行性多巣性白質脳症1，不明2であった。全症例タクロリムスを使用した免疫抑制で，前半は過剰投与によるトラフ値のovershoot傾向がみられたが，後期では調節良好であった。
結論：今回の共同研究結果を参考に，本邦でのHIV陽性患者に対する肝移植も進めることができると考えられた。

キーワード：HIV，HCV，肝移植，血友病，マイアミ

日本エイズ学会誌 13：137-144，2011

1. はじめに

1995年以降，HIV陽性患者の死亡数はHighly Active Anti-Retroviral Therapy（HAART）によるHIVのコントロールの改善により減少するとともに，死因に大きな変化が見られた。米国では1997～2000年に死亡した135人のHIV陽性患者のうち，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[1]。その他の諸国でも同様な問題が指摘されてきている[2~4]。

本邦では，特に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感染者は90%以上がHCVにも重複感染しており，今後，肝移植を念頭においたフォローが必要となってくる[5]。しかし，本邦でも肝移植の報告は約10例程度であり，本邦での患者救済への情報が欠乏している[6]。そこで，2009年に「血液製剤によるHIV/HCV重複感染者に対する肝移植のための組織構築」研究班（兼松班）が立ち上がり，本邦における当該患者に対する肝移植のための情報収集を開始した。研究班の事業の一環として，HIV陽性患者に対する肝移植を積極的に施行しているマイアミ大学へ海外委託事業として共同研究を開始した。その結果を今回マイアミ大学[7]での最新の肝移植成績を解析，公表し，本邦での当該患者に対する肝移植の一般化に向けての考察を行うこととした。

著者連絡先：江口　晋（〒852-8501　長崎市坂本1-7-1　長崎大学大学院移植・消化器外科）

2011年1月5日受付；2011年6月16日受理

2. 患者と方法

マイアミ大学およびその関連施設では1999年より2010年1月までに26人に対して29回の肝移植が施行された。その詳細を表1に示す。HIV感染症の原因は，血友病に対する血液製剤によるものが2例，輸血によるもの1例，iv drug濫用7例，MSM（man who have sex with men）13例，同性間性感染の男性3例であった。患者の移植時の年齢は中央値45歳（36～62歳），男性23例，女性3例，血液型はA型12例，B型2例，O型11例，AB型1例，人種は白人23例（ヒスパニック2例），アフリカンアメリカン3例であった。レシピエントのBMI中央値は24（16～32），ICU管理中2例，入院中8例，自宅待機17例であった。

マイアミ大学でのHIV陽性患者における肝移植適応は，通常の肝移植患者と同様にMELD（model for end-stage liver disease）により決定されていた。加えてHIV感染患者ではHIV検出感度以下で，活動性感染症がないことが適応

表 1　マイアミ大学での HIV 陽性肝移植患者

初回移植/再移植	26/3 計 29 回
移植時年齢	中央値　45 歳（36～62）
性別（男性/女性）	23/3
HIV 感染症の原因 （MSM/iv drug 濫用/性交感染/血友病に対する血液製剤/輸血）	13/7/3/2/1
血液型（A/B/O/AB）	12/2/11/1
人種（白人/アフリカンアメリカン）	23（ヒスパニック 2)/3
BMI	中央値　24（16～32）
レシピエント状態 （ICU 管理中/入院中/自宅待機）	2/8/17
移植時重症度	
2002 年までの 5 例（Status 1/2a/2b）	1/1/2
2002 年以降 24 例	MELD スコア中央値　22（1～43）
ウイルスマーカー （HBV 単独感染/HCV 単独感染/HBV/HCV 共感染，HIV のみ）	10/12/2/5
HCC 合併	5（19.2%）
劇症肝炎	4（3 例は HBV，残りの 1 例は薬剤性）
CD4 実数	中央値　205（23～1,780）
CD4%	中央値　29%（8～56%）
門脈血栓（あり/なし）	6/23

条件となっていた。一方，CD4 の実数は移植適応には加味されていなかった。

移植時の重症度は 2002 年までの 5 症例では医学的緊急度 Status 1（劇症肝炎，移植肝不全など）が 1 例，2a（ICU 待機）が 1 例，2b（在院 ICU 外待機）が 2 例であった。2002 年以降は MELD（model for end-stage liver disease）スコアが計算されており，24 例の MELD スコア中央値 22（1～43）であった。ウイルスマーカー別では HBV 単独感染が 10 例，HCV 単独感染が 12 例，HBV/HCV 共感染が 2 例であり，HCC の合併は 5 例に認めていた。劇症肝炎は 4 例でうち 3 例は HBV によるもので，残りの 1 例は薬剤性であった。CD4 陽性 T 細胞の実数は中央値 155（23～1,045）で，CD4 陽性 T 細胞の％は 26%（8～50%）であった。また，4 例（13.8%）に門脈血栓症を認めていた。

3.　肝移植成績

表 2 に肝移植脳死ドナー，手術概要を示す。手術患者に移植された脳死ドナーは年齢の中央値 46 歳（18～65 歳）で，男性 15 例，女性 14 例であった。

移植手術は conventional 法は 2 例のみで，他は piggy back 法で施行され，バイパスは 8 例で使用されていた。胆道再建法としては胆管空腸吻合が 22 例，胆管胆管吻合は 7 例であった。冷阻血時間中央値 436 分（256～1,946 分），温阻血時間中央値 33 分（25～57 分）で，輸血量は 12U（0～45），FFP 17U（0～97），PC18U（0～98）であった（米国の 1U は日本の 2U に相当する）。

