Liver failures from ultra-short bowel syndrome on the intestinal transplant waiting list: A retrospective study.

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Grant information: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Key words: Liver failure, Short bowel syndrome, Intestinal transplantation, Pediatric

Abbreviations: acute cellular rejection, ACR; acute renal failure, ARF; continuous hemodiafiltration, CHDF; chronic idiopathic intestinal pseudo-obstruction syndrome, CIIPS; catheter related blood stream infection, CRBSI; intestinal failure, IF; intestinal failure associated liver disease, IFALD; intestinal transplantation, ITx; living donor liver transplantation, LDLT; liver failure, LF

Tables: ___2____

Figures: ___1____ (color – No)

Abstract:

BACKGROUND: Patients with intestinal failure (IF) are candidates for intestinal transplantation (ITx). In Japan, these patients have few opportunities to undergo cadaveric ITx because of low rates of organ donation. The donor criteria and recipient priority for ITx are still unknown. We reviewed our cases of IF to investigate which patients should be prioritized for ITx.

METHODS: Patients with IF who were registered as candidates for cadaveric ITx between January 2010 and November 2015 in our institute were included in this retrospective study. Their data were gathered from their charts and analyzed.

RESULTS: Five patients were included. Their primary diseases included total colon aganglionosis (n = 1), chronic idiopathic intestinal pseudo-obstruction syndrome (CIIPS) (n = 2), SMV embolization (n = 1), and graft loss after ITx (n = 1). Two patients died of liver failure (LF) during the waiting period. The remaining three are now alive and waiting for transplantation. The lengths of the remaining intestine were more than 20 cm in living cases, but less than 20 cm in fatal cases. In the fatal cases, they had several episodes of catheter related blood stream infection (CRBSI), which caused LF and acute renal failure (RF).

CONCLUSIONS: We identified two patients with less than 20 cm residual small bowel who died after acute deterioration of liver function. Patients with ultra-short bowel could have a higher risk of LF. Therefore, they should be referred as soon as possible to a specialized hospital where ITx is a choice of treatment for IF.

Manuscript:

Introduction:

Patients with intestinal failure (IF) have been considered as candidates for intestinal transplantation (ITx) owing to the high risk of death from intestinal failure and associated liver disease (IFALD). Some studies showed that significant hepatic fibrosis occurring in patients with IF may regress appreciably after isolated ITx.[1,2] However, patients in Japan have few opportunities for undergoing cadaveric ITx because of the rarity of organ donation.

Historically, patients with short bowel syndrome (SBS), especially those with shorter residual small intestine, have been closely associated with IF and subsequent worse over all patient outcomes. Despite this correlation, however, there are a few studies that specifically address the outcomes of patients with extremely short bowel lengths, also referred to as ultrashort, which have usually been defined as having less than 20–25 cm of small intestine.[3-5] Some of these reports showed that such patients experienced multiple catheter related blood stream infections (CRBSIs) because they remained parenteral nutrition dependent,[5] and that IFALD is the only significant negative prognostic factor that may require referral for ITx in these patients.[3]

The recipient criteria for ITx include some factors, such as the severity of IFALD, the frequency of CRBSI, and the number of residual veins available for central venous access.[6,7] However, even by using such criteria, it is often difficult to decide which patients should be prioritized for transplantation and when the best timing for ITx could be, even if we selected a marginal donor.

In this retrospective study, we reviewed our cases of patients who had been registered as candidates for cadaveric ITx in order to investigate which patients have worse prognoses.

