an indicator of presensitization and as a factor when determining whether or not a liver transplantation should proceed remains a matter of debate.

Allograft rejection is classically thought to be mediated by allospecific T cells that recognize allogeneic epitopes on major histocompatibility antigens. Immunosuppressive therapy strategies, therefore, have focused on the suppression of the T-cell function; and agents, such as cyclosporine and tacrolimus, have enabled organ transplantation to become an established therapy. The role of HLA compatibility in cadaver donor liver transplantation is controversial and has not yet been clearly defined. Nevertheless, it is not practical to select a suitable donor recipient combination according to the results of HLA matching in cadaver donor liver transplantation because of to time constraints. On the other hand, in living donor liver transplantation there is enough time to check for HLA compatibility and to select a donor recipient combination if a good HLA compatibility confers some benefits. In this study, we retrospectively investigated the influence of HLA compatibility on the results of living-related liver transplantation. Doyle et al. (5) reported similar graft survivals in 130 patients with positive cross-matching and 1390 patients with negative T-cell cross-matching. In this study, the early survival rates tended to be lower in the positive cross-matching group. After the 2-year mark, however, these differences became negligible. In contrast to these results, Bathgate et al. (6) showed a positive T-lymphocytotoxic cross-matching to be associated with a decreased 1-year graft survival and an enhanced incidence of steroid-resistant episodes in a small cohort of patients.

In this report, we retrospectively analyzed the impact of a positive T-lymphocytotoxic cross-matching on graft survival, acute and chronic rejection episodes after living donor liver transplantation.

Patients and methods

Between May 1997 and July 2003, 104 adults (42 males and 62 females) who underwent a living donor adult liver transplantation (LDALT) were selected. The main indications for LDALT were fulminant hepatic failure ($n = 26$), cholestatic diseases ($n = 15$), liver cirrhosis ($n = 19$), hepatocellular carcinoma ($n = 37$), and others ($n = 7$). Seventy-six patients received ABO identical grafts and 28 patients received ABO compatible grafts. There were no ABO-incompatible transplants in our series.

Donors were selected from among relatives or spouses who volunteered to be liver donors (7). A preoperative evaluation for potential living-related liver donors included a complete history and physical examination, an abdominal computed tomography scan, and angiogram. The donors consisted of six parents, 62 children, 15 siblings, and 19 spouses.

The recipient operation was performed using a technique described elsewhere (7, 8). The grafts were left lobe plus caudate lobe in 94 cases and right lobe in 10 cases.

Coagulation was intensively controlled for the first week. Therefore, low-dose heparin and fresh-frozen plasma were administered and the prothrombin time and activated clotting time were closely monitored. Fresh-frozen plasma was given during and after LDLT in patients with a prolonged prothrombin time of 20 s or more. Duplex Color Doppler ultrasonography was performed every day postoperatively in all recipients to confirm the patency of blood viscosity.

The initial immunosuppressive regimen consisted of tacrolimus and steroids. Tacrolimus was started from 1 day before transplantation at a dose of 4 mg/day divided into two doses, except for cases with hepatic encephalopathy. The target for the posttransplantation whole-blood trough level of tacrolimus was 10–15 ng/ml during the first 2 weeks and around 10 ng/ml thereafter. Steroids were started at graft reperfusion at a dose of 10 mg/kg, and thereafter were tapered off from 2 to 0.3 mg/kg/day until the end of the first month.

Clinical acute rejection was diagnosed based on an increased AST and/or ALT according to histological evidence. A liver biopsy was carried out if acute rejection was suspected. A histological diagnosis and grading of acute rejection were performed according to the criteria proposed by Demetris et al. Briefly, three specific features in a liver biopsy specimen, portal inflammation, bile duct inflammation/damage, and vascular inflammation were evaluated and semiquantitatively scored on a 0 to 3 (mild, moderate, and severe) scale. We generally do not perform posttransplantation protocol biopsies, and such graft biopsies were only carried out when the need was indicated by liver function tests. In one case tacrolimus was switched to cyclosporine because of a neurological disorder. Additional immunosuppressants for steroid-resistant rejection, e.g., OKT3 were used in two cases.

HLA-A and -B typing of all donor and recipient pairs was performed by a standard complement-dependent microcytotoxicity assay (9). For cytotoxic cross-matching, recipient sera were obtained immediately before transplantation. Cross-

matching between the donor's isolated B and T lymphocytes and the recipient's sera was performed by a standard lymphocytotoxicity test at 4 °C, 22 °C, and 37 °C. In the case of a positive cross-matching, the sera were treated with dithiothreitol to inactivate IgM antibodies and were repeated subsequently. The reaction was defined as positive when more than 20% cell death above background was observed. The results of cross-matching in liver transplant recipients were not known at the time of liver transplantation to the clinical team responsible for the immunosuppressive-induction protocol. The data were expressed as means ± standard deviations. The student *t*-test with continuous variables and the χ^2 test of independence with categorical variables were used to compare the two groups. The survival probability of recipients was determined by the Kaplan–Meier methods. A *P*-value of <0.05 was considered significant.

Results

The relationship between HLA compatibility and post-LDALT complications are summarized in Table 1. The number of patients with zero, one, two and three mismatches were 19, 17, 37, and 31, respectively. No differences were seen in the recipient factors or the incidence of postoperative complications among them except for the mixed lymphocyte culture (MLC) findings. The MLC findings of the patients with three HLA mismatches were significantly higher than the patients with zero HLA mismatches. The incidence of acute cellular rejection (ACR) was higher in the patients with three mismatches than in the other patients, and moderate rejection only occurred in the patients with three mismatches.

Tables 2 and 3 show the relationship between post-LDLT complications and T-cell, B-cell crossmatch positivity. There were eight patients with T-cell crossmatch positive and 22 patients with B-cell crossmatch positive. There was no difference between positive and negative crossmatch group in terms of background factors and complications. However, in T-cell crossmatch-positive patients, two of three rejection patients exhibited steroid-resistant severe rejection. We needed OKT three treatment for these two patients.

In addition, Table 4 shows the relationship between post-LDLT complications and MLC. There was no difference in the incidence of complications between the groups except for the MLC levels in ACR. Sixteen of 31 patients (52%) with MLC levels over 20 demonstrated ACR, otherwise only 19 of 73 patients (26%) with MLC levels lower than 20 showed ACR, and the difference between them was statistically significant ($P<0.05$).

Overall, the 1-, 3- and 5-year graft survival rates were 79.2%, 73.5% and 73.5%, respectively (Fig. 1). Figure 2 demonstrates the Kaplan–Meier graft survival curves of 31 patients with LDALT according to HLA mismatching. The 5-year graft survival rates in each group were 73.7, 85.2, 63.3 and 79.9%, respectively. There were no statistically significant differences among them. Figure 3 shows Kaplan–Meier graft survival curves of 104 patients with LDALT according to T-cell crossmatch positivity. The 5-year graft survival rate in the patients who demonstrated positive T-cell cross-matching was significantly lower than in the patients who were negative for T-cell cross-matching (43.8% vs. 75.9%, $P<0.05$). Figures 4 and 5 show the Kaplan–Meier graft survival curves of 35 patients with LDALT according to B-cell crossmatch positivity and the MLC findings, respectively. No difference was observed between the B-cell cross-matching-positive groups and the MLC findings.

Discussion

We herein investigated the role of HLA mismatching, T-cell crossmatch positivity, B-cell cross-

Table 1. Relationship between HLA compatibility and post-LDALT complications

Complications	*n* (*n* = 104)	0 (*n* = 19)	1 (*n* = 17)	2 (*n* = 37)	3 (*n* = 31)
ACR	35 (34%)	5 (26%)	4 (24%)	13 (35%)	13 (42%)
Vascular	7 (7%)	0 (0%)	1 (6%)	3 (8%)	3 (10%)
Biliary	24 (23%)	3 (16%)	4 (24%)	8 (22%)	9 (29%)
Infections	60 (58%)	8 (42%)	8 (47%)	22 (59%)	22 (71%)
Graft failure	23 (22%)	4 (21%)	2 (12%)	11 (30%)	6 (19%)
MLC	17.4 ± 8.7	3.5 ± 2.8*	4.8 ± 3.7	25.2 ± 12.8	24.6 ± 8.2*
Age	46.0 ± 11.3	45.2 ± 12.8	47.1 ± 10.6	46.2 ± 11.4	45.7 ± 11.2
Sex	42/62	7/12	5/12	17/20	13/18
LL/RL	94/10	17/2	15/2	34/3	28/3
GV/SLV	38.4 ± 7.8	38.1 ± 8.6	37.9 ± 7.5	36.9 ± 8.0	40.6 ± 7.1
GRWR	0.77 ± 0.16	0.76 ± 0.17	0.76 ± 0.15	0.74 ± 0.16	0.81 ± 0.14

*$P<0.05$. HLA, human leukocyte antigen; LDALT, living donor adult liver transplantation; ACR, acute cellular rejection; MLC, mixed lymphocyte culture; LL, left lobe; RL, right lobe; GV, graft volume; SLV, standard liver volume; GRWR, graft recipient weight ratio.

