Table 2 Risk factors for the event

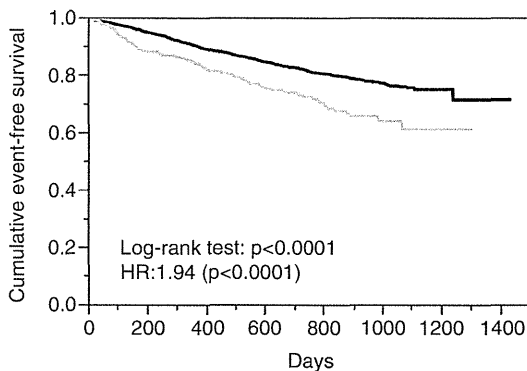| Explanatory variable		Univariate				Multivariate			
		Hazard ratio	P-value	95% CI		Hazard ratio	P-value	95% CI	
				Lower limit	Upper limit			Lower limit	Upper limit
Sex	Male/female	1.18	0.0625	0.99	1.40	1.18	0.0685	0.99	1.42
Age (years)		1.01	0.0190	1.00	1.02	1.02	<0.0001	1.01	1.03
Cause of liver cirrhosis	HBV (yes/no)	1.01	0.9673	0.74	1.34				
	HCV (yes/no)	0.86	0.0928	0.72	1.03				
	Alcohol (yes/no)	1.16	0.1775	0.93	1.42				
Treatment adherence (during 6 months)	Half or less/all	1.74	<0.0001	1.39	2.15	1.94	<0.0001	1.54	2.42
Previous hepatic cancer	Yes/no	1.53	<0.0001	1.25	1.86	1.76	<0.0001	1.42	2.16
Current clinical manifestations	Yes/no	2.21	<0.0001	1.84	2.65	1.66	<0.0001	1.36	2.04
Previous clinical manifestations	Yes/no	1.88	<0.0001	1.59	2.24	1.45	<0.0001	1.20	1.74
Diabetes	Yes/no	1.24	0.0488	1.00	1.52				
Serum albumin (g/dL)	Lower level	2.51	<0.0001	2.02	3.10	2.00	<0.0001	1.57	2.54
Platelet (×10 000/μL)	Lower level	1.04	<0.0001	1.02	1.06	1.03	0.0010	1.01	1.05
AST (IU/L)	Higher level	1.00	0.8840	1.00	1.00				
ALT (IU/L)	Higher level	1.00	0.0156	0.99	1.00				
Serum total bilirubin (mg/dL)	Higher level	1.68	<0.0001	1.47	1.92	1.49	<0.0001	1.29	1.72
BTR	Lower level	1.22	0.0839	0.98	1.59				

Univariate and multivariate analyses were performed using a Cox proportional hazards model, and hazard ratios, P-values and 95% CI of the hazard ratios are shown. For the multivariate analysis, variables were selected and determined by backwards selection (P = 0.2) using a model incorporating all factors except BTR. BTR was excluded from the multivariate analysis because a considerable proportion of patients lacked BTR data.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BTR, branched-chain amino acid/tyrosine ratio; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus.

As treatment adherence was judged based on patients' self-reports, we further attempted to validate the treatment adherence by changes in the BCAA/tyrosine ratio (BTR) as an indicator reflecting true BCAA treatment adherence. Although the number of patients with BTR data was limited ($n = 185$ and 19, respectively), both absolute BTR and relative increase in BTR (increase in BTR/baseline BTR) were higher in the good adherence group (absolute BTR, 4.26 ± 0.65 for the good adherence group and 3.79 ± 0.52 for the poor adherence group; and relative increase in BTR, 0.53 ± 0.8 for the good adherence group and 0.30 ± 0.68 for the poor adherence group; $P < 0.1$ for both) at 6 months of treatment, while there was no significant difference in baseline BTR between the two groups (2.94 ± 0.49 and 2.86 ± 0.46). A comparison between the two groups was thus considered to be feasible.

Treatment adherence and event-free survival

Regarding the primary end-point, Kaplan–Meier analysis and log–rank test showed a significantly higher cumulative event-free survival rate for the good adherence group as compared with the poor adherence group (Fig. 2).
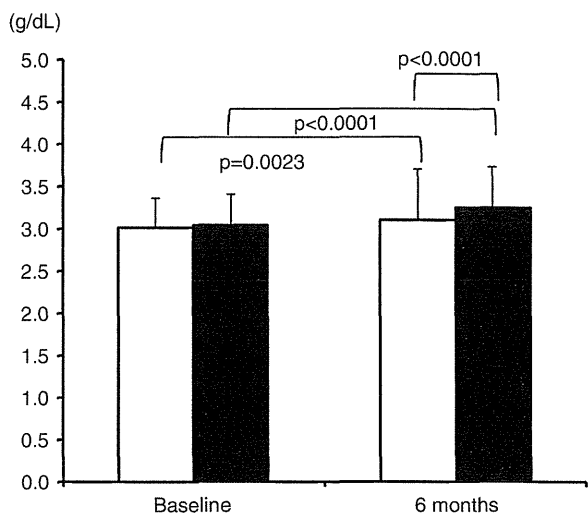

Figure 3 Comparison of serum albumin levels by treatment adherence status. Columns and bars indicate mean and standard deviation of serum albumin levels obtained at baseline and at 6 months of study treatment, respectively. Statistical assessment within each adherence group was carried out by paired Student's t-test. For differences between the groups at baseline and at 6 months, Student's t-test was conducted. (□) Poor adherence ($n = 366$); (■) good adherence ($n = 2378$).

