検査：フォローアップ・維持療法[ ]

更新日時：----

調査年度		年度
維持療法 1	*1	
	詳細	
	目標トラフ値	ng/mL
維持療法 2	*1	
	詳細	
	目標トラフ値	ng/mL
維持療法 3	*1	
	詳細	
	目標トラフ値	ng/mL
維持療法 4	*1	
	詳細	
	目標トラフ値	ng/mL

列挙値一覧

No.	列挙値
*1	1：タクロリムス, 2：シクロスポリン, 3：プレドニゾロン, 4：MMF 5：シロリムス, 6：エベロリムス, 999：その他

検査：フォローアップ・転帰[ ]

更新日時：----

調査年度		年度	
転帰	*1		
死亡日			
死亡理由	☐拒絶反応	☐感染症	☐手術合併症
	☐リンパ腫	☐肝不全	☐その他
	詳細		

列挙値一覧

No.	列挙値
*1	1：生存, 2：死亡, 3：追跡不能

検査：フォローアップ・ドナーの転帰[ ]

更新日時：----

調査年度	年度
ドナー	*1
転帰	*2
最終生存確認日	
死亡日	
死亡理由	

列挙値一覧

No.	列挙値
*1	1：ドナー 1(小腸・多臓器移植の場合), 2：ドナー 2(肝・小腸同時移植にてドナーが異なる場合)
*2	1：生存, 2：死亡, 3：追跡不能

検査：病理診断・病理診断[ ]

更新日時：----

担当医師記入欄

組織採取日	
中央病理番号	
担当医師名	
担当医師の E-mail	
臨床所見	

病理医 1

医療機関名・記入者 1	
所見 1	

病理医 2

医療機関名・記入者 2	
所見 2	

病理医 3

医療機関名・記入者 3	
所見 3	

病理医 4

医療機関名・記入者 4	
所見 4	

病理医 5

医療機関名・記入者 5	
所見 5	

検査：合併症･合併症[ ]

更新日時：----

合併症	*1		
発生日			
転帰確認日			
転帰	*2		
詳細な経過			
拒絶反応の詳細	薬剤名	*3	
	その他詳細		
	投与量		mg/kg
	使用期間		日

列挙値一覧

No.	列挙値
*1	1：手術合併症, 2：拒絶反応, 3：GVHD, 4：感染症, 5：リンパ腫 6：他臓器障害
*2	1：回復, 2：軽快, 3：不変, 4：死亡
*3	1：ステロイドパルス, 2：OKT-3, 3：サイモグロブリン, 4：レミケード 5：ベルケード, 999：その他

検査：ドナーの移植による合併症･ドナーの移植による合併症[ ]

更新日時：----

移植による合併症	
ドナー	*1
発生日	
転帰確認日	
転帰	*2
詳細な経過	

列挙値一覧

No.	列挙値
*1	1：ドナー 1(小腸･多臓器移植の場合), 2：ドナー 2(肝･小腸同時移植にてドナーが異なる場合)
*2	1：回復, 2：軽快, 3：不変, 4：死亡

Ⅲ.研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Ueno T, Wada M, Hoshino K, Uemoto S, Taguchi T, Furukawa H, Fukuzawa M.	Impact of pediatric intestinal transplantation on intestinal failure in Japan: findings based on the Japanese intestinal transplant registry.	Pediatr Surg Int.	29巻 10号	P1065-P1070	2013
Chen W, Oue T, Ueno T, Uehara S, Usui N, Fukuzawa M.	Apelin is a marker of the progression of liver fibrosis and portal hypertension in patients with biliary atresia.	Pediatr Surg Int.	29巻 1号	P79-85	2013
Ueno T, Wada M, Hoshino K, Sakamoto S, Furukawa H, Fukuzawa M.	A national survey of patients with intestinal motility disorders who are potential candidates for intestinal transplantation in Japan.	Transplant Proc.	45巻 5号	P2029-P2031	2013
Ueno T, Takama Y, Masahata K, Uehara S, Ibuka S, Kondou H, Hasegawa Y, Fukuzawa M.	Conversion to prolonged-release tacrolimus for pediatric living related donor liver transplant recipients.	Transplant Proc.	45巻 5号	P1975-P1984	2013
上野豪久、福澤正洋	腸管不全患者における小腸移植の適応	小児外科	45巻 7号	P703-P706	2013
上野豪久、田口智章、福澤正洋	本邦小腸移植登録	移植	48巻 6号	P390-P394	2013
内田浩一郎, 谷口雅彦, 今井浩二, 永生高弘, 渡邉賢二, 宮本正之, 松坂俊, 鈴木和香子, 古川博之.	【肝移植-現状と展望】欧米・アジア移植の現状	臨床消化器内科	28巻 9号	P1217-P1226	2013
和田基、工藤博典、仁尾正記	ここまで来た小児小腸移植 小腸移植における免疫抑制療法	小児外科	45巻 7号	P721-P724	2013
和田基、工藤博典、仁尾正記	ここまで来た小児小腸移植 小腸移植ドナー、グラフトの評価・管理の現状と課題	小児外科	45巻 7号	P707-P710	2013