Table 2. Relationship between T-cell crossmatch positivity and post-LDALT complications

Complications	T-cell crossmatch positive ($n = 8$)	T-cell crossmatch negative ($n = 96$)	*P*-value
ACR	3 (38%)	32 (33%)	0.99
Vascular	1 (13%)	6 (6%)	0.99
Biliary	2 (25%)	22 (23%)	0.99
Infections	2 (67%)	18 (56%)	0.99
Graft failure	4 (50%)	19 (20%)	0.12
MLC	29.6 ± 20.3	15.5 ± 9.6	0.25
Age	44.0 ± 10.9	46.2 ± 11.4	0.60
Sex	2/6	40/56	0.58
LL/RL	6/2	88/8	0.36
GV/SLV	39.8 ± 7.9	38.3 ± 7.8	0.61
GRWR	0.80 ± 0.16	0.77 ± 0.15	0.60

LDALT, living donor adult liver transplantation; ACR, acute cellular rejection; MLC, mixed lymphocyte culture; LL, left lobe; RL, right lobe; GV, graft volume; SLV, standard liver volume; GRWR, graft recipient weight ratio.

Table 3. Relationship between B-cell crossmatch positivity and post-LDALT complications

Complications	B-cell crossmatch positive ($n = 22$)	B-cell crossmatch negative ($n = 82$)	*P*-value
ACR	8 (36%)	27 (33%)	0.96
Vascular	2 (9%)	5 (6%)	0.99
Biliary	5 (23%)	19 (23%)	0.99
Infections	13 (59%)	47 (57%)	0.99
Graft failure	4 (18%)	19 (23%)	0.83
MLC	33.9 ± 20.1	12.4 ± 13.6	0.17
Age	44.5 ± 11.8	46.4 ± 11.3	0.48
Sex	8/14	34/48	0.85
LL/RL	6/2	88/8	0.36
GV/SLV	36.3 ± 7.7	39.0 ± 7.8	0.15
GRWR	0.73 ± 0.15	0.78 ± 0.15	0.16

LDALT, living donor adult liver transplantation; ACR, acute cellular rejection; MLC, mixed lymphocyte culture; LL, left lobe; RL, right lobe; GV, graft volume; SLV, standard liver volume; GRWR, graft recipient weight ratio.

Table 4. Relationship between MLC and post-LDALT complications

Complications	MLC > 20 ($n = 31$)	MLC < 20 ($n = 73$)	*P*-value
ACR	16 (52%)	19 (26%)	0.03
Vascular	4 (13%)	3 (4%)	0.23
Biliary	6 (19%)	18 (25%)	0.73
Infections	2 (67%)	18 (56%)	0.79
Graft failure	19 (61%)	41 (56%)	0.85
Age	45.6 ± 11.2	46.2 ± 11.4	0.84
Sex	13/18	29/44	0.99
LL/RL	28/3	66/7	0.99
GV/SLV	46.2 ± 11.5	45.4 ± 11.2	0.07
GRWR	0.75 ± 0.16	0.81 ± 0.14	0.06

MLC, mixed lymphocyte culture; LDALT, living donor adult liver transplantation; ACR, acute cellular rejection; LL, left lobe; RL, right lobe; GV, graft volume; SLV, standard liver volume; GRWR, graft recipient weight ratio.

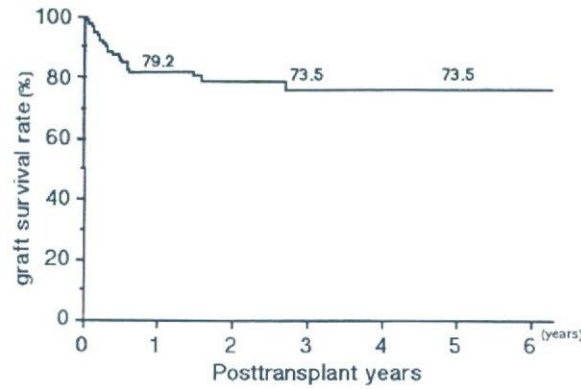

Fig. 1. Kaplan–Meier graft survival curves of 104 patients with LDALT. Overall, the 1-, 3- and 5-year graft survival rates were 79.2%, 73.5% and 73.5%, respectively.

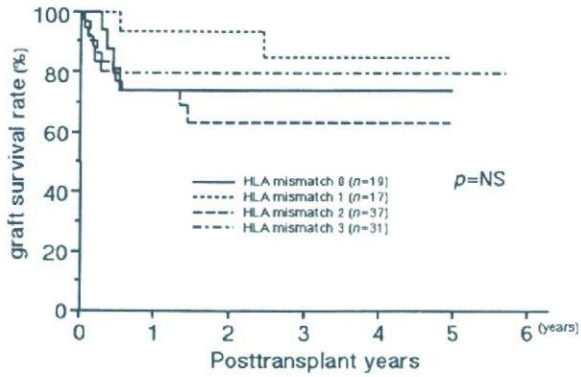

Fig. 2. Kaplan–Meier graft survival curves of 104 patients with LDALT according to the HLA mismatch findings. The 5-year graft survival rates in each group were 73.7%, 85.2%, 63.3% and 79.9%, respectively.

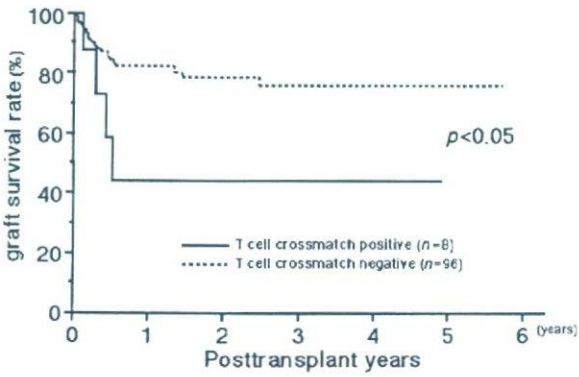

Fig. 3. Kaplan–Meier graft survival curves of 104 patients with LDALT according to T-cell crossmatch positivity. The 5-year graft survival rate in the patients who demonstrated positive T-cell cross-matching was significantly lower than in the patients who were negative for T-cell cross-matching (43.8% vs. 75.9%, $P < 0.05$).

match positivity, and MLC levels on the outcome of living donor adult liver transplantation. Our findings showed a high incidence of moderately ACR in the patients with three mismatches, however, HLA mismatches did not influence graft survival. On the other hand, although, there was no difference in the incidence of complications between T-cell cross-matching positive and negative, individuals, the T-cell cross-matching-positive

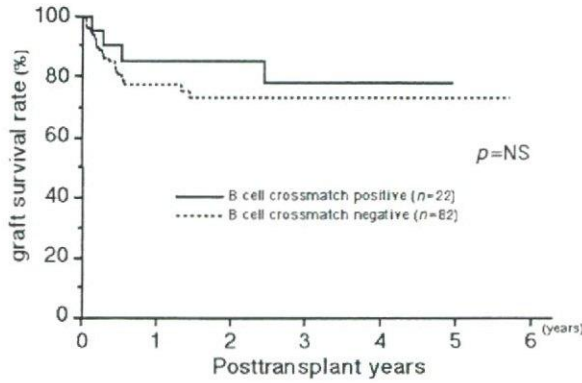

Fig. 4. Kaplan–Meier graft survival curves of 104 patients with LDALT according to B-cell crossmatch positivity. No difference was observed between the groups regarding B-cell crossmatching positivity.

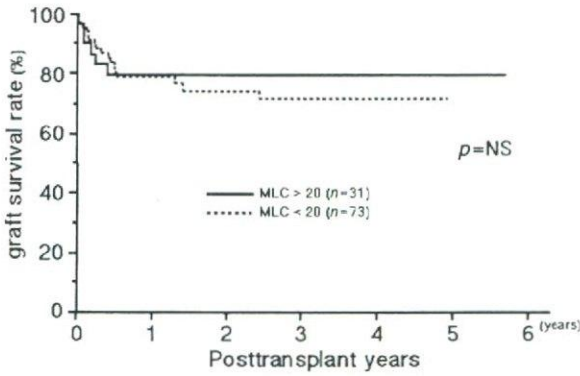

Fig. 5. Kaplan–Meier graft survival curves of 104 patients with LDALT according to mixed lymphocyte culture (MLC) findings. No difference was observed between the groups regarding the MLC findings.

patients showed a significantly lower graft survival rate than those who were negative.