Treatment adherence and blood biochemistry

Changes in liver function-related parameters during 6 months of the study treatment were examined for each of the good adherence and poor adherence groups. No significant difference was noted in platelet count, aspartate aminotransferase or alanine aminotransferase (ALT) between these groups. At 6 months of study treatment, serum total bilirubin level significantly increased in the poor adherence group but not in the good adherence group. Serum albumin level rose significantly in both of these groups at 6 months of study treatment, and the increase was significantly greater for the good adherence group (Fig. 3).

	0	200	400	600	800	1000	1200	1400
Good adherence	2545	2201	1856	1545	981	345	30	2
Poor adherence	439	301	231	182	100	32	4	0

Figure 2 Comparison of cumulative event-free survival rate by treatment adherence status. Cumulative event-free survival rates were estimated for the good adherence and poor adherence groups using the Kaplan–Meier method, and are shown along with the number of patients at risk. Two curves were compared by log–rank test, and hazard ratio (HR) was calculated by Cox proportional hazards model. (—) Good adherence; (--) poor adherence.

Comparison of clinical characteristics between good adherence group and poor adherence group

Baseline clinical characteristics were compared between the good adherence group and poor adherence group as shown in Table 3. Patients of the poor adherence group showed a significantly younger age, lower proportion of

Table 3 Clinical characteristics of patients by adherence status

Characteristics		Good adherence, $n = 2545$	Poor adherence, $n = 439$	P-value
Sex	Male	1334 (52.4%)	250 (56.9%)	$P = 0.0789$
	Female	1211 (47.6%)	189 (43.1%)	
Age (years)	20–29	1 (0.0%)	0 (0.0%)	
	30–39	16 (0.6%)	8 (1.8%)	
	40–49	135 (5.3%)	30 (6.8%)	
	50–59	445 (17.5%)	85 (19.4%)	
	60–69	894 (35.1%)	144 (32.8%)	
	70–79	888 (34.9%)	136 (31.0%)	
	80–89	161 (6.3%)	34 (7.7%)	
	>90	5 (0.2%)	2 (0.5%)	
	Mean ± SD	66.3 ± 9.9	65.2 ± 11.1	$P = 0.0344$
Cause of liver cirrhosis	HBV	184 (7.2%)	33 (7.5%)	$P = 0.0111$
	HCV	1539 (60.5%)	216 (49.2%)	
	Alcohol	393 (15.4%)	94 (21.4%)	
	PBC	59 (2.3%)	15 (3.4%)	
	AIH	52 (2.0%)	11 (2.5%)	
	HBV + HCV	13 (0.5%)	3 (0.7%)	
	HBV + alcohol	23 (0.9%)	6 (1.4%)	
	HCV + alcohol	77 (3.0%)	15 (3.4%)	
	HBV + HCV + alcohol	2 (0.1%)	0 (0.0%)	
	Other	46 (1.8%)	11 (2.5%)	
	Unknown	157 (6.2%)	35 (8.0%)	
Previous hepatic cancer	Yes	448 (17.6%)	56 (12.8%)	$P = 0.0110$
	No	2078 (81.7%)	376 (85.6%)	
	Unknown	19 (0.7%)	7 (1.6%)	
Current clinical manifestations	Yes	1321 (51.9%)	247 (56.3%)	$P = 0.1545$
	No	1218 (47.9%)	192 (43.7%)	
	Unknown	6 (0.2%)	0 (0.0%)	
Previous clinical manifestations	Yes	1094 (43.0%)	197 (44.9%)	$P = 0.6969$
	No	1432 (56.3%)	238 (54.2%)	
	Unknown	19 (0.7%)	4 (0.9%)	
Diabetes	Yes	457 (18.0%)	79 (18.0%)	$P = 0.9844$
	No	2088 (82.0%)	360 (82.0%)	
Serum albumin (g/dL)		3.04 ± 0.36	3.01 ± 0.35	$P = 0.1519$
Platelet (×10 000/μL)		9.56 ± 5.85	10.76 ± 7.63	$P = 0.0002$
AST (IU/L)		67.2 ± 66.1	66.2 ± 38.1	$P = 0.7578$
ALT (IU/L)		48.4 ± 42.7	44.2 ± 28.7	$P = 0.0518$
Serum total bilirubin (mg/dL)		1.29 ± 0.61	1.33 ± 0.66	$P = 0.2430$
BTR		2.98 ± 1.42	2.82 ± 1.07	$P = 0.4400$

For categorical variables, the number of patients and percentage are shown. For continuous variables, the mean ± SD is presented. Statistical analysis was conducted by χ^2-test or by Student's t-test.
AIH, autoimmune hepatitis; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BTR, branched-chain amino acid/tyrosine ratio; HBV, hepatitis B virus; HCV, hepatitis C virus; PBC, primary biliary cirrhosis; SD, standard deviation.

hepatitis C virus positivity and higher proportion of alcoholic cirrhosis, lower incidence of previous hepatic cancer, and higher platelet count (Table 3). Also, they tended to be male patients with lower serum ALT activity (Table 3).