工藤博典、和田基、佐々木英之、佐藤智行、風間理郎、西功太郎、田中拡、中村恵美、山本聡史、仁尾正記	ここまで来た小児小腸移植　小腸グラフトストーマ閉鎖の経験	小児外科	45巻 7号	P745-P748	2013
和田基、工藤博典、山本聡史、仁尾正記	小児臓器移植の最前線 小児小腸移植	医学のあゆみ	244巻 10号	P913-P918	2013
星野健、高橋信博、石濱秀雄、藤村匠、富田紘史、阿部雄太、日比造、八木洋、藤野明浩、北郷実、板野理、篠田昌宏、尾原秀明、加藤友朗、北川雄光、黒田達夫.	小腸移植後長期生存の管理 小腸移植後術後合併症の諸問題.	移植	48巻 総会臨時	P254	2013
下島直樹、星野健、石濱秀雄、清水隆弘、藤村匠、加藤源俊、狩野元宏、富田 紘史、高里文香、藤野明浩、加藤友朗、田邉稔、広部誠一、北川雄光、黒田達夫.	【ここまで来た小児小腸移植】生体小腸移植における免疫抑制療法の工夫と治療成績	小児外科	45巻 7号	P729-P733	2013
Yamamoto Y, Fukuda K, Fuchimoto Y, Matsuzaki Y, Saikawa Y, Kitagawa Y, Morikawa Y, Kuroda T.	Cetuximab promotes anticancer drug toxicity in rhabdomyosarcomas with EGFR amplification in vitro.	Oncol Rep.	30巻 3号	P1081- P1086	2013
Tsuruyama T, Okamoto S, Fujimoto Y, Yoshizawa A, Yoshitoshi E, Egawa H, Nakase H, Aini W, Miyao M, Tamaki K, Yamabe H, Haga H, Uemoto S.	Histology of intestinal allografts: lymphocyte apoptosis and phagocytosis of lymphocytic apoptotic bodies are diagnostic findings of acute rejection in addition to crypt apoptosis.	Am J Surg Pathol	37巻	P178-P184	2013
Watanabe Y, Kanamori Y, Uchida K, Taguchi T.	Isolated hypoganglionosis: results of a nationwide survey in Japan.	Pediatr Surg Int	29巻 11号	P1127- P1130	2013

Honda S, Miyagi H, Suzuki H, Minato M, Haruta M, Kaneko Y, Hatanaka KC, Hiyama E, Kamijo T, Okada T, Taketomi A.	RASSF1A methylation indicates a poor prognosis in hepatoblastoma patients.	Pediatr Surg Int	29巻 11号	P1147-P1152	2013
Honda S, Okada T, Miyagi H, Minato M, Suzuki H, Taketomi A.	Spontaneous rupture of an advanced pancreatoblastoma: aberrant RASSF1A methylation and CTNNB1mutation as molecular genetic markers.	J Pediatr Surg.	48巻 4号	P29-P32	2013
Utsumi M, Umeda Y, Sadamori H, Nagasaka T, Takaki A, Matsuda H, Shinoura S, Yoshida R, Nobuoka D, Satoh D, Fuji T, Yagi T, Fujiwara T.	Risk factors for acute renal injury in living donor liver transplantation	evaluation of the RIFLE criteria	26巻 8号	P842-P852	2013
重田孝信、阪本靖介、李小康、黒川亮介、佐藤文平	ここまで来た小児小腸移植】 小腸虚血再灌流障害に対する水素の効果	小児外科	45巻 7号	P774-P778	2013
Maeda A, Kawamura T, Ueno T, Usui N, Eguchi H, Miyagawa S.	The suppression of inflammatory macrophage-mediated cytotoxicity and proinflammatory cytokine production by transgenic expression of HLA-E	Transpl Immunol	29巻 1-4号	P76-P81	2013
Ueno T, Wada M, Hoshino K, Uemoto S, Taguchi T, Furukawa H, Fukuzawa M.	Impact of pediatric intestinal transplantation on intestinal failure in Japan: findings based on the Japanese intestinal transplant registry	Pediatr Surg Int	29巻 10号	P1065-P1070	2013
Uehara S, Usui N, Kamiyama M, Masahata K, Nara K, Ueno T, Soh H, Oue T, Fukuzawa M.	Repair of congenital diaphragmatic hernias through umbilical skin incisions	Pediatr Surg Int	29巻 5号	P529-P532	2013
Ueno T, Wada M, Hoshino K, Sakamoto S, Furukawa H, Fukuzawa M.	A national survey of patients with intestinal motility disorders who are potential candidates for intestinal transplantation in Japan.	Transplant Proc	45巻 5号	P2029-P2031	2013