In 1996, the largest clinical series of liver graft recipients with positive cross-matching (130 patients) was published by Doyle et al. (5) Although the graft failure rate was high in the early posttransplant period (until POD 28), when grafting in the presence of a positive T-lymphocytotoxic cross-matching, the difference disappeared in the second year in this study. Positive cross-matching grafts were more likely (without statistical significance) to fail because of rejection or sepsis in the early period after OLT. The investigators concluded that cross-matching should therefore not be a consideration for transplantation but should instead be used to identify a high-risk group of patients who require special attention and probably a more aggressive immunosuppressive regimen than is normally administered (10, 11). These data conflict with other recent reports on small cohorts, which reported an improved graft survival in transplants with negative cytotoxic T-cell cross-matching in patients after OLT with CsA-based triple immunosuppression.

We studied the effect of positive cross-matching on the outcome after liver transplantation in our own patient population. The graft survival and frequency of rejection were similar in grafts with positive cross-matching and those with negative cytotoxic cross-matching (12–14). However, in contrast to Doyle et al. (5), our study showed similar graft and patient survival figures in the early and late period after OLT in transplants with positive cross-matching. A possible explanation for these differences is that in our study positive cross-matching was defined as 20% cell death vs. 50% in the Doyle study in addition to the exclusion of retransplants in our study population. This may result in a later conversion to a negative cross-matching test in these patients and may also increase the risk for developing acute and chronic rejection. Francavilla et al. (15) reported no overall influence of HLA mismatching on graft and patient survival rates after liver transplantation in pediatric patients. Doyle et al. (5) studied T-cell crossmatch positivity in 1520 liver transplant patients and found no difference in the overall graft survival. However, they also found early survival to be lower in the positive cross-matching group than in the negative cross-matching group, and these differences became negligible by the 2-year mark. We could not find any relationship between T-cell crossmatch positivity and other immunogenic and perioperative factors, and this study showed that positive lymphocytotoxic cross-matching was associated with a higher incidence of acute, corticoresistant and chronic rejection. The graft survival rate was lower for patients with positive cross-matching. In this group, we did not observe any early graft loss in the first few postoperative days, thus suggesting hyperacute rejection which is usually observed after the transplantation of other organs. Nevertheless, all graft losses in patients with positive cross-matching were observed within the first year after liver transplantation. All but one patient (who died because of postoperative complications) lost their graft because of rejection or infectious complications after treatment for severe acute rejection. Lethal infectious complications were probably related to the increased immunosuppression. These results correlate with those of other studies showing a high incidence of graft loss within the first year after liver transplantation because of complications related to severe rejection in cases with positive cross-matching (16). Although there have been many reports on the influence of HLA matching in cadaver donor liver transplantation, the results

have varied and the role of HLA matching has not yet been fully clarified. One of the reasons for these diverse results may be that factors other than HLA compatibility, such as donor organ quality, surgical techniques, and pre and postoperative management, may have an important influence on the mortality and morbidity of the recipients. The survival rate of our patients was 91.7%. This good survival rate may indicate the influence of HLA compatibility in contrast to previous reports (11, 17).

Living donor liver transplantation is performed using properly HLA-matched donor recipient combinations. It is of interest that, even in living-related liver transplantation, HLA class 1 matching has been shown to have a significant influence on the incidence of acute rejection (18–20).

In an *in vitro* study, lymphocytes isolated from human hepatic allografts have been reported to show alloreactivity against donor HLA antigen. Nikaein et al. (3) found a significant impact on patient survival, when comparing zero to two vs. six HLA-A, -B, -DR mismatches among 800 liver transplantation recipients. To draw any definite conclusion on the impact on HLA matching in LRLT, further investigations are needed using a larger sample size. In other posttransplant complications, Takaya et al. (21) reported the incidence of bile duct complications to increase according to crossmatch positivity. However, we did not find any difference between positive and negative cross-matching. Recently, Sugawara et al. (22) reported that patients with HLA DR zero mismatching ($P = 0.02$) or negative T-lymphocytotoxic crossmatch ($P = 0.04$) had a significantly lower chance of rejection within 6 week after LDLT, although the results had no influence on the patient survival. Evrard et al. (23) also found a negative T-cell crossmatch ($P = 0.016$) was independently correlated with better rejection-free graft survival.

It remains controversial as to whether liver transplantation recipients with positive-lymphocyte cross-matching demonstrate a worse patient survival than those with negative-lymphocyte cross-matching. In living donor adult liver transplantation, there are many haplotype-identical cases. The graft failure rates were higher in the positive cross-matching cases and therefore a strong immuosuppressant might be needed for positive cross-matching cases.

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九州大学病院において

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特集　ウイルス肝炎と肝移植　Ⅱ．施設における現状と対策：外科医より

Living-donor liver transplantation for patients with viral hepatitis: a Kyushu University experience

ウイルス肝炎(B型，C型肝炎)は肝移植の適応疾患として最も頻度が高い疾患である．B型肝炎に対する肝移植はHBIGとラミブジンによる再発予防法が確立しているがコストがかかる．今後は高価なHBIGに代わりうるワクチンなどによる予防法の開発が課題である．C型肝炎に対する肝移植の問題点は，その100%に近い再発率と重症化である．肝移植に関する技術的な問題点がほぼ解決されたと考えられる現在，C型肝炎の再発とその重症化の問題は，いまだ解決できていない肝移植の最大の課題であるといえる．本稿では，九州大学におけるウイルス肝炎に対する肝移植の現状と今後の方向性について私見を述べる．

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key word：生体肝移植，B型肝炎，ワクチン，C型肝炎，インターフェロン(IFN)

ウイルス性肝硬変に対する肝移植とは，B型肝炎ウイルス(HBV)およびC型肝炎ウイルス(HCV)による肝硬変のことを指すと考えてよい．

HBV肝硬変に対する肝移植は1990年代初頭まで，高い再発率，予後のわるさより肝移植の適応外とされていたが，抗B型肝炎ウイルス免疫グロブリン(HBIG)の高い再発予防効果が報告され，状況が一変した．さらにラミブジンの登場，HBIGとラミブジンの併用によりほぼ100%近く再発予防が可能となり，現在では肝移植のよい適応疾患となっている．しかし，高額なHBIGによるコストの問題，ラミブジン耐性株(YMDD変異株)の出現などが問題となっている．

一方1990年代に入り，HCV肝硬変は肝移植の最大の適応疾患となり，いまや海外においては全適応疾患の30～50%を占めるようになり，最もポピュラーな適応疾患となった．本邦でも成人間生体肝移植が増加するにつれ，HCV肝硬変の症例数が急速に増加している．

HCV肝硬変に対する肝移植における問題点は，なんといっても移植後の再発である．HCV肝硬変の移植ではほとんど全例で術後早期にHCV-RNAが検出され，ほぼ全例にウイルス学的再発は起こる．また移植後1年以内に約50～60%，長期的には75～100%のレシピエントに組織学的慢性活動性肝炎が再発する．

また，5年以内に約20～30%の患者が肝硬変に進行することが知られている．いったん肝硬変と診断されれば，40%以上が1年以内に非代償性となる．非代償性になれば予後は非常にわるく，1年，3年生存率はそれぞれ40%，10%程度である[1]．

HCV再発後の臨床経過はこれまで，B型肝炎再発にくらべて比較的緩徐であり，移植成績は他の疾患と変わらないとされてきた．しかし，最近HCV肝硬変患者の長期移植成績が，明らかに非HCV肝硬変患者のそれより劣り，しかも以前に比較して有意に悪化していることが報告され大きな話題をよんでいる[2]．

肝移植後のC型肝炎再発治療にはインターフェロン(IFN)とリバビリン(RIB)が一般的に用いられているが，その副作用のため約50%が治

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療を脱落し，しかもウイルス学的著効に至るのは12～30%にすぎない．ほぼ全例に再発することも相まって，再発後の治療成績が非常にわるいことが全世界の移植医を悩ませている所以である．

本稿では，九州大学で行っているHBV肝硬変，HCV肝硬変に対する対応，移植成績を供覧し，今後の展望を述べたい．

B型肝炎への対応

1．HBsAg陽性レシピエント

HBIG登場以前のHBV肝硬変に対する肝移植では，移植後グラフトに高率に再感染がみられ，fibrosing cholestatic hepatitis(FCH)と称される重症型肝炎や慢性肝炎，肝硬変に短期間に進行し，術後3年の死亡率が50%とその予後はきわめて不良であった[3]．したがって，多くの施設でHBVに対する肝移植はウイルス抗原量や抗体の存在による基準で適応が制限されていた．ウイルスの再感染率は移植時のウイルス量に相関すると考えられ，感染対策を行わなかった場合，HBV DNA陽性例では約8割，HBeAg陽性例では約6割の再感染率と考えられている[4]．