DISCUSSION

THE LOTUS STUDY demonstrated that the outcome of patients with advanced liver cirrhosis was improved by the treatment with BCAA granules at three

sachets/day, compared with the dietary treatment.[4] As utilized in that study, the recommended dosage of BCAA granules is one sachet three times a day p.o. after meals; however, some patients may not take all three sachets in a day due to problems such as treatment adherence. We therefore conducted the present prospective cohort study to examine how differences in the actual intake of BCAA granules may influence the prognosis of patients with liver cirrhosis.

Assessment of clinical characteristics of the patients included in the present study indicated that these patients shared average clinical features of liver cirrhosis in Japanese patients such as accountable etiologies.[1] Logistic analysis revealed that none of these causes was an independent risk factor for patients' outcome. Indeed, the prognosis of patients with liver cirrhosis was determined by eight factors including treatment adherence, regardless of the cause of liver cirrhosis (Table 2).

We focused on the treatment adherence among the eight independent risk factors in the present study, because the clinical significance of the other seven factors has already been described.[19,20] For this concern, patients were divided into the good adherence group (those who reported to have taken "nearly all" prescribed doses) and the poor adherence group (those who reported to have taken "approximately half" or "less" doses), because such stratification was validated by treatment responses in plasma BCAA/tyrosine ratio. Actually, 85.3% of patients reported to have taken "nearly all" three sachets of BCAA granules/day as prescribed. This result was comparable to the 86% adherence in the patients of the LOTUS study.[4] In the present study, treatment adherence was monitored longer after the first 6 months continuously, and remained similar: 81.1% for 7–12 months, 80.6% for 13–18 months and 79.7% for 19–24 months. These data indicate that treatment adherence observed for the first 6-month period was kept over longer treatment periods and, therefore, suggest that it is reasonable to monitor the treatment adherence of the first 6-month period for the long-term prognosis.

Improvement of hypoalbuminemia was reported to depend on the prescribed daily BCAA doses (8, 12 or 16 g),[10] but the present study first showed that, at the fixed prescribed dose (three sachets or 12 g/day), serum albumin level rose sufficiently only when the patient had good adherence (Fig. 3). Thus, good treatment adherence resulted in an improved serum albumin level (Fig. 3), and, consequently brought about a higher event-free survival (Fig. 2), as a decreased serum albumin level was also an independent risk factor for the patients (Table 2).

As to possible clinical factors that affect patients' BCAA adherence, we detected male sex, younger age, distribution of etiologies of liver cirrhosis, lower incidence of previous hepatic cancer, higher platelet count and lower serum ALT activities in the poor adherence group (Table 3). Among these factors, only male sex was also a possible unfavorable outcome marker (Table 2), but other factors were rather favorable or had no significance (e.g. cause of liver cirrhosis) for patients' outcome (Table 2). Such observation suggests that particular caution should be paid for drug adherence in male cirrhotics.

The limitation of such studies on advanced liver cirrhosis is the possibility that earlier development of events shortly after the start of the study influenced treatment adherence. To address this concern, we additionally performed analysis after excluding the patients who developed any event within 6 months of the study, and the cumulative event-free survival rate was still significantly higher for the good adherence group than that for the poor adherence group (hazard ratio = 1.57, $P = 0.0043$), as was the case with the analysis on the whole analysis set.

In conclusion, higher treatment adherence for BCAA is considered to be associated with an improved serum albumin level, thereby leading to improved patient outcome. These results indicate the importance of patient instruction for the adequate use of BCAA granules.

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Inhibition of hepatocellular carcinoma by PegIFNα-2a in patients with chronic hepatitis C: a nationwide multicenter cooperative study

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Abstract

Background We investigated whether the administration of maintenance doses of interferon prevented hepatocellular carcinoma (HCC) in patients with chronic hepatitis C.
Methods Study 1: A multicenter, retrospective, cooperative study was carried out to determine whether long-term administration of low-dose peginterferon alpha-2a

(PegIFNα-2a) prevented HCC development in patients with chronic hepatitis C. In total, 594 chronic hepatitis C patients without a history of HCC were enrolled and treated with 90 μg PegIFNα-2a administered weekly or bi-weekly for at least 1 year. Study 2: HCC developed in 16 of 99 additional patients without PegIFNα-2a treatment during 3.8 years of observation. A propensity-matched control study was then carried out to compare the incidence of

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HCC between the 59 patients who received low-dose PegIFNα-2a (PegIFNα-2a group) and 59 patients who did not receive PegIFNα-2a treatment (control group), matched for sex, age, platelet count, and total bilirubin levels.

Results Study 1: HCC developed in 49 patients. The risk of HCC was lower in patients with undetectable hepatitis C virus RNA, ≤40 IU/L alanine aminotransferase (ALT), or ≤10 ng/L alpha-fetoprotein (AFP) 24 weeks after the start of therapy. Study 2: The incidence of HCC was significantly lower in the PegIFNα-2a group than in the control group.