Ueno T, Takama Y, Masahata K, Uehara S, Ibuka S, Kondou H, Haisegawa Y, Fukuzawa M.	Conversion to prolonged-release tacrolimus for pediatric living related donor liver transplant recipients	Transplant Proc	45巻 5号	P1975- P1978	2013
上野豪久、正畠和典、井深秦司、銭谷昌弘、中畠賢吾、奈良啓悟、大割貢、上原秀一郎、大植孝治、臼井規朗	新生児嚢胞型総胆管拡張症に対する肝管空腸吻合術	小児外科	45巻 11号	P1185- P1191	2013
上野豪久、正畠和典、井深秦司、銭谷昌弘、中畠賢吾、奈良啓悟、上原秀一郎、大植孝治、臼井規朗	小腸移植術（レシピエント手術）	小児外科	45巻 8号	P851-P858	2013
上野豪久、福澤正洋	腸管不全患者における小腸移植の適応	小児外科	45巻 7号	P703-P706	2013
井深秦司、上野豪久	小腸移植における急性拒絶反応の抗ヒト胸腺細胞ウサギ免疫グロブリン（サイモグロブリン®）治療	小児外科	45巻 7号	P734-P737	2013
Nishida N, Sasaki M, Kurihara M, Ichimaru S, Wakita M, Bamba S, Andoh A, Fujiyama Y, Amagai T.	Changes of energy metabolism, nutritional status and serum cytokine levels in patients with Crohn's disease after anti-tumor necrosis factor-α therapy	J Clin Biochem Nutr	53巻 2号	P122-P127	2013
Takahashi K, Imaeda H, Fujimoto T, Ban H, Bamba S, Tsujikawa T, Sasaki M, Fujiyama Y, Andoh A.	Regulation of eotaxin-3/CC chemokine ligand 26 expression by T helper type 2 cytokines in human colonic myofibroblasts	Clin Exp Immunol	173巻 2号	P323-P331	2013
Wada N, Zhan M, Hori Y, Honma K, Ikeda J, Morii E.	Characterization of subpopulation lacking both B-cell and plasma cell markers in Waldenstrom macroglobulinemia cell line.	Lab Invest	94巻 1号	P79-P88	2014

位田忍.	小腸不全（長期ＴＰＮ患者、H類縁疾患、CIIPなど）特集小児科から内科へのシームレスな診療を目指して	診断と治療社	101	P1867-P1872	2013
位田忍、蛇口達造.	Child first Go together!成長のきせき－軌跡・奇跡－をともに歩もう．小児の在宅栄養支援の問題点と今後の展開	日本小児栄養消化器肝臓学会雑誌	27巻 1号	P54	2013

Ⅳ.研究成果の刊行物・別刷

Pediatr Surg Int (2013) 29:1065–1070
DOI 10.1007/s00383-013-3392-7

ORIGINAL ARTICLE

Impact of pediatric intestinal transplantation on intestinal failure in Japan: findings based on the Japanese intestinal transplant registry

Takehisa Ueno · Motoshi Wada · Ken Hoshino · Shinji Uemoto · Tomoaki Taguchi · Hiroyuki Furukawa · Masahiro Fukuzawa

Published online: 28 August 2013

Abstract
Introduction We assessed the impact of intestinal transplantation on Japanese pediatric patients with intestinal failure with data from the Japanese intestinal transplant registry.
Methods Standardized forms were sent to all known intestinal transplantation programs, requesting information on transplants performed between 1996 and June 30, 2012. Patients younger than 18 years were analyzed. Patient and graft survival estimates were obtained using the Kaplan–Meier method.
Results Of the 14 intestinal transplants, 4 were deceased and 10 were living donor transplants. The primary indications were: short gut syndrome ($n = 7$), intestinal functional disorder ($n = 6$), and re-transplantation ($n = 1$). The overall 1- and 5-year patient survival rates were 77 and 57 %, respectively. In transplants performed after 2006 ($n = 6$), the one-year patient survival rate was 83 %, and the 5-year survival rate was 83 %. Graft one- and 5-year survival rates were 83 and 83 %, respectively. The living-related transplant survival rate was 80 % at 1 year and 68 % at 2 years, compared to 67 and 67 % for cadaveric transplant recipients. There were no statistically significant differences in patient ($p = 0.88$) and graft ($p = 0.76$) survival rates between living donor and cadaveric transplant recipients. All current survivors discontinued PN.
Conclusion Intestinal transplantation has become an effective therapy for patients with intestinal failure who cannot tolerate PN.

Keywords Intestinal transplant · Pediatric transplant · Japanese registry

T. Ueno (✉)
Department of Pediatric Surgery, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan
e-mail: ueno@pedsurg.med.osaka-u.ac.jp

M. Wada
Department of Pediatric Surgery, Tohoku University School of Medicine, Sendai, Japan

K. Hoshino
Department of Surgery, Keio University Graduate School of Medicine, Tokyo, Japan

S. Uemoto
Department of HBP Surgery and Transplantation, Kyoto University, Kyoto, Japan

T. Taguchi
Department of Pediatric Surgery, Kyusyu University School of Medicine, Fukuoka, Japan

H. Furukawa
Department of Gastroenterologic and General Surgery, Asahikawa Medical University, Asahikawa, Japan

M. Fukuzawa
Osaka Medical Center and Research Institute for Maternal and Child Health, Izumi, Japan

Introduction

Intestinal failure is caused by a critical reduction of functional gut mass to below the minimal amount necessary for adequate digestion and absorption to satisfy nutrient and fluid requirements for maintenance in adults and growth in children [1]. The most common type of intestinal failure is short bowel syndrome with an estimated incidence of 3–5 cases per 100 000 births per year

[2]. Advances in neonatal intensive care, anesthesia, nutritional support, and surgical techniques have improved the survival of children, so the prevalence of common causes of short bowel syndrome, including gastroschisis, necrotizing enterocolitis, and intestinal atresia has likely increased in recent years [3]. Some survivors, however, develop irreversible intestinal failure. The prognosis for intestinal failure related to short gut syndrome and intestinal motility disorders has improved dramatically owing to the development of parenteral nutrition (PN). Some children achieve long-term survival with PN at home with a relatively good quality of life, but others develop serious side effects that can eventually lead to death. However, PN-related complications, such as loss of venous access and intestinal failure-associated liver disease (IFALD), are still major problems for patients with intestinal failure [4]. Intestinal transplantation can significantly improve their prognosis and quality of life. Early efforts to transplant the small bowel have failed due to refractory graft rejection and sepsis. Outcomes improved during the early 1990s, but survival rates were still inferior to those for other organ transplants. Over the past 5 years, individual centers have reported improved outcomes with better long-term intestinal engraftment.