移植後再発の予防として1987年にHBIGが用いられ，同抗体を大量，長期に用いることにより再発率およそ33%と満足すべき結果が得られるようになった．98年にはSawyerら[5]が，HBIG単独使用にて1年生存率95%，3年生存率81%と報告している．しかし，移植前ウイルス量が多い症例(HBV DNA陽性例やHBeAg陽性例)では依然として再発率が高率であり，HBIG単独での再発率は，overallでおよそ15～50%と報告されている．またHBIGの別の問題点として，非常に高価であることや副作用もあり，その使用も限られていた．

1995年に逆転写酵素阻害剤であるラミブジンのB型慢性肝炎に対する臨床効果が報告されると同時に，肝移植後のB型肝炎再発に対してラミブジンが用いられるようになった．99年に発表された多施設試験によれば[6]，ラミブジン100 mg/日，52週の投与により60%の症例がHBV DNA陰性となり，HBeAg陽性者の31%が陰性となった．さらに71%の症例でALTの正常化がみられた．しかしながら，薬剤耐性に関係するHBVのYMDD耐性株が27%に出現したと報告している．さらにラミブジン投与終了後のHBV DNAの再増加，ALT再上昇が5～20%にみられることから，その単独使用には限界があるといわざるをえない．

ラミブジンの予防的投与に関しては，Grellierら[7]が移植前4週から移植後6カ月までラミブジンを単独投与し，移植後6カ月の時点で10%という再感染率を達成している．現時点での最も有効なB型肝炎再発の予防法はHBIGとラミブジンの併用療法である．Markowitzら[8]は，ラミブジン150 mg/日とHBIGの併用により観察期間は1年と短いものの再発率0%と劇的な結果を達成している．観察期間が短く長期予後を論じることはできないが，現時点では最も有望な治療法であることは間違いないようである．

この併用療法は，日本における生体肝移植でも一般的に用いられ良好な成績をおさめている．現在では，HBV DNA陽性，HBeAg陽性の症例などウイルス量の多い症例も適応となっている．

九州大学では，2004年12月までの生体肝移植症例174例のうちB型肝炎関連疾患は20例で，その内訳は劇症肝炎(9例，うち8例はHBsAg陽性)，HBV肝硬変(11例：HBeAg陽性5例，HBV DNA陽性7例，YMDD変異株5例，肝細胞がん(HCC)合併6例)である．ドナーHBcAb陽性症例は27例で，**図1**のプロトコールに従い再発予防を行った．

九州大学ではHBsAg陽性レシピエントに対しては，(術前～)術後永久的にラミブジン100～150 mg/日の経口投与およびHBIG 1万単位を無肝期および術後1～7日目まで毎日，以後1年間はHBsAb抗体価500 IU/L以上を，2年目以降は200 IU/L以上を目標に，1カ月から2カ月ごとにHBIG 5,000～1万単位を点滴静注するプロトコールを採用している．

HBsAg陽性レシピエント20例の5年生存率は89%であった．平均観察期間27カ月で18例には

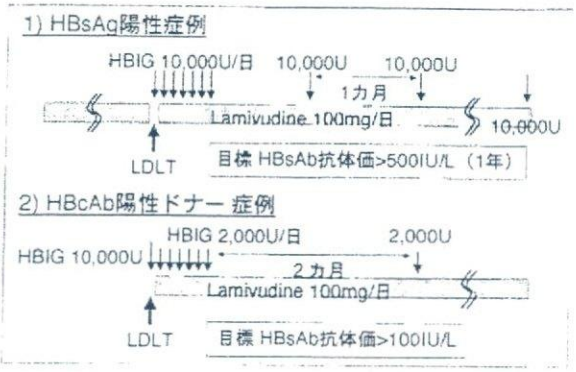

図1　B型肝炎再発予防プロトコール（九州大学）

再発を認めていないが，2例にウイルス学的再発を認めた．

うち1例はHBsAg陽性ドナーの症例であり，HBIG使用にもかかわらず術後早期よりHBsAg陽性化・HBsAb陰性化したが，ラミブジンとアデフォビルの併用により術後2年現在，肝機能は正常で持続的にHBV DNA陰性であり組織学的にも肝炎の再発は認めていない．

もう1例はワクチン接種に伴うHBIG減量中にHBV DNA陽性となった症例で，YMDD変異株の出現に伴いHBsAg陽性化・HBsAb陰性化した．ラミブジンとアデフォビルの併用により術後2年6カ月現在，肝機能は正常であるがHBV DNA陽性である．

2. ラミブジン耐性HBV陽性レシピエント

B型慢性肝炎や肝硬変に対してラミブジンが広く使用されるに伴い，耐性株の出現が問題になっている．熊田らは，長期(5年)投与例においてHBeAg陽性例では66.7%，HBeAg陰性例では60%のラミブジン耐性株の出現を認めたことを報告している．当然のことながら，今後末期肝不全の肝移植レシピエントにも同様にラミブジン耐性株陽性の症例が増加してくることが予測され，その予防戦略が重要となってくる．

九州大学では，これまで5例の術前ラミブジン耐性株陽性症例に対して生体肝移植を行った．通常のプロトコールに加え，アデフォビルを術前・術後に連日投与するプロトコールで術後の再発予防を行っており，現在まで再発例はない．

術前のラミブジン投与の有効性に関しては，あまりエビデンスがない．移植前の耐性株の出現を最小限に抑え，かつウイルス量の減少を図るために，術前2週間から1カ月にラミブジンを投与することにしているが，まったく投与しない場合もある．東京大学では，耐性株の出現を抑制するために術前・術後にまったくラミブジンを投与しないプロトコールを採用している．

3. HBcAb陽性ドナー

わが国では全人口におけるB型肝炎既感染(HBcAb陽性)率が10%にのぼるとされており，HBcAb陽性ドナーを生体肝移植ドナーとして選択せざるをえないことがまれでない．しかしHBcAb陽性ドナーからの肝移植では免疫抑制下でもあり，予防なしでは移植後高率(ほぼ100%)にB型肝炎再発が起こること，移植肝にウイルスが存在することが確認されている．再発予防法にはHBIGを用いるプロトコールやラミブジンのみを用いるプロトコール，その両者を用いるプロトコールがある．

九州大学では，術後永久的にラミブジン100～150 mg/日およびHBIGを無肝期に1万単位，術後1～7日目まで2,000単位/日，以後2カ月おきに2,000単位を点滴静注，HBsAb抗体価100 IU/L以上を維持するというプロトコールを採用し，本プロトコールにてこれまでに27例のHBcAb陽性ドナーからの生体肝移植を行った．27例のレシピエントの5年生存率は59.8%(P＝NS)にとどまったが，生存例の術後血中HBV DNAは全例陰性のまま経過し，再発例を経験していない．

4. B型肝炎ワクチン

健常者においては，リコンビナントB型肝炎ワクチン投与により90～98%のseroconversionが起こることが知られており，安全性も確立されている．このような能動免疫がHBcAb陽性ドナーからの移植患者におけるB型肝炎再発予防として行われた報告はない．

表1 九州大学におけるB型肝炎ワクチン施行例

症例	年齢/性別	原疾患	ドナーHBcAb	移植後日数*1	FK trough (ng/mL)	Steroid (mg)	直前抗体価 (IU/L)	ワクチン回数	観察期間*2 (日)	ピーク抗体価 (IU/L)	最終抗体価 (IU/L)	抗体陽転化	転帰
1.	58/男	B型劇症肝炎	−	1,463	6.1	0	< 10	3	521	< 10	< 10	無	無再発・生存
2.	31/女	B型劇症肝炎	−	1,379	7.8	0	97.1	3	420	1050.0	1000 <	高	無再発・生存
3.	24/男	原発性硬化性胆管炎	+	1,236	3.3	5	116.0	3	560	5440.0	299.3	高	無再発・生存
4.	13/女	胆道閉鎖症	+	1,230	4.5	0	191.0	3	468	359.0	164.1	低	無再発・生存
5.	13/女	胆道閉鎖症	+	1,215	5.9	0	76.2	3	428	161.0	< 10	無	無再発・死亡
6.	44/女	B型劇症肝炎	−	1,149	5.6	0	37.1	5	511	25.1	15.3	低	無再発・生存
7.	40/男	C型肝炎	+	947	6.5	0	< 10	5	448	< 10	< 10	無	無再発・生存
8.	63/男	肝細胞がん・C型肝炎	+	473	4.6	0	27.3	3	453	< 10	< 10	無	無再発・生存
9.	18/女	胆道閉鎖症	+	459	3.6	0	58.9	3	523	1000 <	1000 <	高	無再発・生存
10.	23/女	胆道閉鎖症	+	310	7.4	0	135.0	3	406	20.8	20.8	低	無再発・生存
11.	38/女	原発性胆汁性肝硬変	−	398	4.8	5	61.2	3	84	61.2	22.6	無	無再発・生存