Conclusions Low-dose and long-term maintenance administration of PegIFNα-2a decreased the incidence of HCC in patients with normalized ALT and AFP levels at 24 weeks compared with patients without normal ALT and AFP levels.

Keywords Chronic hepatitis C · Hepatocellular carcinoma · Peginterferon

Introduction

Hepatocellular carcinoma (HCC), the sixth most common cancer worldwide, often develops because of long-term hepatitis B or C virus infection [1, 2]. In particular, chronic hepatitis C and hepatic cirrhosis increase the risk of HCC; the annual incidence of tumor development in such patients may be as high as 2–4 % [3–5]. The incidence of HCC decreases in patients who achieve a sustained virological response (SVR) to interferon (IFN) treatment, although the incidence remains high in non-SVR patients [6–9]. A detailed analysis of HCC development revealed that chronic hepatitis C patients aged 65 years or more, especially those with advanced fibrosis of the liver, were at an increased risk of developing HCC [10]. For patients

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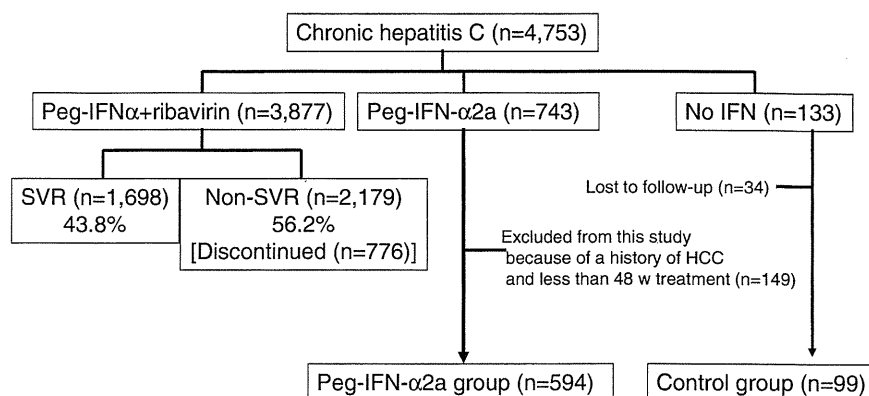Nagasaki Medical Center, Nagasaki, Japan

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65 years or older with advanced liver fibrosis, the dose of ribavirin is often reduced or the agent is discontinued, resulting in lower SVR rates in those with discontinuation of ribavirin. Establishing an effective treatment strategy for preventing the development of HCC is important for these high-risk patients.

Factors related to the development of HCC have been analyzed in patients who did not achieve an SVR even after IFN treatment; advanced fibrosis of the liver and high levels of serum alanine aminotransferase (ALT), and alpha-fetoprotein (AFP) are risk factors for HCC development [11, 12]. A randomized controlled trial was conducted in Western countries to determine whether combined peginterferon and ribavirin treatment with weekly administration of 90 μg peginterferon alpha-2a (PegIFNα-2a) could prevent HCC in non-responders. A 3.5-year follow up showed that administration of a maintenance dose of PegIFNα-2a did not reduce tumor incidence in these patients [13]. However, after 8.5 years of observation, the incidence of HCC was decreased among those in the PegIFNα-2a group with cirrhosis [14]. Meanwhile, Bruix et al. [15] reported that maintenance therapy with PegIFNα-2b did not prevent HCC in chronic hepatitis C patients with cirrhosis. In Japan, long-term low-dose administration of natural IFN has been reported to decrease the incidence of HCC [16]. In light of these conflicting results, investigations should be carried out in a large number of patients with chronic hepatitis C to resolve the question of whether IFN treatment prevents the development of HCC.

We carried out a multicenter retrospective cooperative study of patients with chronic hepatitis C to determine whether those treated with 90 μg PegIFNα-2a without ribavirin had a reduced incidence of HCC compared with those not treated with IFN.

Patients and methods

Study 1: analysis of risk factors for HCC in patients treated with long-term low-dose-PegIFNα-2a

In total, at 21 hepatitis centers throughout Japan, 743 patients with hepatitis C who had received 90 μg of PegIFNα-2a therapy weekly or bi-weekly for 1 year or more without having received the full dose (180 μg) since December 2003 were examined retrospectively for the development of HCC. The end of enrollment in this study was the end of December 2008 and the end of follow up was the end of December 2010. Patients with a history of HCC before the start of therapy and those with a therapy period of less than 48 weeks were excluded, leaving 594 patients who had undergone long-term administration of PegIFNα-2a for analysis. At the 21 centers involved in this

Fig. 1 Flow diagram of the patients' enrollment in the study. *Peg-IFNα* pegylated interferon α, *SVR* sustained viral response, *HCC* hepatocellular carcinoma, *w* week

study, 4,753 patients with chronic hepatitis C had been treated; Peg-IFN and ribavirin combination treatment had been administered to 3,877 patients, 743 patients had received Peg-IFN alone, and 133 patients had not agreed to receive IFN (a flow diagram of the enrollment of patients in this study is shown in Fig. 1). In the patients with Peg-IFN and ribavirin combination treatment, the SVR rate was 43.8 %; SVR was not achieved in 2,179 patients, and in 776 of these patients, the combination therapy was discontinued owing to adverse events or the patient's choice. Patients who failed to achieve an SVR were not included in this study, because the incidence of HCC is known to be reduced even in non-responders to IFN [17].

