Impact of Intraportal Donor-Specific Leukocyte Transfusion for Adult ABO-Incompatible Liver Transplantation

H. Oya, Y. Sato, S. Yamamoto, H. Nakatsuka, T. Kobayashi, T. Watanabe, Y. Hara, H. Kokai, and K. Hatakeyama

ABSTRACT

Introduction. We have reported that repeated donor-specific leukocyte transfusions (DSLT) via the portal vein allow rapid reduction of immunosuppressants and decrease the occurrence of acute cellular rejection. Herein, we examined the immunological benefits of DSLT in adult ABO-incompatible living donor liver transplantation (LDLT).

Materials and Methods. Ten adult patients (MELD score, 19.4 ± 7.3; range, 12–29) underwent LDLT from ABO-incompatible donors from August 2003 to November 2007. The antirejection therapy included multiple perioperative plasmaphereses, splenectomy, and quadruple immunosuppression. In addition to these conventional approaches, we performed 4 intraportal administrations of DSLT after transplantation.

Results. There was no humoral rejection in any patient. Two patients experienced mild cellular rejection requiring steroid pulse therapy. Both donor-specific immunoglobulin (Ig)M and IgG A/B antibodies in all patients decreased following transplantation by 16 fold. By flow cytometry, donor type of CD56+NK T cells existed in the liver graft showing macrochimerism at 1 month after liver transplantation. Furthermore, interleukin (IL)-10 production of Th2 type cytokines was up-regulated after transplantation. Three patients died of sepsis and infection. The 5-year survival rate was 70% by the Kaplan-Meier method.

Conclusion. Adult ABO-incompatible liver transplantation can be performed with acceptable patient and graft survival rates with a low risk of antibody-mediated rejection using intraportal administration of DSLT. Donor type CD56+NK T cells may induce tolerance by a veto or an anti-idiotype network mechanism.

ANTIBODY-mediated rejection of organ allografts may be mediated by recipient anti–donor-specific human leukocyte antigen (HLA) antibodies in presensitized recipients or by anti-A or anti-B isohemagglutinins in recipients of ABO-incompatible allografts. The risk of antibody-mediated rejection in ABO-incompatible kidney transplant recipients can be reduced by pretransplantation removal of anti-A or anti-B isohemagglutinins using total plasma exchange (TPE) or immunoadsorbent columns, splenectomy, and quadruple immunosuppression.[1] Although the liver seems to be more resistant to hyperacute rejection than the kidney or the heart, hyperacute rejection has been reported among presensitized recipients or those receiving ABO-incompatible liver allografts.

We have reported that repeated donor-specific transfusions (DST) via the portal vein allow rapid reduction of immunosuppressants and decreased occurrence of acute cellular rejection.[2–4] Moreover, we have reported that intraportal DST inhibit hyperacute and acute rejection of grafts by recipients showing strongly positive pretransplantation complement-dependent cytotoxicity (CDC), despite an early postoperative rapid elevation in immunoglobulin (Ig)M+CD3+ and IgG+CD3+ cells in flow cytometry crossmatches (FCXM).[5] Interestingly, neither IgG+CD3+ cells nor IgM+CD3+ cells were detected in FCXM at 189

From the Division of Digestive and General Surgery, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan.

Address reprint requests to Hiroshi Oya, MD, Niigata University Graduate School of Medical and Dental Sciences, 1-757 Asahimachi-Dori, Niigata 9518510, Japan.

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Table 1. Profiles of ABO-Incompatible LDLT

No.	Diagnosis	Age	M/F	Child-Pugh	MELD	Blood Type Combination	Graft	GRWR
1	AIH	55	F	C (12)	24	B→O	Left	0.66%
2	LC type C	60	M	C (10)	17	A→O	Left	0.54%
3	Wilson's disease	40	F	B (8)	12	B→O	Left	0.83%
4	LC type C, HCC	55	M	C (12)	17	A→O	Left	0.63%
5	LC type C	57	F	C (11)	29	A→O	Left	1.2%
6	PBC	48	F	C (10)	12	B→A	Left	0.78%
7	Alcoholic LC Spur cell anemia	31	F	C (13)	29	AB→B	Right	1.02%
8	LC type C	50	F	B (9)	13	B→O	Right	1.46%
9	LC type B, HCC	56	M	B (8)	13	A→B	Right	0.81%
10	PBC	59	M	C (12)	29	AB→O	Right	0.98%

Abbreviations: M, male; F, female; MELD, model for end-stage liver disease; GRWR, graft-to-recipient weight ratio; AIH, autoimmune hepatitis; LC, liver cirrhosis; HCC, hepatocellular carcinoma; PBC, primary biliary cirrhosis.

days after transplantation. We speculated that repeated donor whole blood administration via the portal vein lead to the production of anti-idiotype antibody, preventing sensitization and humoral rejection. Therefore in this study, we investigated whether immunosuppression by intraportal transfusion of donor-specific leukocytes (DSLT) separated from donor whole blood would evoke immunological benefits in adult ABO-incompatible living donor liver transplantation (LDLT).