Methods:

Patients with IF who had been registered as candidates for cadaveric ITx between January 2010 and November 2015 in our institute were included in this study. The data of these patients,

including outcome (dead or alive), primary disease, sex, age at registration, laboratory data (total bilirubin, albumin, prothrombin time [PT], citrulline, pre-albumin), the pathological status of liver fibrosis, the residual intestinal length at registration, and the duration of being a candidate were collected from their charts and analyzed. We selected those laboratory data to evaluate the status of the liver, small intestine, and nutrition of these patients. Liver fibrosis status was evaluated with the new Inuyama classification system (F0, no fibrosis; F1, portal fibrosis widening; F2, portal fibrosis widening with bridging fibrosis; F3, bridging fibrosis plus lobular distortion; F4, liver cirrhosis). Survival was estimated with the Kaplan-Meier method. The survival estimates were compared by using the log-rank test between the patients with less than 20 cm of small intestine and those with more than 20 cm. The threshold for significance was $P < 0.05$. Statistical analyses were conducted using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

Results:

Five patients (two men and three women) were enrolled in this study. Their demographic characteristics are shown in Table 1. The median age at registration of these patients was 24 years (range 13–27). The primary diseases were total colon aganglionosis (n = 1), chronic idiopathic intestinal pseudo-obstruction syndrome (CIIPS) (n = 2), SMV embolization (n = 1), and graft loss after ITx (n = 1). The residual length of the small intestine ranged from 0 to 80 cm. Two patients died and the remaining three patients are still alive. The residual lengths in the dead patients were both less than 20 cm, whereas those in the living patients were more than 20 cm.

The clinical courses of these patients are shown in Figure 1. Liver fibrosis status progressed from F2 to F3–4 despite omegaven and GLP-2 analog administration in case 1, remained at F2 in case 2, rapidly progressed from F2 to F4 with repetitive infections in case 3, and remained at F2 and F0 without any infections in cases 4 and 5, respectively. In the dead patients, their fibrosis status

deteriorated more rapidly with several episodes of CRBSI than the living patients during the waiting period for ITx. In consequence, they died 4 months (case 3) and 1 month (case 1) after the point when an acute deterioration of liver function occurred, respectively.

Table 2 shows the comparison of liver fibrosis status and laboratory data between the living and dead patients. The dead patients tended to have higher total bilirubin at the time of registration than the living patients. They also had lower albumin, PT, and citrulline. The differences of these values tended to be more apparent at the last time in a healthy state. These data could indicate that these dead patients had worse liver and intestinal function at the time of registration, and these functions and their nutritional status deteriorated more rapidly than living patients during the waiting period for ITx.

In the survival curve (not shown), although there was not a significant difference between patients with less than 20 cm of small intestine and those with more than 20 cm because of the small number of patients in this study ($p = 0.225$), patients with less than 20 cm tended to die earlier than those with more than 20 cm.

Discussion:

Patients with SBS are at risk of severe metabolic, renal, and hepatobiliary complications in addition to central venous catheter infections, and SBS severity depends on the residual intestinal length.[8] The interruption of the normal enterohepatic circulation of biliary salts causes an abnormal metabolism of biliary acids. This predisposes to bacterial translocation and systemic sepsis, causing hepatobiliary dysfunction commonly referred to as IFALD, one of the most prevalent and severe complications in SBS patients.[9]

There are few reports on patients with ultra-short bowel (USB) syndrome so far, and one of these reports demonstrated that patients who died showed an earlier onset of liver disease with clinical and laboratory features of severe cholestasis and fibrosis, and the authors concluded that early onset

and advanced liver disease was the only significant extraintestinal factor influencing the clinical outcome of patients with USB syndrome.[3] Our results are consistent with these reports and indicate that patients with SBS, especially with less than 20 cm of small intestine, or USB, could easily have worse liver function, and CRBSI could serve as a trigger to further deterioration to end stage liver disease.

A recent study has shown that patients with end stage liver cirrhosis together with extremely poor nutritional status or with renal insufficiency were excluded from ITx and the 7-year survival rate of such patients was only 16.6%, whereas that the 7-year survival rate of the patients who were listed for ITx and actually underwent ITx was 74.6%.[10] A previous report demonstrated that residual small bowel length was the major predictor of mortality in SBS.[11] These data could indicate that patients with USB lose their opportunities for undergoing ITx once they develop end stage liver disease and/or renal failure, and that, as a result, such patients have poorer prognoses. On the other hand, Fiel et al demonstrated that hepatic fibrosis in patients with IF could regress to some extent after ITx, and concluded that cirrhosis related to IF might be rapidly reversible after ITx.[1,2] Our results together with these reports could indicate that patients with less than 20 cm of small intestine, or USB, should be referred as soon as possible to a specialized hospital where ITx is one of the treatments for IF before liver damage reaches the end stage.