The backgrounds of the 594 patients studied are shown in Table 1. Findings from the liver biopsies of the patients were classified according to international standards [18]. Long-term PegIFNα-2a treatment is approved by the Japanese Medical Insurance system. Written informed consent was obtained from all patients prior to participation in this study. The study design was approved by the regional ethics committees of the 21 centers involved in this study, including the Musashino Red Cross Hospital, in accordance with the Helsinki Declaration. The 743 patients treated with PegIFNα-2a alone were not indicated for Peg-IFNα and ribavirin combination therapy because of anemia or heart disease. The 133 patients who did not agree to receive IFN served as the control group (see Fig. 1). A large proportion of the 594 study patients had advanced fibrosis of the liver and active inflammation. A dose of 90 μg PegIFNα-2a was administered to 512 and 82 patients weekly and biweekly, respectively, according to the patients' wishes. There were no significant differences between the weekly and biweekly groups in the patients' background data (data not shown).

The median duration of follow up in the PegIFNα-2a group was 1,273 days (range 228–2,768 days) and HCC was observed in 49 of the 594 patients (Table 1). Pretreatment and on-treatment factors associated with the development of HCC were analyzed by Student's *t*-test, the

Table 1 Background data of patients treated with PegIFNα-2a (*n* = 594)

	n = 594
Age (years)	61.7 ± 11.7
Sex (male/female)	258/336
BMI	23.2 ± 3.3
Genotype (1/2)	443/151
Diagnosis (ASC/CH/LC)	4/460/130
History of excess alcohol consumption (≥60 g/day; yes/no)	118/376
Fibrosis (F0, 1, 2/F3, 4)	443/151
Inflammatory activity (A0, 1/A2, 3)	469/125
Diabetes mellitus (no/yes)	499/95
LDL cholesterol (mg/dL)	94.2 ± 31.1
Fasting blood sugar (mg/dL)	106.3 ± 28.5
White blood cell count (/mm^3)	4,360 ± 1,470
Red blood cell count (×10^6/μL)	423.8 ± 56.4
Hemoglobin (g/dL)	13.3 ± 1.8
Platelet count (×10^3/μL)	137 ± 56
Albumin (g/dL)	4.0 ± 0.5
Total bilirubin (mg/dL)	0.8 ± 0.6
AST (IU/L)	65.8 ± 47.8
ALT (IU/L)	72.1 ± 68.0
Gamma-GTP (IU/L)	55.2 ± 51.3
Esophageal varices (no/yes)	344/31
Alpha fetoprotein (ng/L)	6.9 (4.2–13.8)
Once weekly or biweekly PegIFNα-2a	512:82
Baseline HCV RNA (KIU/mL)	1,024 (73–2,130)
Development of HCC (no/yes)	545/49

PegIFN pegylated interferon, *BMI* body mass index, *ASC* asymtomatic carrier, *CH* chronic hepatitis, *LC* liver cirrhosis, *LDL* low-density lipoprotein, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *GTP* guanosine triphosphate, *HCV* hepatitis C virus, *HCC* hepatocellular carcinoma

Values are means ± SD, with ranges in parentheses

Mann–Whitney *U*-test, and the χ^2 test (Table 2). Independent factors for the development of HCC were assessed by multivariate analysis using logistic regression. The

incidence of HCC was analyzed according to the ALT, AFP, and hepatitis C virus (HCV) RNA levels 24 weeks after the start of PegIFNα-2a administration by using the Kaplan–Meier method. The risk of HCC was analyzed, using the Kaplan–Meier method, only in the non-responders with detectable HCV RNA during PegIFNα-2a administration by dividing them according to the ALT and AFP levels 24 weeks after the start of therapy. The incidence of HCC was compared between the patients with ALT levels of <41 IU/L and those with levels of ≥41 IU/L, and between patients with serum AFP levels of <10 ng/L and those with levels of ≥10 ng/mL at 24 weeks after starting treatment, because at most of the centers participating in the this study, the upper normal range of serum ALT is set at 40 IU/L, and the most significant difference in the incidence of HCC was observed between the PegIFNα-2a and control group with the cut-off serum ALT set at 41 IU/L and cutoff serum AFP set at 10 ng/mL, 24 weeks after starting treatment. The HCV RNA level was measured using the Amplicor Monitor method with a lower detection limit of 50 IU/L (Roche Diagnostics, Tokyo, Japan). A history of excess alcohol consumption was determined as >60 g alcohol per day in order to exclude alcoholic liver disease.

An asymptomatic carrier was defined as a patient with a serum ALT level within the normal range and minimal inflammation or fibrosis in the biopsied tissues of the liver. Chronic hepatitis was defined as mild-to-severe fibrosis of the liver according to liver biopsy [18]. The diagnosis of liver cirrhosis was based on the results of histological examination of the biopsied liver tissues.

