The Relationship Between Recurrences and Immunosuppression on Living Donor Liver Transplantation for Hepatocellular Carcinoma

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ABSTRACT

Objectives. Living donor liver transplantation (LDLT) offers timely transplantation for patients with hepatocellular carcinoma (HCC). If ABO-incompatible LDLT is feasible, the needs for pretransplantation treatments may be eliminated. It is known that negative impacts of immunosuppression are limited among LDLT for HCC, however, we believe that excessive immunosuppression is one of the risk factors for recurrence. We compared the impacts of immunosuppression for LDLT with hepatectomy outcomes for HCC.

Methods. From 1991 to 2010, we performed 144 LDLTs including 14 patients with HCC. Seven met the Milan criteria. Immunosuppressive therapies were based on tacrolimus plus methylprednisolone plus CD25 antibody. For ABO-incompatible cases, we also used mycophenolate mofetil and rituximab. Five cases underwent strong imunosuppressive therapy (steroid pulse or rituximab) within 180 days. In addition, we performed hepatectomy for 180 HCC cases from 1997 to 2010.

Results. Overall survival rates of the LDLT cohort and hepatectomy groups were similar, but disease-free 5-year survival rates (DFS) of the LDLT cohort were significantly better than those of the hepatectomy group (total = 54.4% versus 27.4%, within the Milan criteria cases, 71.4% versus 33.8%). Thus, the negative impact of immunosuppression on recurrence was less than the benefit of a whole liver resection. Among strongly immunosuppressed cases, 5-years DFS rates were significantly worse than among other immunosuppressed cases (20.0% versus 76.2%). Upon univariate analysis, the factors associated with HCC recurrence were alpha-fetoprotein levels and steroid doses within 180 days, but multivariate analysis did not show a predictor for recurrence.

Conclusion. Patients who are strongly immunosuppressed may have several negative impacts for recurrences. More careful indications must be selected for ABO-incompatible cases.

ORTHOTOPIC liver transplantation (OLT) for hepatocellular carcinoma (HCC) in a cirrhotic unresectable liver is the generally accepted treatment to cure both the tumor and the cirrhosis.[1–4] However, donor with the shortage, particularly in japan, living donor liver transplantation (LDLT) has become a frequent therapy. We believe that the first choice for OLT is a cadaveric donor, but especially in an HCC with rapid growth there is no time to await this possibility: LDLT offers timely transplantation. If ABO-incompatible LDLT is feasible, the need for pretransplantation treatment may be eliminated. There are several reports about the relationship between recurrences and immunosuppression for OLTx due to HCC.[3–6] They claim the negative impacts of immunosuppression to be limited,

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Supported by Grants-in-Aid for Scientific Research from the Ministry of Education, Science, and Culture of Japan, and from the Ministry of Welfare of Japan, and by a grant from Tohoku University Graduate School of Medicine.

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0041-1345/–see front matter
doi:10.1016/j.transproceed.2012.01.012

but other reports suggest intense treatment is major risk factors for cancer recurrence, especially among renal transplant patients.[7,8] We have also experienced one ABO-incompatible patient who underwent LDLT for a solitary, early-stage HCC with cirrhosis, who was treated with strong immunosuppression and displayed recurrence within 3 years thereafter. Therefore, we believe that excessive immunosuppression is one risk factor for recurrence, especially in ABO-incompatible or severe rejection cases. Herein, we compared recurrences among immunosuppressed LDLT with hepatectomy patients.

MATERIALS AND METHODS

All procedures were reviewed and approved by our ethical committee and performed in accordance with the Declaration of Helsinki.

From 1991 to December 2010, we performed 144 LDLTs including 14 patients with HCC: male: female ratio 9:5; and overall mean Age, 53.1 ± 4.6 years (Table 1). All patients were Child-Pugh class C except for one Child-Pugh class A, the frequently recurrent type. Nine patients were included within Milan criteria preoperatively, but the specimen showed, only seven (50%) meet these standards. All LDLT patients had negative lymph nodes. Pretransplantation therapy was performed on 4 patients: radiofrequency ablation or transcatheter arterial chemoembolization (TACE). According to the International Union Against Cancer (UICC) TNM classification, 1 patient (7.1%) was stage I, 9 (64.3%), stage II; and four (28.6%), stage IIIA.