The first intestinal transplant in Japan was performed in 1996. The total number of intestinal transplants in Japan has increased to 24 as of June 2011. We assessed the impact of intestinal transplantation on Japanese pediatric patients with intestinal failure based on data from the Japanese intestinal transplant registry.

Methods

Standardized forms were sent to all known intestinal transplantation programs, requesting information on intestinal transplants performed between 1996 and June 30, 2012. The data included age, sex, date of birth, date of transplant, type of donor (deceased or living), pre-transplant status (home or hospital), underlying disease, procedure, ABO blood type, immunosuppression regimen (induction and maintenance therapy), and post-transplant status (PN requirement, intravenous (IV) fluid requirement, and daily life restrictions). Patients under 18 years of age were analyzed. The data were entered into a Microsoft Excel spreadsheet and analyzed with JMP version 10.0 (SAS Institute Inc, USA). Patient and graft survival estimates were obtained using the Kaplan–Meier method. For survival analysis, failure was defined as occurring on the date of graft removal or death. A p value <0.05 was considered statistically significant. This study was approved by the institutional review board.

Results

Four programs provided data on 14 grafts in 13 patients who were received transplants between 1 April 1996, and 30 June 2012 in Japan. The participation rate was 100 %. All intestinal transplants performed in Japan are captured in the registry database. All patients were followed, unless the patient has passed way. Ten grafts were obtained from living donors, and four cases involved deceased donors. The annual number of intestinal transplants, according to organ donation type, is shown in Fig. 1. Prior to 2005, 25 % of patients who underwent transplantation were called in from home, as compared with 66 % in the last 5 years (Fig. 2).

There were nine male and five female recipients. The age distribution of the recipients is shown in Fig. 3. Two-thirds of the patients were over 6 years old. The youngest recipient was 8 months. The causes of intestinal failure requiring intestinal transplantation are shown in Fig. 4. Approximately half of the patients had conditions that result in short gut syndrome.

Most patients ($n = 13$) received isolated intestinal transplants. There was only one case of simultaneous liver-intestinal transplantation from two living-related donors. Twelve patients received grafts from donors with an identical ABO blood type. Two patients received grafts from ABO compatible donors. There were no transplants involving ABO incompatibility. All patients were on tacrolimus maintenance therapy. The types of induction therapy used are shown in Fig. 5. Antibody-based induction therapy and tacrolimus-based maintenance immunosuppression were used even if the medication was not commercially available in Japan.

Graft and patient overall survival as of June 2011 are shown in Kaplan–Meier plots (Fig. 6a, b, respectively). The one-year and 5-year patient survival rates were 77 and 57 %, respectively, comparable with rates from the international intestinal transplant registry. Five recipients died.