Study 2: incidence of HCC in the PegIFNα-2a therapy and non-administration (control) groups in comparison with propensity-matched controls

Ninety-nine of the 133 chronic hepatitis C patients who had not received IFN were examined as controls; patients in this group received liver-protective agents such as glycyrrhizin or were untreated, and the group was observed for more than 1 year. None of the individuals in the control groups had received IFN alone or PegIFNα and ribavirin combination treatment. They were treated for a median of 1,395 days (range 75–6,556 days). Fifty-nine of these patients underwent liver biopsy before the treatment and were considered the control group for the propensity-matched study. For the propensity-matched study, 59 patients were selected from the PegIFNα-2a group according to their age, sex, platelet count, and total bilirubin levels, which had been identified as independent pretreatment risk factors for the development of HCC in Study 1. The rates of HCC were analyzed using the Kaplan–Meier method, and the risk of HCC was analyzed particularly in patients with advanced fibrosis of the liver (F3 and F4).

Table 2 Comparison of HCC and non-HCC patients with long-term PegIFNα-2a administration ($n = 594$)

	Patients with or without development of HCC		p value
	With HCC ($n = 49$)	Without HCC ($n = 545$)	
Pretreatment parameters			
Age (years)	63.8 ± 1.7	61.3 ± 0.5	<0.05
Sex (male/female)	32/17	226/319	<0.01
BMI	24.0 ± 0.5	23.1 ± 0.2	n.s.
Genotype (1/2)	47/6	397/148	n.s.
History of excess alcohol consumption (≥60 g/day; yes/no)	11/38	107/338	n.s.
Fibrosis (F0, 1, 2/F3, 4)	25/24	418/127	<0.001
Inflammatory activity (A0, 1/A2, 3)	7/42	462/83	<0.001
Diabetes mellitus (no/yes)	38/11	461/84	n.s.
LDL cholesterol (mg/dL)	88.2 ± 9.0	94.7 ± 2.6	n.s.
White blood cell count (/mm³)	4,355 ± 210	4,360 ± 64	n.s.
Red blood cell count (×10⁶/μL)	420.8 ± 8.1	424.1 ± 2.6	n.s.
Hemoglobin (g/dL)	13.6 ± 0.3	13.3 ± 0.1	n.s.
Platelet count (×10³/μL)	106 ± 8	140 ± 2	<0.001
Albumin (g/dL)	3.8 ± 0.1	4.0 ± 0.1	<0.001
Total bilirubin (mg/dL)	1.2 ± 0.1	0.8 ± 0.1	<0.001
AST (IU/L)	78.1 ± 6.8	64.6 ± 2.1	n.s.
ALT (IU/L)	72.8 ± 9.7	72.0 ± 2.9	n.s.
Gamma-GTP (IU/L)	68.7 ± 7.5	53.9 ± 2.3	n.s.
Alpha fetoprotein (ng/L)	17.1 (4.4–36.8)	16.7 (4.1–23.1)	n.s.
Esophageal varices	29.0 % (9/31)	6.4 % (22/344)	<0.01
On-treatment parameters			
ALT (IU/L)	59.4 ± 5.7	44.6 ± 1.8	<0.05
Alpha fetoprotein (ng/L)	9.8 (4.6–17.4)	5.5 (3.7–11.1)	<0.01
HCV RNA level (KIU/mL)	236 (<0.5–2,210)	21 (<0.5–1,780)	<0.05

n.s. not significant

Statistical analysis

Categorical data were compared using the χ^2 test or Fisher's exact test. The distributions of continuous variables were analyzed using Student's t-test and the Mann–Whitney U-test for two groups. Multivariate analysis was

conducted using logistic regression. The cumulative incidence curve was determined using the Kaplan–Meier method and differences between groups were assessed by the log-rank test. For all methods, the level of significance was set at $p < 0.05$. Multivariate analysis of the risk of HCC was carried out using the Cox proportional hazard model. Statistical analyses were performed using the Statistical Package for the Social Sciences software version 11.0 (SPSS, Chicago, IL, USA). In Study 1, age, sex, platelet count, and total bilirubin levels were identified as independent factors for the development of HCC; therefore, these factors were selected for the propensity-matched control study (Study 2) in which 59 patients from the PegIFNα-2a group were included.

Results

Study 1

We analyzed the factors involved in the development of HCC in patients who received 90 µg PegIFNα-2a weekly or biweekly for more than a year. The incidence of HCC did not differ significantly between the groups treated with PegIFNα-2a weekly and biweekly (34 of 512 vs. 15 of 82, respectively). As shown in Table 2, univariate analysis revealed statistically significant differences in the pre-treatment parameters including age, sex, fibrosis of the liver, platelet count, albumin level, and total bilirubin, between patients who developed HCC and those who did not. Endoscopy was carried out in 375 patients, and esophageal varices were noted in 31 of them. The incidence of HCC was higher in patients with esophageal varices than in those without varices [29.0 % (9 of 31) vs. 6.4 % (22 of 344)]. Assessment of on-treatment factors by univariate analysis revealed statistically significant differences in serum ALT, AFP, and HCV RNA levels 24 weeks after the start of PegIFNα-2a maintenance treatment (Table 2).