*1 肝移植より初回ワクチン接種までの日数. *2 初回ワクチン接種からの観察期間

HBIGとラミブジン併用療法の最大の問題点はその高額なコストである．特にHBIGは移植後初年度のコストだけでも100万～200万円がかかる．したがって，ワクチンによる能動免疫によりHBsAb抗体価を獲得できれば，HBIGの省略が可能で，生体肝移植患者のQOL，および特に医療コストの面から非常に意義が大きいと考えられる．

そこでHBsAg陰性劇症肝炎レシピエントおよびHBcAb陽性ドナーからの生体肝移植を受けたレシピエントで，① 術後12カ月以上経過(HBIGを12カ月以上投与)し，② 肝機能が正常あるいはほぼ正常で，③ 低い免疫抑制状態(プレドニゾロン5 mg/日以下)，④ HBV DNA陰性およびHBsAg陰性の症例にはHBIG中止のうえ，リコンビナントB型肝炎ワクチン(Heptavax-II. BANYU PHARM. CO. LTD., Japan)20 μg(通常の倍量)，3回投与(0, 1, 6カ月)を1クールとし，無効例にはもう1クール追加するプロトコールでB型肝炎ワクチンによる能動免疫を施行し，同ワクチンの移植後B型肝炎再発に対する予防効果を検討した．

これまでに11例に対して，上記プロトコールに従ってワクチンの接種を行った(表1)．平均年齢は33.2歳(18～63歳)，男女比は4：7であった．適応疾患はB型劇症肝炎3例，胆道閉鎖症4例，原発性胆汁性肝硬変1例，原発性硬化性胆管炎1例，C型肝炎2例(1例はHCC合併症例)であった．移植より初回ワクチン接種までの期間は平均933日(310～1,463日)であった．

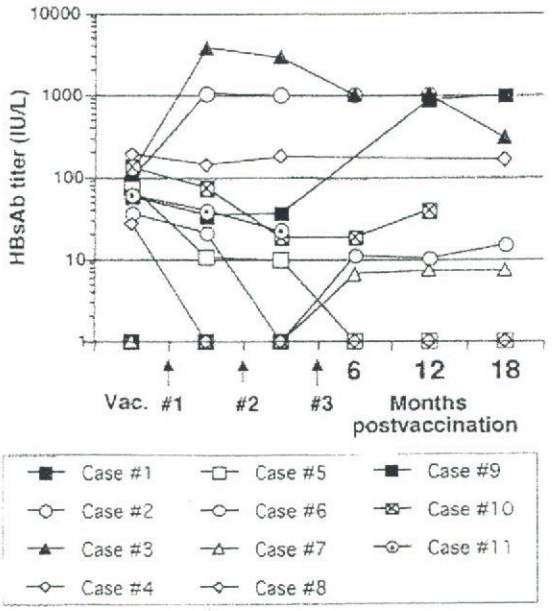

図2 HBsAb抗体価の推移

免疫抑制剤は全例タクロリムスおよびプレドニゾロンで導入し，初回接種時は2例のみがプレドニゾロン5 mgを服用中で残りの9例はプレドニゾロンを中止されていた．タクロリムスの平均血

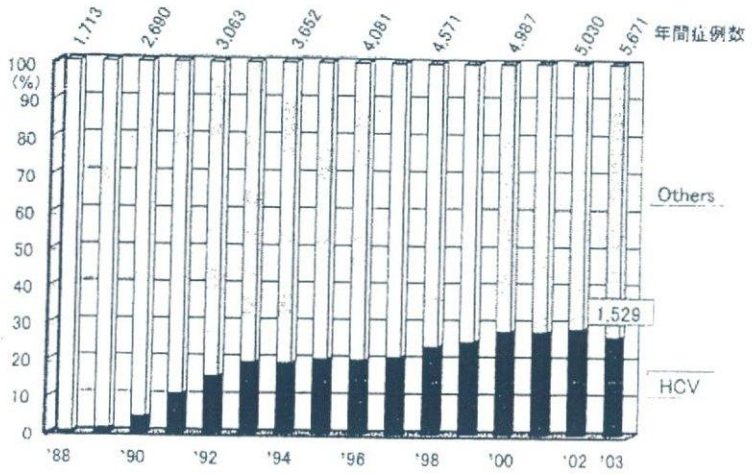

図3
C型肝炎症例数の推移(UNOS)

中濃度は5.5 ng/mL(3.3 ～ 7.8 ng/mL)であった．初回接種よりの観察期間は平均438日(84 ～ 560日)で，1例(慢性拒絶)を除く10例が生存中である．

図2に，ワクチン接種直前から接種後のHBsAb抗体価の推移を示す．観察期間中，6例(54.5%)が予防抗体価10 mIU/mL以上の抗体価を得(responder)，HBIGを離脱した．残りの5例はいずれも抗体価＜10 mIU/mLであり，non-responderと判断した．non-responderのうち2例は死亡(慢性拒絶)あるいは合併症(免疫抑制剤ノンコンプライアンスによる慢性拒絶)によりHBIGを中止しラミブジンのみで維持した．残る3例は2クール目のワクチンを施行中である．

一方，responderのうち3例はピーク抗体価1,000 mIU/mL以上(high responder)以上であった．high responderのうち2例は観察期間420日，523日で抗体価1,000 mIU/mLを維持しているが，1例は最終フォローアップ時(560日)の抗体価が299.3 mIU/mLと抗体価の減衰を認めた．すなわち約55%の抗体陽転率であった．

この陽転率は一般健常人の90 ～ 95%の陽転率に比較して明らかに少なく，免疫抑制剤の関与が推測された．全症例において経過中，B型肝炎の再発(HBV DNAの出現，HBsAgの陽性化)は認めなかった．またワクチン施行時，施行後を通じて副作用はまったく認められなかった．

したがって，この方法がHBIG大量投与(受動免疫)による予防よりも安全性，コスト的にも有利であることが証明され，HBcAb陽性ドナーからの肝移植の標準的なB型肝炎再発予防法となりうることが期待される．今後，さらに陽転率を改善する方法の研究が必要となろう．

C型肝炎への対応

1. 移植症例数と成績

UNOSのデータによれば，2003年の全米肝移植総数は5,671例で，うち1,529例(27%)がC型肝炎症例であった．ここ数年全症例数の30%前後(施設によっては50%)で推移しており，C型肝炎が最も頻度の高い適応疾患である(図3)．

一般的にC型肝炎に対する肝移植の成績は良好で，他疾患のそれと差がないとされてきた．King's Collegeからの報告[9]では，HCV肝硬変症例149例の1年生存率79%，3年74%，5年70%と，非HCV肝硬変症例と差を認めなかった．長期予後を検討したUCLAからの報告[10]では，1年，5年，10年生存率はそれぞれ84%，68%，60%と良好であった．

しかし最近，HCV肝硬変患者の長期移植成績が，明らかに非HCV肝硬変患者のそれより劣り，しかも以前に比較して有意に悪化しているという報告が相次ぎ，大きな話題となっている[11]．

本邦では，信州大学の中澤らが2003年に全国調査を行っている．1998～2003年3月までに218例のHCV陽性患者(全症例1,671例の13%，119例60%がHCC合併)に対して生体肝移植が行われた．平均14カ月のフォローアップで1年，2年，4年生存率はそれぞれ79%，72%，68%であり，現在のところ脳死肝移植の成績とほぼ同等である．

2. 再発重症化の因子

C型肝炎の再発はほぼ100%に起こると考えられるため，その有効な予防法がない現状では，いかにして再発の重症化を防ぐのかが最大の課題である．

重症化に関与する因子として確立されているものには，非白人人種，術前高ウイルス量，術後早期の高ウイルス量，ステロイドパルス・OKT3などによる急性拒絶の治療歴，再発までの時間，サイトメガロウイルス感染症，高齢ドナーなどがある．特に近年における高齢ドナーの増加とC型肝炎再発の重症化頻度の増加との関連は注目に値する[12]．そのほか，HLA，genotype 1b，生体肝移植，冷保存時間などが危険因子としてあげられているが確定していない．