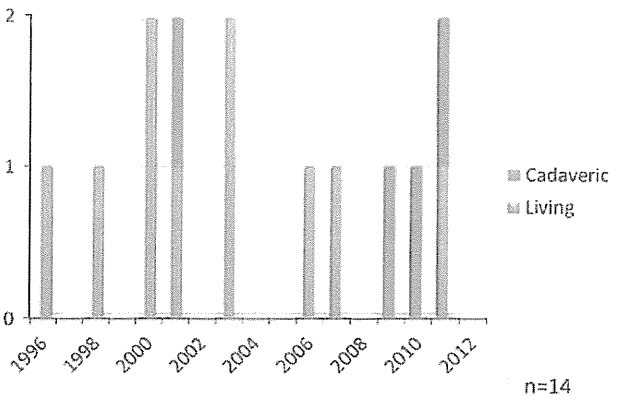

Fig. 1 Number of intestinal transplants by year

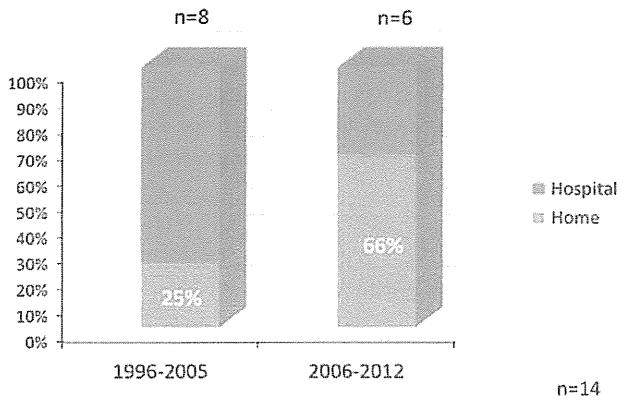

Fig. 2 Pre-transplant patient status

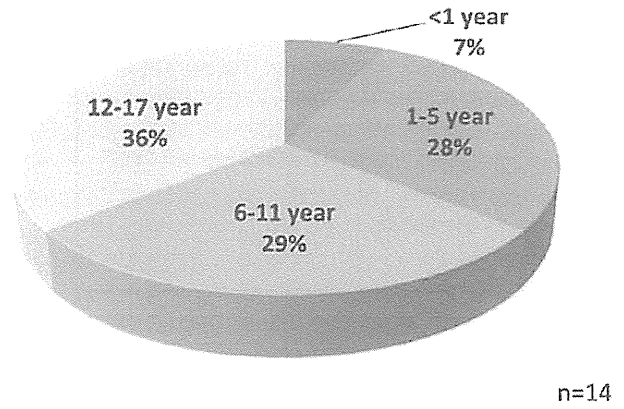

Fig. 3 Recipient age at transplant

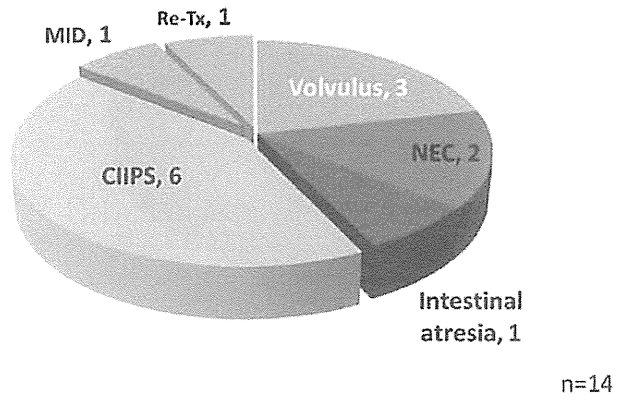

Fig. 4 Cause of intestinal failure *NEC* necrotizing enterocolitis, *CIIPS* chronic idiopathic intestinal pseudo-obstruction syndrome, *MID* microvillus inclusion disease, *Re-Tx* Re-transplant

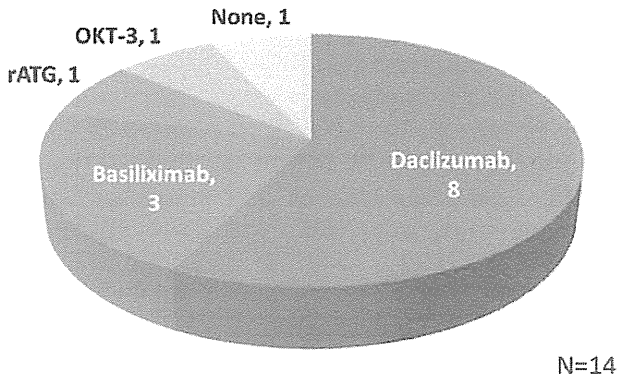

Fig. 5 Induction immunosuppression therapy *rATG* rabbit anti-thymus globulin, *OKT-3* anti-CD3 monoclonal antibody

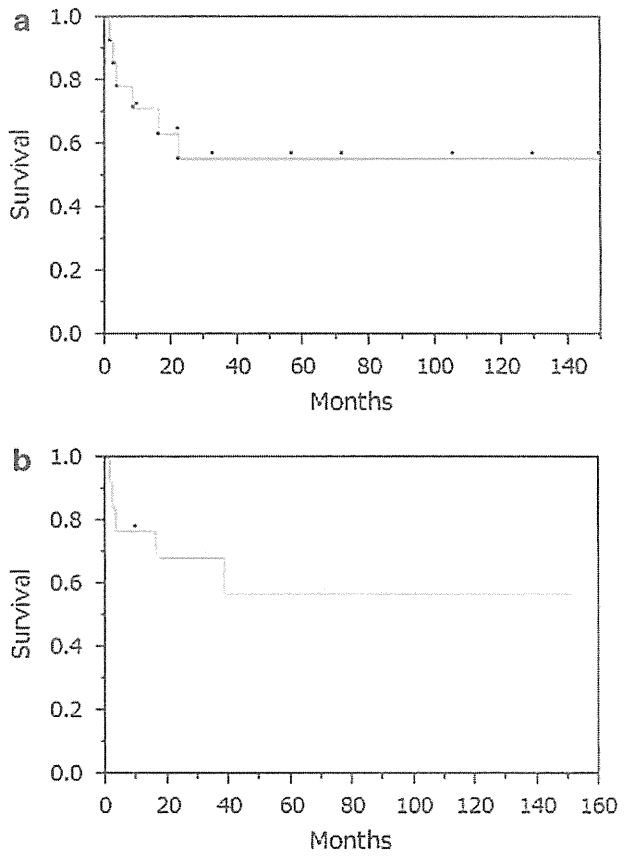

Fig. 6 Overall graft (a) and patient (b) survival

The causes of death included sepsis ($n = 3$), post-transplant lymphoma ($n = 1$) and intra cranial hemorrhage ($n = 1$).

The 1-year overall graft survival rate was 80 % for cadaveric grafts versus 50 % for living donor grafts ($p = 0.76$), as shown in Fig. 7a. The 1-year overall patient survival rate was 80 % for cadaveric grafts versus 67 % for living donor grafts ($p = 0.88$), as shown in Fig. 7b.

Graft survival improved over the last 5 years. The one- and five-year graft survival rates were 83 and 83 % for 2006–2011 versus 63 and 38 % for 1996–2005 ($p = 0.14$), as shown in Fig. 8a. The 1- and 5-year patient survival rates were 83 and 83 % for 2006–2011 versus 71 and 43 % for 1996–2005 ($p = 0.27$), as shown in Fig. 8b.