In conclusion, we identified two patients with less than 20 cm of small intestine who experienced an acute deterioration of liver function and died due to LF. Patients with such extremely short bowel lengths can die from LF earlier than others. Therefore, these patients should be prioritized for ITx and marginal donors or living donor ITx might be considered for them.

Acknowledgement:

We would like to thank Editage (www.editage.jp) for English language editing.

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Table 1. Patients' characteristics

Case	Age at registration (year)	Sex	Primary disease	Residual intestinal length (cm)	Waiting time (month)	Outcome
1	31	M	Acute cellular rejection after ITx	15	31	Dead
2	27	F	Total colon aganglionosis	80	36	Alive
3	24	F	SMV embolization	0	14	Dead
4	13	M	CIIPS	70	8	Alive
5	6	F	CIIPS	50	9	Alive

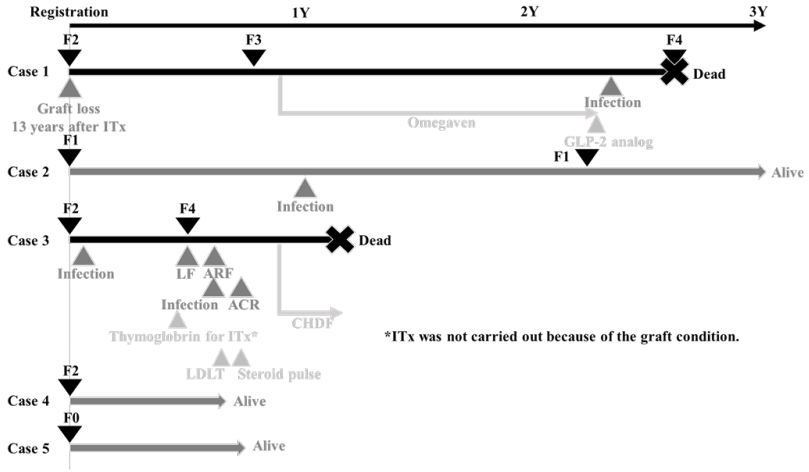
CIIPS: chronic idiopathic intestinal pseudo-obstruction syndrome

Table 2. Representative laboratory data

		Dead	Alive	P
at registration	**Liver fibrosis (F)**	1.50 (1.25-1.75)	1.00 (0.50-1.50)	0.76
	T-Bil (mg/dL)	1.45 (0.88-2.03)	0.80 (0.50-0.85)	0.80
	Alb (g/dL)	3.20 (2.95-3.45)	3.80 (3.75-4.00)	0.24
	PT (%)	57.5 (49.8-65.3)	69.0 (62.5-79.5)	0.80
	Citrulline (μmol/L)	16.2 (13.7-18.6)	28.9 (20.5-29.1)	0.40
	Pre-Alb (mg/dL)	17.8 (16.2-19.3)	17.1 (15.0-19.8)	1.00
at the latest	**Liver fibrosis (F)**	2.50 (2.25-2.75)	1.50 (1.25-1.75)	0.41
	T-Bil (mg/dL)	1.85 (1.63-2.08)	0.50 (0.35-1.05)	0.40
	Alb (g/dL)	2.85 (2.73-2.98)	3.50 (3.45-3.90)	0.20
	PT (%)	41.0 (41.0-41.0)	75.0 (72.5-78.5)	0.14
	Citrulline (μmol/L)	2.70 (1.35-4.05)	16.5 (14.0-22.4)	0.20
	Pre-Alb (mg/dL)	10.0 (9.85-10.2)	22.5 (18.2-23.3)	0.20

median (range)

Figure 1. Patients' clinical course and results of liver biopsy



F: liver fibrosis status evaluated with the new Inuyama classification system. acute cellular rejection, ACR; acute renal failure, ARF; continuous hemodiafiltration, CHDF; intestinal transplantation, ITx; living donor liver transplantation, LDLT; liver failure, LF.