最近，生体肝移植が移植後早期のC型肝炎再発と重症化に関与しているとの報告も多い．Garcia-Retotillo ら[13]は，脳死肝移植95例，生体肝移植22例のプロトコール肝生検を行い，再発の重症化頻度を比較した．移植後2年の時点での重症化頻度は脳死22%，生体45%と生体肝移植で有意に高頻度であった．一方，Russo ら[14]は，UNOSのデータベースを用いて脳死肝移植(3,955例)と生体肝移植(279例)の生存率比較を行ったが，移植後2年までの短期では両群に患者・グラフト生存率の差はなかった．

このように，現在のところC型肝炎再発がおよぼす生体肝移植の影響については意見が別れている．

3. 再発の治療

移植後のC型肝炎再発の治療および予防に関しては，インターフェロン(IFN)単独投与は無効である．現在，最も広く行われているのはIFNとリバビリン(RIB)の併用療法であるが，end-of-treatment(EOT) responseが得られるのは約25～30%であるがsustained viral response(SVR)，すなわちウイルス学的著効が得られるのは10～20%にすぎないことがわかっている．しかも移植後の患者ではコンプライアンスがきわめてわるく50%程度が脱落あるいは減量を余儀なくされ，とても満足できる治療とはいい難い．

最近，より副作用が少なく，週1回の投与で効果は通常のIFNと同様とされるPegylated interferon alfa-2b(PEG-IFN)が登場し，欧米ではPEG-IFN + RIBが再発後の治療の第一選択となっている．

Neff ら[15]は，57人(初回群29例，IFN + RIB治療のnonresponder群28例)の患者にPEG-IFN(0.5～1.5 μg/kg/週) + RIB(400～1,000 mg/日)による治療を行い，EOTはそれぞれの群で27.6%，21%にすぎず，副作用により7%が輸血を，40%がエリスロポエチンを，30%がG-CSFを必要としたことを報告している．一方Rodriguez-Luna[16]は，37人の患者で12人(63%)が治療を完遂，48週の時点でEOT 37%，SVR 26%であったことを報告している．Dumortier ら[17]は，20人の患者に治療を行い，EOT 55%，SVR 45%であったことを報告している．

このようにPEG-IFN + RIBも満足できる治療法とはいい難い．

移植後早期に治療を開始する，いわゆるpreemptive治療の報告も散見されるようになった．

Shergill ら[18]は，移植後2～6週目にIFNまたはIFN(PEG-IFN) + RIBによるpreemptive治療を行ったが，C型肝炎移植患者124人中51人(41%)にのみpreemptive治療が施行可能であったこと，51人中15%のみがfull dose治療が可能であったこと，EOT，SVRは13.6%，9.1%にすぎなかったこと，生体肝移植患者のほうがpreemptive治療の対象になりやすいことを報告した．東京大学の菅原ら[19]は，生体肝移植症例23

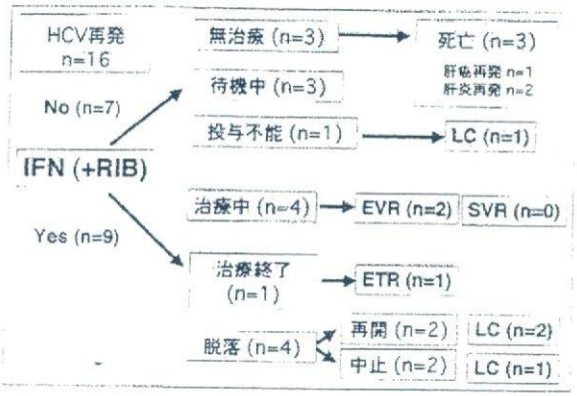

図4　C型肝炎再発に対する治療成績
（九州大学）

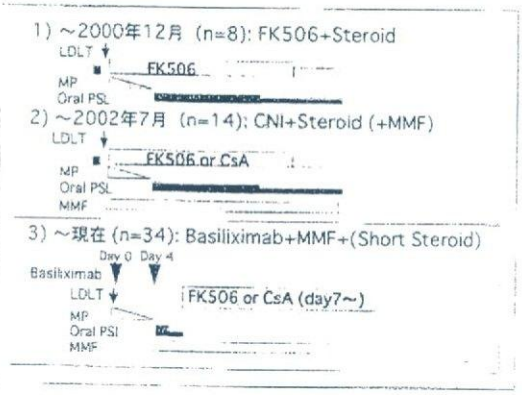

図5　HCV肝硬変に対する免疫抑制プロトコール
（九州大学）

例にIFN + RIBのpreemptive治療を行い，SVR 39%，脱落例25%であり，従来のIFN + RIBに比較して良好であったことを報告している．

今後，有望な治療オプションとなっていくことが見込まれるが，大規模なランダム化試験が必要であろう．

移植患者に対しては，IFN + RIBの減量・脱落例をいかに減らし，目標量をいかに投与できるかが重要である．G-CSFやエリスロポエチンなどを用いた積極的な治療が必要である．

4. 九州大学における生体肝移植の成績

九州大学では2004年12月までに，174例の生体肝移植を施行した．

成人149例中57例(38.3%)がHCV肝硬変症例(うち43例75.4%はHCCを合併)であった．HCC合併を含めたHCV陽性症例58例(1例は劇症肝炎症例)の生存率は1年80.5%，3年64.9%，5年64.9%であり，HCV陰性症例と有意差はなかった．ウイルス学的には術前HCV RNA陰性であった2例を除き，55例に術後HCV RNAを検出した．組織学的再発は16例(32%)に認めた．累積再発率は6カ月29%，1年34%，3年50%，5年62%であった．C型肝炎再発により2例を失った．

再発後の治療成績を図4に示す．やはり副作用のために治療を中断あるいは減量せざるをえないことがほとんどである．

観察期間16～1,388日で，再発16例中9例に組織学的肝硬変(あるいは前肝硬変)を認めており，すでに9例中6例は非代償性(腹水など)となっている．9例中4例では術後半年以内に組織学的肝硬変を認めた．興味深いことに，9例中8例(89%)で胆管狭窄の既往を認めた．

九州大学では，最近プロトコール肝生検をはじめているが，術後数年経過し肝機能が正常な症例でも，肝生検をしてみると肝組織上明らかな肝炎・線維化のある症例に遭遇する．このような症例の長期予後は不明であるが，C型肝炎症例を血液検査のみでフォローするのは危険であると考える．

5. 術前治療の意義

再発後の治療成績がわるいとなると，移植前にウイルスを排除しようという考えが生まれる．市田らは，移植前に速効性のIFNβを短期間用いることでHCV RNAを陰性化させたのち，生体肝移植を行い，術後3年間HCV RNA陰性，肝機能正常化をもたらした症例を報告している．

このように散発的な報告はあるものの，移植患者は通常非代償性肝硬変であり，コンプライアンス等の問題から術前の抗ウイルス療法によりウイルスを排除することはきわめて困難であり，あまり現実的でない．また，術前のウイルス排除が果たして術後再発率を低下させるのか不明である．HCC合併例などの肝機能良好な症例が術前治療

の対象になるものと考えられる.

九州大学では,いずれもHCV肝硬変にHCCを合併した比較的肝機能のよい移植患者3例にIFNβによる術前治療を試みた.

1例目は副作用のため治療中止となり,そのまま術前にウイルスの消失なく生体肝移植を施行,移植後早期に再発した.2例目は術前にウイルスの消失が得られたが,やはり副作用のため術前1週間で治療を中止した.移植後1カ月間HCV RNA陰性が得られたが,以後再発した.3例目は術直前まで治療を継続し,HCV RNA陰性の状態で移植することができた.術当日の血液・自己肝組織・リンパ節でもHCV RNA陰性であり,術後1カ月HCV RNA陰性を維持したが,やはり以後再発をみている.

6. 移植後の免疫抑制剤

最近,シクロスポリンが*in vitro*でHCV増殖抑制効果を発揮することが証明され話題をよんでいる[20].HCV患者に対する移植後の免疫抑制剤,特にカルシニューリンインヒビターであるタクロリムスとシクロスポリンの選択については議論の別れるところである.臨床的に再発に対する優位性を証明した報告はない.ステロイドフリーのプロトコールがC型肝炎の再発にどのような影響を与えるのか不明である.

九州大学では現在,バシリキシマブ(シムレクト)+ミコフェノール酸モフェチル(MMF)+シクロスポリンによるステロイドフリーのプロトコールで免疫抑制を行っているが(図5),通常の2剤併用プロトコールに対するウイルス学的な優位性は現在のところ証明できていない.

筆者は正確な組織学的再発の診断,早期治療の開始,抗ウイルス療法の成績の比較のためには,そのリスクを考慮に入れてもプロトコール肝生検は必須であると考える.プロトコール肝生検がC型肝炎移植患者の予後を改善したとの報告はないが,移植後1年の時点でのプロトコール肝生検の結果がそれ以後の予後をよく反映するとの報告がある.