PATIENTS AND METHODS

Ten patients of mean age 51 ± 9 years (range, 31–60 years) underwent LDLT from ABO-incompatible donors (graft-to-recipient weight ratio, 0.90 ± 0.28; range, 0.54–1.46) between August 2003 and November 2007. The patient demographics are shown in Table 1. The primary liver diseases included the following: type C viral liver cirrhosis (n = 4), primary biliary cirrhosis (n = 2), autoimmune hepatitis (n = 1), type B liver cirrhosis with hepatocellular carcinoma (HCC; n = 1), Wilson's disease (n = 1), and Spur cell anemia caused by alcoholic cirrhosis (n = 1). Mean model for end-stage liver disease (MELD) score was 19.4 ± 7.3 (range, 12–29). Methicillin-resistant *Staphylococcus aureus* (MRSA) was positive in bacterial cultures of the pleural effusion and the TPE catheter in 2 patients.

Immunosuppression

The antirejection therapy included multiple preoperative plasmapheresis treatments, splenectomy, immunosuppression with FK506, steroid, and mycophenolate mofetil (MMF), as well as DSLT (Table 2). Two patients did not undergo preoperative TPE because of a low titer (<16 times) of donor-specific anti-A/B antibody. All patients underwent splenectomy at the time of transplantation. All subjects except 1 patient were preoperatively administered immunosuppression with FK506 and cyclophosphamide (CP) or MMF. One patient was not given preoperative immunosuppression because of a poor preoperative status. All patients were treated intraoperatively with rabbit anti-thymocyte globulin (RATG; 1.5 mg/kg intravenously, IV) and methylprednisolone (1 g intravenously [IV]). Postoperatively the patients were given RATG (1.5 mg/kg IV) on day 1. Intraportal bolus methylprednisolone was used for the first 7 days posttransplantation: 500 mg on day 1, 250 mg on days 2–4, and 120 mg on days 5–7. MMF was administered at 1 g/d from day 4; prednisolone (15 mg/body) was tapered to 5 mg/body from day 7 to 1 month after surgery and withdrawn within 2 months. FK506 was introduced on postoperative day 1 (0.15 mg/kg/d IV) as a continuous infusion to day 4. The target trough level of FK506 was 10–15 ng/mL on days 1–7, 8–10 ng/mL on days 8–21, and 5–8 ng/mL thereafter.

In addition to these conventional approaches, we performed 4 intraportal administrations of DSLT on days 1, 4, 7, and 10 after

Table 2. Perioperative Immunosuppression of ABO-Incompatible LDLT

	Preoperative				Operative		Postoperative			
No.	IgM/IgG	TPE	CP	FK506	Splenectomy	RATG	Steroid	MMF	PGE1	DSLT
1	32/0 → 2/0	2	50 mg–7 d	7 d	(+)	(+)	2 mo	26 mo	12 d	(+)
2	64/128 → 2/32	3	100 mg–2 d	2 d	(+)	(+)	28 d	10 d	12 d	(+)
3	4/8	0	100 mg–7 d	7 d	(+)	(+)	52 d	5 mo	16 d	(+)
4	32/64 → 8/32	3	50 mg–7 d	4 d	(+)	(+)	2 mo	12 d	14 d	(+)
5	32/128 → 4/64	3	MMF 500 mg–7 d	7 d	(+)	(+)	2 mo	2 mo	11 d	(+)
6	32/4 → 4/0	1	50 mg–6 d	3 d	(+)	(+)	53 d	AZA 1 mo	10 d	(+)
7	8/0	0	(−)	(−)	(+)	(+)	54 d	(−)	7 d	(+)
8	16/2 → 8/2	1	50 mg–2 d	1 d	(+)	(+)	22 d	(−)	13 d	(+)
9	32/4 → 32/4	2	50 mg–7 d	1 d	(+)	(+)	53 d	2 mo	12 d	(+)
10	A 64/128 → 16/64 B 64/128 → 16/64	2	25 mg–5 d	1 d	(+)	(+)	48 d	AZA 12 d	14 d	(+)

Abbreviations: IgM, Immunoglobulin M; IgG, Immunoglobulin G; TPE, total plasma exchange; CP, cyclophosphamide; RATG, rabbit anti-thymocyte globulin; MMF, mycophenolate mofetil; PGE1, prostaglandin E1; DSLT, donor-specific leukocyte transfusion; AZA, azathioprine.