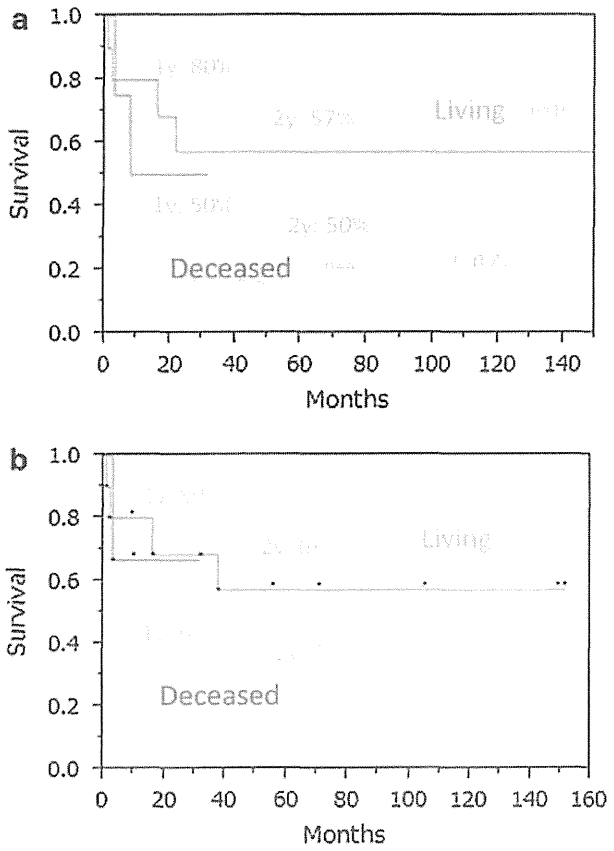

Fig. 7 Graft (a) and patient (b) survival according to graft type

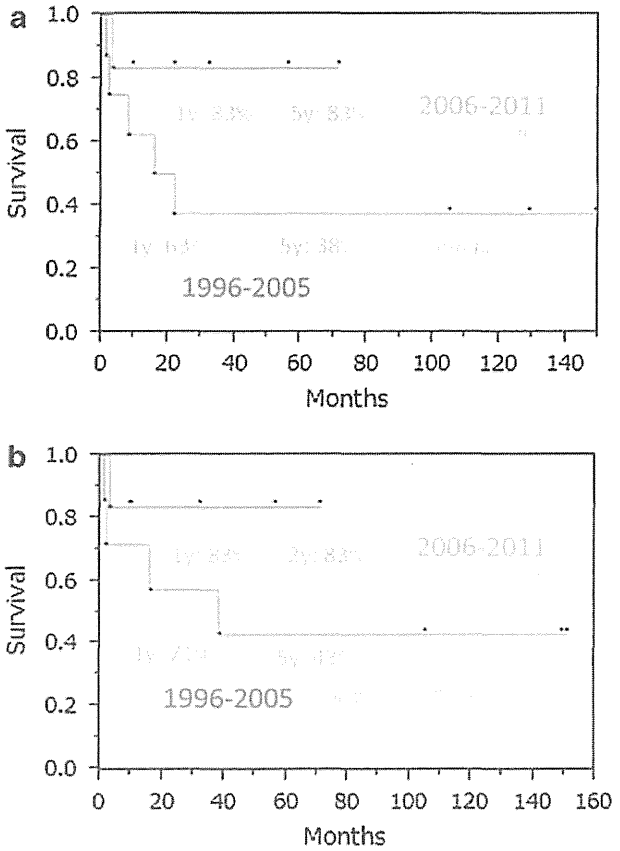

Fig. 8 Graft (a) and patient (b) survival by era

Graft function in terms of PN dependence was excellent. All patients became PN-free after intestinal transplantation, although two-thirds of patients require continuous or intermittent intravenous fluid support. Of the eight patients who were alive at the time of data collection, all patients were off parenteral nutrition, with three patients requiring intravenous fluids daily, two patients requiring intravenous fluids occasionally (Fig. 9). Most recipients stopped parenteral supplementation, eat, and have resumed normal activities. Of the seven surviving patients 1 year after transplant, six lead a full life.

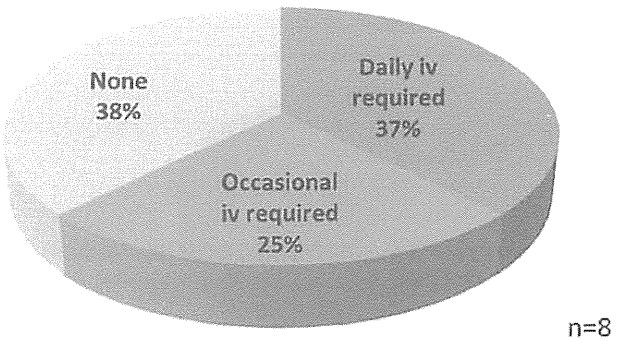

Fig. 9 Intravenous (IV) fluid requirement after intestinal transplantation

Discussion

Children with intestinal failure are at risk for numerous complications, especially PN-related complications. For example, loss of venous access and IFALD are still major problems for patients with intestinal failure because they are potentially life-threatening [4].