Multivariate analysis including pretreatment parameters revealed that age, sex, fibrosis of the liver, platelet count, and total bilirubin were independent risk factors for HCC development (Table 3). Multivariate analysis including on-treatment parameters identified ALT levels of ≥ 41 IU/L and AFP levels of ≥ 10 ng/L 24 weeks after the start of the PegIFNα-2a therapy as independent risk factors for HCC development (Table 3).

The incidence of HCC was significantly lower in patients with ALT levels of ≤ 40 IU/L than in those with ALT levels of ≥ 41 IU/L 24 weeks after the start of observation (Fig. 2). The incidence of HCC was also significantly lower in patients with AFP concentrations of <10 ng/mL at 24 weeks after the start of observation than in those with AFP concentrations of

≥ 10 ng/mL (Fig. 3). The dose of PegIFNα-2a was reduced to 45 µg in 16 patients because of neutropenia and thrombocytopenia. In addition, PegIFNα-2a was discontinued in 18 patients because of adverse events, including depression (7 patients), interstitial pneumonitis (3 patients), thrombocytopenia (3 patients), neutropenia (1 patient), itching (1 patient), and ascites (3 patients). No statistically significant differences were found between the patients with reduced dosage or treatment interruption and those without treatment modifications with respect to overall survival, HCC incidence, ascites formation, variceal bleeding, hepatic encephalopathy, and 2-point increases in the Child-Pugh score. No patients underwent liver transplantation.

Table 3 Independent risk factors for HCC development in patients treated with 90 µg PegIFNα-2a weekly or bi-weekly, evaluated by multivariate analysis (logistic regression analysis)

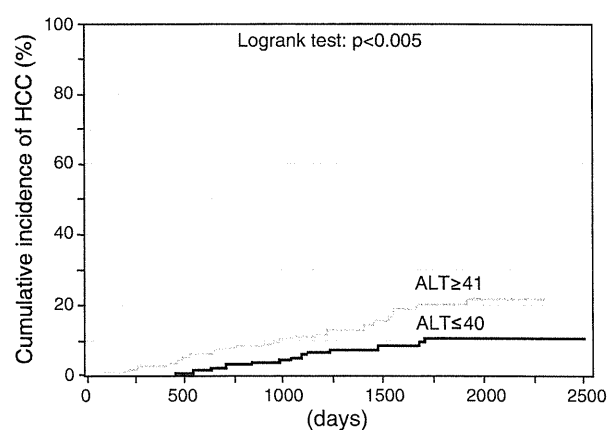|	Multivariate analysis		
	Odds ratio	95 % Confidence interval (CI)	p
Age (years) (every 5 years)	2.24	1.76–9.33	<0.005
Sex (male/female)	3.16	1.56–10.7	<0.005
Fibrosis (F3, 4/F0, 1, 2)	1.69	1.18–5.2	<0.01
Platelet count (<120 × 10³/µL vs. ≥120 × 10³/µL)	3.24	1.44–27.6	<0.01
Total bilirubin (mg/dL)	1.59	1.09–2.58	<0.05
ALT (at 24 weeks) (≥41 vs. <40 IU/L)	2.49	1.51–8.28	<0.05
AFP (at 24 weeks) (≥10 vs. <10 ng/L)	3.78	1.92–11.8	<0.01

Fig. 2 Comparison of HCC rates in patients administered with PegIFNα-2a ($n = 594$) with respect to alanine aminotransferase (*ALT*) levels 24 weeks after the start of therapy. *Black line* patients with ALT ≥41 IU/L in the first 24 weeks, *gray line* patients with ALT ≤40 IU/L in the first 24 weeks
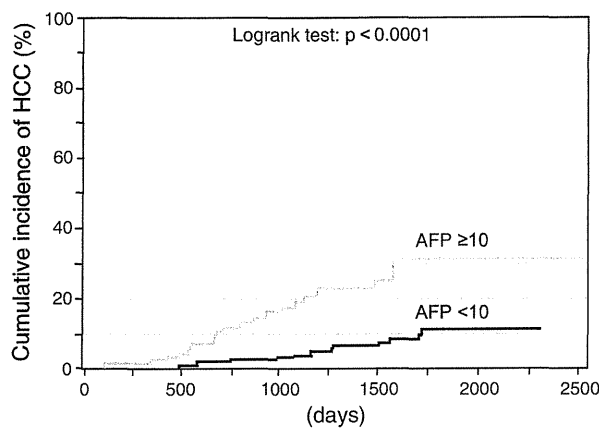
Fig. 3 Comparison of HCC rates in patients administered PegIFNα-2a ($n = 594$) with respect to alpha-fetoprotein (*AFP*) levels in the first 24 weeks after the start of therapy. *Black line* patients with AFP ≥ 10 ng/mL at 24 weeks, *gray line* patients with AFP <10 ng/mL at 24 weeks

Study 2

We compared the incidence of HCC between 59 patients in the control group and the same number of patients in the PegIFNα-2a group using the matched-pair test. The backgrounds of the patients are shown in Table 4. The PegIFNα-2a group had higher rates of advanced fibrosis (F3 and F4) and active inflammation (A2 and A3). No other differences were found between the two groups, except for the white blood cell count (Table 4).