7. 基礎研究の重要性

HCVには,チンパンジー以外の感染実験動物モデルや効率のよい培養細胞感染複製系がないために,細胞への感染メカニズム,複製メカニズムがいまだ不明である.ここを明らかにすることが移植後の再発・重症化メカニズムの解明・抗HCV薬開発のブレイクスルーになると思われる.

現在,レプリコン細胞(培養細胞にHCV非構造蛋白質RNAを組み込んだ細胞)による肝細胞内HCV RNA複製増殖機構や薬剤作用の解析[20],トランスジェニックマウス(HCVのcDNAを組み込んだマウス)を用いた生体防御反応の解析[21],シュードタイプウイルス(水疱性口内炎ウイルスやレトロウイルスにHCVエンベロープ糖蛋白を組み込んだウイルス)を用いたCD81やSR-BI(スカベンジャーレセプターclass-B, type I)などのHCVレセプターの同定や機能解析[22]など重要な基礎研究がつぎつぎと発表されている.

移植肝はいわばHCVの初感染・増殖モデルである.今後われわれ外科医も移植肝を用いた基礎研究をすすめ,HCV研究に貢献したいと考えている.

おわりに

HBVの再発予防法に関してはほぼ確立されたといってよいが,肝移植後のHCV再発の治療・予防法の確立は,いまだ解決できていない最大の難題であり,それゆえに移植外科医・内科医にとってやりがいのある仕事である.

今後,移植後HCV再感染機構の解明や重症化メカニズムの解明,有効な再発治療法の開発などの研究が不可欠である.

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Clinical Transplantation

Splenectomy and preemptive interferon therapy for hepatitis C patients after living-donor liver transplantation

Kishi Y, Sugawara Y, Akamatsu N, Kaneko J, Tamura S, Kokudo N, Makuuchi M. Splenectomy and preemptive interferon therapy for hepatitis C patients after living-donor liver transplantation.
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Abstract: Recurrent hepatitis C after liver transplantation is a major cause of graft failure. We routinely perform preemptive interferon and ribavirin therapy in patients after living-donor liver transplantation indicated for hepatitis C-related cirrhosis. One of the obstacles for the therapy includes blood cytopenia. To overcome this problem, we recently performed splenectomy concurrently with liver transplantation. Thirty-five patients underwent liver transplantation and received preemptive therapy for hepatitis C. They were divided into two groups: those with splenectomy (group A, n = 21) and those without (group B, n = 14). There was no significant difference in the frequency of morbidity between the groups. Platelet counts were well maintained in group A patients during the therapy, and cytopenia led to the discontinuation of the therapy in one group B patient. The results of the preliminary study warrant a randomized control trial to examine the feasibility of splenectomy and preemptive viral therapy during liver transplantation for hepatitis C.

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Key words: hepatitis C – interferon – liver transplantation – splenectomy – thrombocytopenia

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Hepatitis C virus (HCV) infection is one of the leading etiologies for liver transplantation. The main problem of the post-transplantation course is recurrent hepatitis with 11–14% of recipients redeveloping hepatitis leading to graft failure (1, 2). However, retransplantation provides poor results, with a 3-yr survival rate of only 40–56% (3, 4).

Although interferon (IFN) and ribavirin therapy is one of the standard treatments, the sustained virologic response ratio of the therapy for recurrent HCV after transplantation is limited to approximately 30% (5–7). We routinely perform preemptive IFN therapy for recipients of living-donor liver transplantation (LDLT) indicated for HCV cirrhosis (8). One of the obstacles for starting or continuing combined IFN and ribavirin therapy includes blood cytopenia. To overcome this problem, we recently performed splenectomy concurrently with liver transplantation (9). Here we analyze the results of these patients to evaluate the feasibility of simultaneous splenectomy and combined therapy against HCV.

Patients and methods

From January 1996 to September 2004, 165 adult patients underwent LDLT. Of these, 39 recipients were indicated for HCV cirrhosis and received preemptive IFN and ribavirin therapy. Of these, four were excluded from the study because two died before the start of therapy due to uncontrolled cytomegalovirus infection or resistant acute cellular rejection, and two patients were followed up at

other hospitals and detailed laboratory data could not be obtained. The remaining 35 patients were the subjects of this study. They were divided into two groups: those with splenectomy (group A, n = 21) and those without (group B, n = 14).

The protocol of the preemptive IFN and ribavirin therapy was reported previously (8). In brief, the therapy was started when the white blood cell count was >4000 mm^3, hemoglobin level >10 g/dL, and platelet count $>100\,000/mm^3$. The therapy was initiated with 3 million units of IFN-alpha2b (Intron A; Schering-Plough K.K., Osaka, Japan) three times per week and 400 mg of ribavirin per day, which was increased up to twice the initial dose according to patient tolerance. The therapy was discontinued when there was significant leucopenia ($<1500/mm^3$), thrompocytopenia ($<50\,000/mm^3$) despite application of granulocyte colony-stimulating factor (G-CSF), hemolytic anemia (hemoglobin level <8 g/dL), renal dysfunction (serum creatinine >2 mg/dL) or depressive psychologic status.

Preoperative blood cell count, platelet count (mm^3), leukocyte count (mm^3), and hemoglobin (g/dL) were taken just before IFN therapy, and the numbers of days from transplantation to the start of therapy were evaluated. Blood cell counts during the therapy were examined weekly for the first month, monthly for the first year, and annually later on. The frequency of discontinuation of the therapy and its cause were reviewed. Completion of the therapy was defined as the elimination of HCV (<500 copies/mL by Amplicor HCV; Roche Molecular Systems, Pleasanton, CA, USA). Here, HCV was considered to be eliminated when the serum HCV-RNA level was consistently negative for at least 6 months after cessation of combination therapy. Protocol liver biopsy was not performed.

Data are expressed as median and range. Statistical comparison was performed using Mann–Whitney test, Fisher's exact test or repeated measure analysis of variance where appropriate. p-value <0.05 was considered statistically significant.

Results

Patient profiles

In the 17 patients of group A, the duration between LDLT and starting the therapy ranged from 18 to 59 d (Table 1). In the other four patients of group A, it was longer than 2 months as we had to wait till they recovered from pneumonia, abdominal abscess, heart failure or renal failure. The number of the patients of HCV genotype 1b (HCV_{1b}) and those of the other genotypes (HCV_{non1b}) was 5 of 16 in group A and 2 of 12 in group B. There was no significant difference in preoperative blood cell counts or liver function between the groups.

Table 1. Patients profiles

	A (n = 21)		B (n = 14)		
Group	Median	Range	Median	Range	p-value
MELD score	14	4–34	10.9	2.4–25.3	0.22
Preoperative plt ($\times10^4$/mm^3)	5.0	2.9–13.5	5.6	4.1–15.0	0.30
Preoperative WBC ($\times10^3$/mm^3)	3.3	1.3–20.5	2.8	1.6–9.8	0.51
Preoperative Hb (g/dL)	9.0	5.5–12.7	10.5	5.6–13.3	0.24
Start day (d)	41	18–120	30	7–130	0.34
HCV-RNA before therapy (kcopies/mL)	663	186–3350	510	46–1700	0.66

MELD, model for end-stage liver disease; plt, platelet; WBC, white blood cell; Hb, hemoglobin.

Postoperative infectious diseases

In group A, six (29%) patients suffered from infectious disease: four from abdominal abscess, one from fungal pneumonia and one from bacterial pneumonia. Two of the four abdominal abscesses were related to the splenectomy because there was pancreatic juice leakage from the drainage tube in the left subphrenic space. Both of the patients responded well to surgical re-exploration. In group B, five (36%) patients had infection episode with no mortality including three abdominal abscesses, one sepsis and one osteomyelitis.

Blood cell counts after interferon and ribavirin therapy

In group A patients, platelet count significantly increased soon after LDLT and was maintained during the treatment for up to 2 yr (Fig. 1). Platelet count was kept higher in group A patients ($p = 0.008$) during the observation period. Leukocytopenia $<3000/mm^3$ were observed in three patients of group A and seven in group B. All of them were well controlled by G-CSF except for one in group B who discontinued the therapy because of cytopenia.