Catheter-related bloodstream infections were common in patients with intestinal failure [5]. Survival of children with chronic intestinal failure has increased as result of home PN. Adequate central venous accesses crucial for the successful management of home PN, but venous access can be complicated by episodes of catheter-associated infection, repeated procedures to replace catheters, and catheter-related thrombosis. Management and prevention of catheter-related thrombosis are of vital importance. [6].

IFALD can be a progressive and fatal entity in children with short gut syndrome. Parenteral fish oil-based fat emulsions are safe and may be effective in the treatment of PN-associated liver disease [7]. A lipid reduction protocol may prevent cholestasis [8]. Despite all efforts to prevent

complications, some children develop end-stage intestinal failure.

As outcomes of intestinal transplantation have improved, it has become the definitive treatment for patients with intestinal failure who cannot tolerate PN. Over the past decade, intestinal transplantation has become accepted as standard therapy for patients with life-threatening complications of PN in many countries [9, 10].

Currently, evaluation for transplant is recommended for pediatric patients with intestinal failure who are doing poorly on PN due to loss of more than 50 % of the major intravenous access sites (two out of four sites include both internal jugular veins and subclavian veins); recurrent severe catheter-related sepsis; progressive liver dysfunction; or impaired renal function due to massive gastrointestinal fluid loss.

Timely referral to an intestinal transplant program is important for children with intestinal failure because intestinal transplantation is easier and safer with adequate central venous access and normal liver function [11]. For patients who undergo intestinal transplantation, patient survival is similar to remaining on PN. The inclination is therefore to move towards earlier transplantation and avoiding the need for concomitant liver transplantation [12].

The 2011 report of the intestinal transplant registry confirmed that intestinal transplantation has become a definitive therapeutic option for patients with intestinal failure. By 2011, 2,611 intestinal transplants had been performed throughout the world with 79 participating centers worldwide. Three types of intestinal transplantation are performed: (1) isolated intestinal transplantation (1,184 cases); (2) liver and intestine transplantation (845 cases); and (3) multivisceral transplantation (619 cases). In pediatric patients, two-thirds acquired short gut syndrome as a result of congenital disease, including gastroschisis, intestinal atresia, and necrotizing enterocolitis [10].

On the other hand, only 14 intestinal transplants have been performed in patients under 18 years of age in Japan. The number is relatively small, although it is estimated that 40 pediatric patients require intestinal transplants nationwide [13]. In the Japanese experience, the 1- and 5-year overall patient survival rates are 77 and 57 %. The one-year survival rate was 83 % for the last 5 years. These are considered acceptable results for the treatment of intestinal failure. Our results in Japan are comparable with results worldwide, even though there are only one or two cases per year performed in Japan compared to over 100 intestinal transplants yearly performed in the world. In our opinion, children with intestinal failure should be treated with intestinal transplantation in Japan as well as in other countries when feasible.

There were two major reasons for the low number of intestinal transplants in Japan. One reason is the lack of available organs. For a long time, relatively few donations from deceased donors were obtainable in Japan. As with other solid organs, most intestinal transplants in Japan are performed with living-related donors. Although the situation has changed due to the new Act on Organ Transplantation, which went into effect in 2010, the number of deceased donations has not increased dramatically, especially among pediatric donors.

The financial barrier is the other, more profound reason preventing the greater use of intestinal transplantation in Japan. Since the procedure is not covered by health insurance, either the patient or the transplant center must pay the considerable costs out of pocket.

Some patients develop liver failure with short gut syndrome. These patients need simultaneous liver-intestinal transplants. A combined liver-intestine transplant has less risk of acute rejection than an isolated intestinal transplant because the liver may have protective effects on the intestine [10]. Combined liver and intestine transplants are the most frequent procedure in infants and children, accounting for half of the cases. Current organ allocation guidelines have not allowed for simultaneous combined liver–intestine organ retrieval until the law was revised in 2010; thus, simultaneous liver–intestine transplantation with a deceased donor graft had been impossible. Isolated intestinal transplantation, the preferred procedure, was offered to patients with limited IV access or recurrent line infections. Combined liver–intestine transplants are performed for treatment of irreversible liver disease caused by PN. Isolated intestinal transplantation from deceased donors following living-related liver transplantation, referred to as sequential combined liver-intestine transplantation, has been attempted.

Previously, the law on organ transplantation banned donors below 15 years of age. This is the main reason why there were relatively few pediatric transplant recipients. Intestinal transplant for infants was previously not possible because of donor-recipient size mismatch. Only a small number of pediatric transplants have been performed. Pediatric patients still await the opportunity to benefit from intestinal transplantation. Moreover, younger patients sometimes develop liver failure [3]. Multivisceral transplants are recommended for the treatment of severe gastrointestinal motility disorders [14]. However organ allocation guidelines do not allow for multivisceral organ retrieval. Further reform of allocation guidelines is needed.

This analysis found that improved induction immunosuppression is strongly associated with higher survival rates. The use of antibody induction therapy appears to be particularly important for the success of intestinal transplantation, possibly due to the large lymphoid mass of this type of graft [15]. Induction with rabbit anti-thymus globulin (rATG) minimized the amount of tacrolimus needed for

maintenance immunosuppression, facilitated the long-term control of rejection, and decreased the incidence of opportunistic infections, resulting in a high rate of patient and graft survival [16]. The combination of rATG and rituximab was an effective induction therapy according to our preliminary data. The number and severity of rejection episodes increased when the liver was not included as part of the graft. An immunosuppression regimen including rATG, rituximab, and steroids may have a protective effect against post-transplant lympho proliferative disease (PTLD) and chronic rejection [17]. Sirolimus is a safe rescue therapy in children with intestinal transplants when tacrolimus is not well tolerated. Renal function and hematologic disorders seem to improve, although other simultaneous strategies could be involved [18]. However, those medications are not commercially available with insurance coverage in Japan. Children after intestinal transplant should be managed with limited immunosuppression.