Immunosuppressive regimens were tacrolimus plus methylprednisolone plus CD25 antibody (n = 11), tacrolimus plus methylprednisolone (n = 1), tacrolimus plus methylprednisolone plus mycophenolate mofetil (MMF; n = 1), and tacrolimus plus methylprednisolone plus MMF plus rituximab (n = 1; ABO = incompatible case). The antirejection therapy for the ABO=incompatible case, included multiple preoperative plasmaphereses and splenectomy. Because of an acute rejection episode or ABO incompatibility, 5 cases underwent strong immunosuppressive therapy: steroid pulse therapy or rituximab plus steroid minipulse therapy within 180 days.

In addition, from 1997 to April 2010, we performed 232 hepatectomies, including intrahepatic cholangiocarcinoma, mixed type, and other diseases, namely, 180 cases for HCC. Their male: female ratio was 136:44, and mean overall age was 63.5 ± 10.7 years (Table 1). Child-Pugh class A described 163 cases (90.6%), whereas 17 (9.4%) Child-Pugh class B. According to the UICC TNM classification, 64 cases were stage I (35.6%); 47, stage II (26.1%); 44, stage IIIA (24.4%); 6, stage IIIB (3.3%); 3, stage IV (1.7%); and 16 unknown (8.9%) due to insufficient pathological data. Seventy-five cases (41.7%) met the Milan criteria.

We investigated overall (OS) and disease-free survival rates (DFS) among those within the Milan criteria and at each TNM stages. In addition we examined the perioperative mortality rates of both LDLT and hepatectomy groups. We also evaluated the influence of steroid pulse therapy and rituximab plus steroid minipulse therapy on HCC recurrence seeking the sensitivity specificity, positive predictive values (PPV), negative predictive values (NPV), and receiver-operator characteristic (ROC) curve analysis. Furthermore, univariate analysis and multivariate analysis sought to identify independent risk factors for recurrence.

Satistics

All calculations were made with the Stat View software package (SAS Institute, Cary, NC). The results are shown as mean values ± standard deviations (SDs). Kaplan-Meier survival curves were constructed for both study groups. The effects of management on OS and DFS rates were examined initially using the Kaplan-Meier method with log-rank tests. *P* values less than .05 were considered significant. Univariate analysis was performed using Fisher exact test for categorical and Mann-Whitney U-test for continuous variables. *P* values less than .05 were considered statistically significant. The factors identified by univariate analysis to be associated with a *P* value less than .20 were then entered into a multivariate regression analysis to identify independent risk factors for recurrence.

RESULTS

The perioperative mortality rates of LDLT and hepatectomy cohorts were 0% and 1.1% (n = 2), respectively. OS rates at 1, 3, and 5 years for the LDLT versus the hepatectomy group were 92.9%, 78.6%, and 62.9% versus 89.7%, 75.7%, and 58.9%, respectively. Among cases within the Milan criteria, the OS rates of the LDLT versus the hepatectomy group at 1, 3, and 5 years were 100%, 85.7%, and 68.6% versus 100%, 90.6%, and 69.5%, respectively. (*P* = NS; Fig 1). DFS at 1, 3, and 5 years among LDLT subjects group were significantly better than those from the hepatectomy group: 85.7%, 71.4%, and 54.4% versus 69.7%, 45.5%, and 27.4% (log-rank test; *P* = .046). Among cases within the Milan criteria, DFS at 1, 3, and 5 years from the LDLT group were also better than those of the hepatectomy group: 100%, 71.4%, and 71.4% versus 83,7%, 60.6%, and 33.8% respectively (Fig 2), showing that the negative impact of immunosuppression on recurrence was less than the benefit of whole liver resection. In this limited study, there was no significant negative impact of immunosuppression on HCC recurrence.

Among the LDLT group, DFS at 1, 3, and 5 years in the strongly immunosuppressed cases was significantly worse than the normally immunosuppressed cases: 80.0%, 40.0%, and 20% versus 88.9%, 88.9%, and 76.2%, respectively (log-rank test; *P* = .046; Fig 3). Furthermore, among cases within the Milan criteria, DFS at 1, 3, and 5 years rates from the normally immunosuppressed cases were 100%, 100%, and 100%, respectively, suggesting that excessive immunosuppression in the early phase had negative impact on

Table 1. Background of Patients

	M:F	Age	Virus B:C:B+C:O the	Child A:B:C	UICC TNM I: II: IIIA: IIIB: IV	Within Milano
LDLT	9:5	53.1 ± 4.6	7:5:1:1	1:0:13	1:9:4:0:0	7/14
Hepatectomy	136:44	63.5 ± 10.7	45:92:3:40	163:0:17	64:47:44:6:3(unknown=16)	75/180

Abbreviations: M:F, male-female; Child, Child classification; UICC TNM, ; LDLT, living donor transplantation.