移植後入院期間の中央値は 12 日（1～107 日）で，移植成績としては，2010 年 1 月までで 17 例生存，12 例死亡で，3 例に再移植が施行されていた。再移植 3 例中 2 例は死亡していた。患者生存中央値は 112 日（1～1,928）であった。Overall の患者生存は 3 年 69.1%，5 年 61.4%であった（図 1）。また門脈血栓の有無でも肝移植成績に有意差を認めなかった（図 1）。CD4 陽性 T 細胞の実数別で患者生存を分類してみても，肝移植成績に有意差を認めなかった（図 2）。

死亡例 12 例の死因は敗血症 4 例，HCV 再燃 3 例（1 例は慢性拒絶合併），再発 HCC1 例，移植後リンパ増殖性疾患 1 例，進行性多巣性白質脳症 1 例，不明 2 例であった。

免疫抑制剤はすべての症例でタクロリムスを使用した免疫抑制を行った。各症例でトラフ値は様々であったが，前半はリトナビルと FK の相互作用による FK トラフ値の overshoot 傾向がみられた（図 3（1），(2)。後半は 1 週間に 1 回投与などの工夫により通常の免疫抑制レベルでコントロール良好な症例が多かった（図 3（3））。

表 2 マイアミ大学での HIV 陽性患者に対する肝移植手術（1999～2010. 1）

脳死ドナー年齢	46 歳（18～65）
冷阻血時間	436 分（256～1,946）
温阻血時間	33 分（25～57）
輸血量（日本の 2U が米国 1U）	12U（0～45），FFP 17U（0～97），PC18U（0～98）
胆道再建	胆管空腸吻合 22，胆管胆管吻合 7
免疫抑制剤開始	中央値 1 日（0～20）
HAART 再開	中央値 1 日（0～109）
インターフェロン開始日	中央値 44 日（2～220）
移植後入院期間	12 日（1～107）
	17 例生存，12 例死亡
死因	
敗血症	4
HCV 再燃	4（1 例は慢性拒絶合併）
再発 HCC	1
PTLD	1
進行性多発性白質脳症	1
不明	2

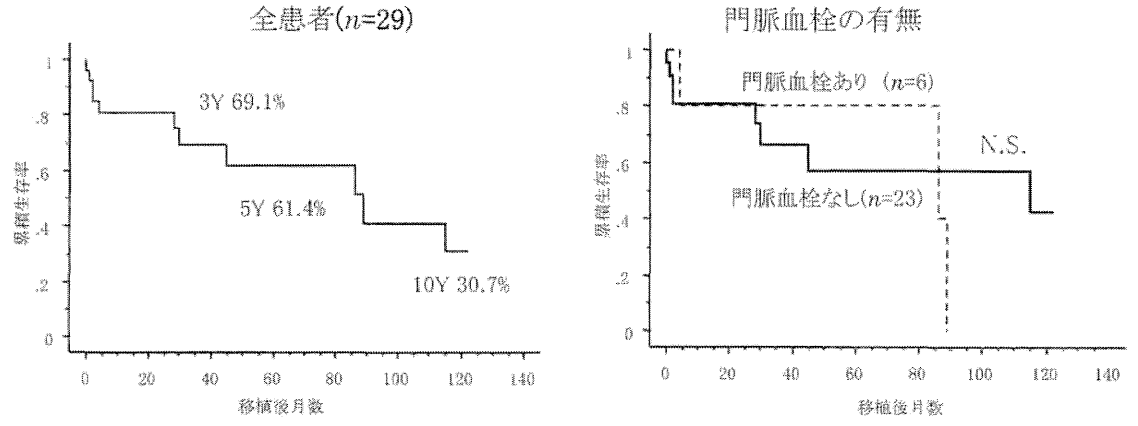

図 1 肝移植後患者生存率―マイアミ大学（1999～2010. 1）

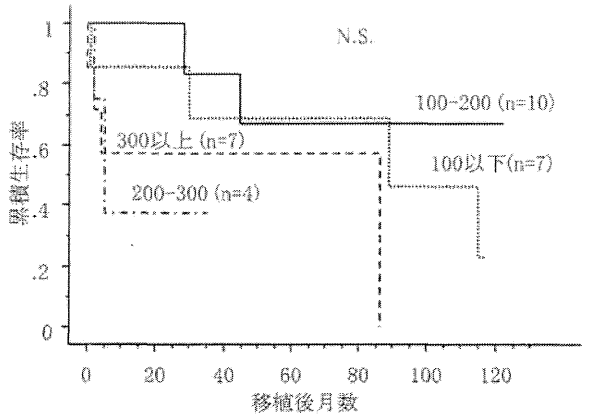

図 2 CD4 実数別 HIV 陽性患者に対する肝移植後患者生存率

4. 考　　察

移植適応に関しては，基本的には非 HIV 陽性患者と同様に肝不全（特に C 型肝硬変）の状態となり，長期予後が望めない患者が適応となる。また，肝不全には至っていないが，HAART による（C 型慢性肝炎をベースとした）肝障害が高度で，HAART の中断・中止が必要な場合も適応とされる[8]。HAART 施行中の患者では肝予備能，HIV 感染症の状況の双方からの適応検討が必要である。また経過中に肝細胞癌を発症した場合も適応となることがある[9]。マイアミ大学での HIV 陽性患者における肝移植適応は，米国での通常の肝移植患者と同様に MELD（model for end-stage liver disease）により決定されていた。加えて HIV 感