Preemptive assessments are recommended, even for patients doing well on PN, and for infants and adults with an ultra-short gut or for infants with total intestinal aganglionosis or microvillus inclusion disease, since patients with these findings have very poor survival rates on PN [15].

Early referral and listing are important for successful outcomes. Presently, because of the risks involved as well as financial reasons, transplants are rarely offered to pediatric patients in Japan. However, this treatment will undoubtedly become more common over time as the results of intestinal transplantation continue to improve.

Conclusion

Intestinal transplantation has become the definitive treatment for patients with chronic intestinal failure. Since intestinal transplantation in Japan has yielded satisfactory results, indications for the procedure should be expanded. The national health insurance should cover intestinal transplants to reduce the incidence of PN-related complications. Systems facilitating combined simultaneous liver–intestine and multi-organ transplants should be developed. We continue to work on reforming national health insurance coverage and realizing multi-organ transplantation in Japan.

Acknowledgments This research was partially supported by Health Labor Sciences Research Grant of Ministry of Health, Labor and Welfare, Japan. Japanese intestinal transplant registry is managed by the Japanese Society for Intestinal Transplantation. Also, the authors thank the following institutions for the cooperation in the survey.HBP Surgery and transplantation, Kyoto University: Pediatric Surgery, Tohoku University School of Medicine; Surgery, Keio University Graduate School of Medicine; Pediatric Surgery, Kyusyu University School of Medicine; Pediatric Surgery, Osaka University Graduate School of Medicine.

References

1. Goulet O, Ruemmele F (2006) Causes and management of intestinal failure in children. Gastroenterology 130(2 Suppl 1): S16–S28
2. DeLegge M, Alsolaiman MM, Barbour E et al (2007) Short bowel syndrome: parenteral nutrition versus intestinal transplantation. Where are we today? Dig Dis Sci 52(4):876–892
3. Wales PW, de Silva N, Kim J et al (2004) Neonatal short bowel syndrome: population-based estimates of incidence and mortality rates. J Pediatr Surg 39(5):690–695
4. Maroulis J, Kalfarentzos F (2000) Complications of parenteral nutrition at the end of the century. Clin Nutr 19(5):295–304
5. Cole CR, Frem JC, Schmotzer B et al (2010) The rate of bloodstream infection is high in infants with short bowel syndrome: relationship with small bowel bacterial overgrowth, enteral feeding, and inflammatory and immune responses. J Pediatr 156(6):941–947 947. e1
6. van Ommen CH, Tabbers MM (2010) Catheter-related thrombosis in children with intestinal failure and long-term parenteral nutrition: how to treat and to prevent? Thromb Res 126(6):465–470
7. Gura KM, Lee S, Valim C et al (2008) Safety and efficacy of a fish-oil-based fat emulsion in the treatment of parenteral nutrition-associated liver disease. Pediatrics 121(3):e678–e686
8. Cober MP, Teitelbaum DH (2010) Prevention of parenteral nutrition-associated liver disease: lipid minimization. Curr Opin Organ Transpl 15(3):330–333
9. Magee JC, Krishnan SM, Benfield MR et al (2008) Pediatric transplantation in the US, 1997–2006. Am J Transpl 8(4 Pt 2):935–945
10. Grant D (2011) Small bowel transplant Registry. In: 12th International Small Bowel Transplant Symposium. Washington DC
11. Rodrigues AF, van Mourik ID, Sharif K et al (2006) Management of end-stage central venous access in children referred for possible small bowel transplantation. J Pediatr Gastroenterol Nutr 42(4):427–433
12. Sudan D (2010) Long-term outcomes and quality of life after intestinal transplantation. Curr Opin Organ Transpl 15(3):357–360
13. Ueno TW, Hoshino M, Sakamoto K, Furukawa S, Fukuzawa H, M. (2013) A national survey of patients with intestinal motility disorder who are potential candidate for intestinal transplantation in Japan. Transpl Proc 45(5):2029–2031
14. Tzakis AG, Kato T, Levi DM et al (2005) 100 multivisceral transplants at a single center. Ann Surg 242(4):480–490 discussion 491–3
15. Grant D, Abu-Elmagd K, Reyes J et al (2005) 2003 report of the intestinal transplant registry: a new era has dawned. Ann Surg 241(4):607–613
16. Reyes J, Mazariegos GV, Abu-Elmagd K et al (2005) Intestinal transplantation under tacrolimus monotherapy after perioperative lymphoid depletion with rabbit anti-thymocyte globulin (thymoglobulin). Am J Transpl 5(6):1430–1436
17. Vianna RM, Mangus RS, Fridell JA et al (2008) Induction immunosuppression with thymoglobulin and rituximab in intestinal and multivisceral transplantation. Transplantation 85(9): 1290–1293
18. Andres AM, Lopez Santamaria M, Ramos E et al (2010) The use of sirolimus as a rescue therapy in pediatric intestinal transplant recipients. Pediatr Transpl 14(7):931–935