Continuation of therapy

Six (29%) patients in group A and three (21%) in group B discontinued therapy before the HCV was eradicated (Table 2). A 40-yr-old male in group A underwent retransplantation for cholestatic

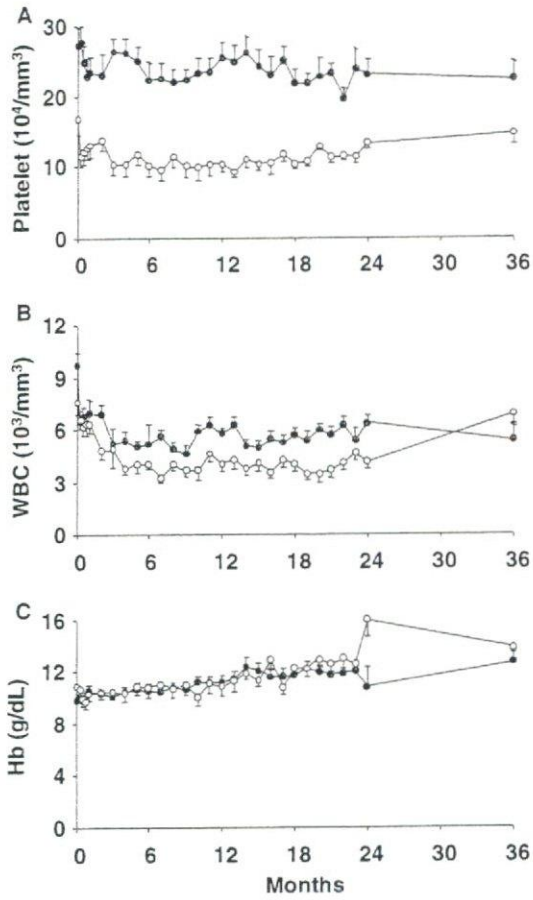

Fig. 1. Changes of platelet (A), white blood cell count (B) and hemoglobin (C). Levels after interferon therapy in group A (thick line with close circles) and group B (thin line with open circles). The bar represents a standard error value. There was a significant difference between the groups in the platelet count ($p = 0.008$).

Table 2. Timing [months after the start of interferon (IFN) therapy] and the reason of cessation of IFN therapy

Group	Patient	Timing	Reason
A	1	14	Renal dysfunction
	2	7	Depression
	3	7	Death caused by thrombotic thrombocytopenia
	4	18	Retransplantation because of cholestatic hepatitis
	5	19	Renal dysfunction
	6	3	Depression
B	1	4	Death caused by virus associated hemophagocytotic syndrome
	2	9	Thrombocytopenia
	3	6	Death because of hepatocellular carcinoma recurrence

hepatitis 18 months after the primary LDLT and died of liver failure 4 months after the retransplantation. Four patients in group A and three in group B completed the therapy. Eleven patients in group A and eight in group B continued the therapy for 21 (range: 11–47) and 24 (range: 11–66) months, respectively.

Effect of genotype

In group A, HCV-RNA became negative in 44% (7/16) of HCV_{1b} patients and 60% (3/5) of the HCV_{non1b}. Median periods of treatment until the RNA level became negative was 15 (range: 1–18) months and 2 (range: 2–8) months in each group, respectively. There was no significant difference in the period by genotype ($p = 0.30$). In group B, HCV-RNA became negative in 17% (2/12) of HCV_{1b}, and 100% (2/2) of HCV_{non1b}.

Discussion

Preemptive IFN and ribavirin therapy to prevent cholestatic hepatitis has not been established. Only a few centers, including ours, report using this strategy (8, 10–13). Among the 39 patients who underwent preemptive IFN therapy after liver transplantation with or without splenectomy, we experienced cholestatic hepatitis in only one patient, which might indicate the possibility that long-term IFN and ribavirin therapy prevents the occurrence of cholestatic hepatitis. Gopal and Rosen (14) reported the results of IFN and ribavirin therapy in seven cholestatic hepatitis patients with only two patients who survived for an average of 32 months. They emphasized the importance of continuing the therapy indefinitely because the cessation of the therapy even after 12 months or more of treatment with sustained HCV-RNA negativity led to rapid recurrence of cholestatic hepatitis. IFN and ribavirin therapy might be worth continuing over the long term, especially in patients with HCV_{1b}. The preemptive therapy is effective in cases with lower HCV-RNA levels and less graft injury by the virus (11, 13). Accordingly, the treatment should be started within a short interval of transplantation.

The indications for simultaneous splenectomy in liver transplantation for reducing portal hypertension to protect the graft from congestion, especially in small left liver graft, or repairing portal flow regurgitation are established (15, 16). The effectiveness of splenectomy against thrombocytopenia is reported (9, 17). Several authors, however, have objected to perform splenectomy as a therapeutic option for thrombocytopenia because it might increase the risk of septic complications postoperatively, and instead recommend splenic artery ligation or radiologic partial splenic embolization (18–21). Several reports, however, suggest that

the indication of such ligation or embolization methods should also be considered with care because of the low success rate and risk of complications (22, 23). We previously reported the safety of concomitant splenectomy and several other centers report similar good results (9, 24). The results of the present study suggest that splenectomy is feasible for starting combination therapy early after transplantation and continuing for up to 4 yr with an acceptable morbidity rate.

The long-term effect of splenectomy as a therapeutic option for blood cytopenia because of portal hypertension remains unclear in patients undergoing IFN and ribavirin therapy. Randomized control trials to examine the risk and benefits of splenectomy for patients undergoing liver transplantation and combined therapy for hepatitis C are necessary.

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Living Donor Liver Transplantation for Patients With Hepatitis C Virus Cirrhosis: Tokyo Experience

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Living donor liver transplantation is an alternative therapeutic option for patients with end-stage HCV cirrhosis because of the cadaveric organ shortage. Preliminary results, however, indicate that live donor grafts might be disadvantageous for HCV patients. Sixty-seven patients underwent living donor liver transplantation for HCV cirrhosis between 1996 and 2004. All the patients preemptively received antiviral therapy consisting of interferon alfa-2b and ribavirin, which was started approximately 1 month after the operation. The therapy continued for 12 months after the first negative HCV RNA test. The patients were then observed without the therapy for 6 months. The therapy was continued for at least 12 months, even when the HCV RNA test remained positive. The subjects were removed from the protocol if they could not continue the therapy for 12 months because of adverse effects or could not start the therapy because of early death. Twelve patients were removed from the protocol as a result of early death (n = 9) or cessation of the drug (n = 3). Another 16 patients are currently on the protocol. Of the remaining 39 patients, 16 patients (41%) had a sustained virologic response. The cumulative 5-year survival of the HCV-positive patients was 84%, which was comparable with that of patients negative for HCV (n = 168, 86%). The present preemptive antiviral protocol after living donor liver transplantation is safe and warrants a controlled study to confirm its benefit on graft survival.

Living donor liver transplantation (LDLT) is now a common alternative procedure to deceased donor liver transplantation (DDLT), which reduces waiting-time mortality in an era of deceased donor shortage. By June 2003, 1275 LDLT cases were recorded in the European Liver Transplantation Registry.[1] The 3-year graft survival rates were 71%, although the survival rates of HCV-positive patients are unknown. In the United States,[2] 1526 adult LDLT cases were performed by May 2004. HCV is the most common indication for LDLT, and the number of HCV-positive patients is stable, approximately 100 per year between 2000 and 2002. According to the Japanese Liver Transplantation Society,[3] 1335 adult LDLT procedures were performed in Japan by the end of 2003, and of these 297 (22%) were performed for HCV cirrhosis.

A current debate in the field of liver transplantation is the possibility of increased severity of recurrent HCV infection in LDLT patients. If HCV recurs earlier and more severely after LDLT, a specific strategy for preventing the detrimental effects of HCV on living donor grafts must be developed. Preemptive interferon therapy (prophylaxis) during the early post-transplantation period might reduce the incidence and severity of HCV recurrence. In the present study, we report our results of LDLT for chronic hepatitis C and discuss the feasibility of an antiviral protocol.

Patients and Methods

We performed preemptive therapy for LDLT patients with HCV infection. From 1996–2004, 67 patients underwent LDLT for HCV cirrhosis at the Tokyo University Hospital. The patients were 51 men and 16 women, and their ages ranged from 23–63 years (median, 55 years). The HCV genotype was 1b in 53 patients (79%). Forty-one patients (61%) had hepatocellular carcinoma. Our surgical technique for recipient and donor surgery is described elsewhere.[4] All the patients received the same immunosuppressive regimens with tacrolimus (Prograf; Astellas Pharma Inc, Tokyo, Japan) and methylprednisolone as described previously.[5]

All the patients preemptively received antiviral therapy consisting of interferon alfa-2b and ribavirin, which was started approximately 1 month after the operation. The therapy was continued for 12 months after the first negative HCV RNA test. The standard regimen included interferon alfa-2b (3 million units [MU] ×3 per week) and ribavirin (800 mg/day) for 6 months. The patients were then observed without the therapy for 6 months. The therapy was continued for at least 12 months, even if the HCV RNA test remained positive.

Therapy was discontinued when there was significant leukopenia (<1500/mL), thrombocytopenia (<50,000/mL) de-

Abbreviations used in this paper: DDLT, deceased donor liver transplantation; LDLT, living donor liver transplantation.

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