Development of HCC was observed in 2 patients in the PegIFNα-2a group and 8 in the control group. The incidence of HCC was compared between the two groups, using the Kaplan–Meier method. The incidence of HCC in the PegIFNα-2a group was significantly lower than that in the control group (log-rank test, $p = 0.0187$; Fig. 4). Among the patients with advanced fibrosis of the liver (F3 and F4), those in the PegIFNα-2a group had a lower incidence of HCC than those in the control group. The independent risk factors for the development of HCC were analyzed using the stepwise Cox proportional hazard model. Only PegIFNα-2a administration and age were identified as independent risk factors for the development of HCC (Table 5).

Discussion

The number of HCC cases resulting from HCV infection continues to increase worldwide [19]. To date, IFN therapy is the most effective preventive measure against HCC in patients with chronic hepatitis C; furthermore, the

Table 4 Backgrounds of the patients in the propensity-matched control study (PegIFNα-2a group, $n = 59$; control group, $n = 59$)

	PegIFNα-2a group ($n = 59$)	Control group ($n = 59$)	p value
Age (years)	60.5 ± 13.0	63.3 ± 10.5	n.s.
Gender (male/female)	24/35	25/34	n.s.
BMI	22.9 ± 3.6	22.9 ± 3.4	n.s.
Genotype (1/2)	49/10	46/13	n.s.
History of excess alcohol consumption (60 g/day; yes/no)	10/49	4/55	n.s.
Fibrosis (F0, 1, 2/F3, 4)	37/22	43/16	<0.05
Development of HCC (F0–2/F3, 4)	1/1	1/7	n.s.
Inflammatory activity (A0,1/A2, 3)	19/40	30/29	<0.05
Diabetes mellitus (no/yes)	57/2	56/3	n.s.
LDL cholesterol (mg/dL)	95.3 ± 23.8	117.0 ± 4.2	n.s.
White blood cell count (/mm^3)	$4,260 \pm 1,239$	$5,193 \pm 2,078$	<0.05
Red blood cell count ($\times 10^{-4}$/μL)	430 ± 57.8	441 ± 44.9	n.s.
Hemoglobin (g/dL)	13.6 ± 1.5	13.6 ± 1.9	n.s.
Platelet count ($\times 10^{-3}$/μL)	14.5 ± 5.7	15.8 ± 5.7	n.s.
Albumin (g/dL)	4.1 ± 0.5	4.1 ± 0.4	n.s.
Total bilirubin (mg/dL)	0.7 ± 0.5	0.9 ± 0.7	n.s.
AST (IU/L)	58.3 ± 47.7	49.7 ± 26.6	n.s.
ALT (IU/L)	63.6 ± 68.7	58.0 ± 39.2	n.s.
Gamma-GTP (IU/L)	78.3 ± 81.3	55.3 ± 75.1	n.s.
Baseline alpha-fetoprotein (AFP) (ng/L)	7.2 (4.3–14.2)	7.7 (3.9–13.8)	n.s.
Baseline HCV RNA level (KIU/mL)	1,230 (24–3,870)	1,024 (38–3,110)	n.s.

incidence of HCC is reduced in patients who achieve an SVR to IFN [6–9] Therefore, achieving an SVR is the most effective approach for reducing the risk of developing HCC. In Japan, the incidence of HCC is elevated in older patients with hepatitis C. Corroborating this finding, the results of a Japanese study show a higher risk of HCC in patients aged 65 years and more [10]. Therefore, prevention of HCC in aged patients is an important challenge.

In the present multicenter, cooperative, retrospective study conducted in Japan, the incidence of HCC was reduced in patients who received 90 μg PegIFNα-2a weekly or biweekly and had AFP values of <10 ng/mL and ALT values of ≤ 40 IU/L 24 weeks after the start of the treatment. The results of the matched case–control study of the PegIFNα-2a group and the non-IFN control group show that the incidence of HCC was significantly lower in the PegIFNα-2a group than in the control group, especially in patients with advanced fibrosis of the liver (F3 and F4). However, there could have been a selection bias between
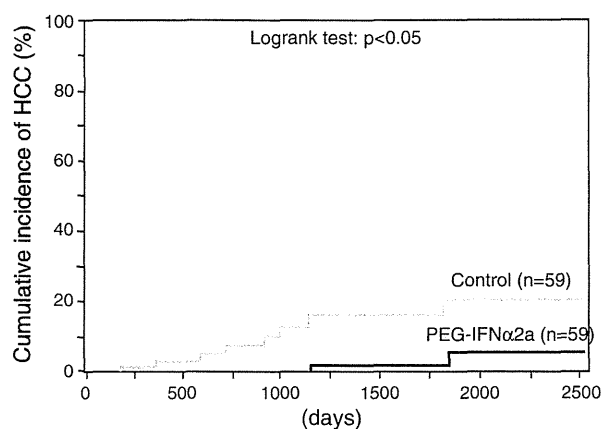
Fig. 4 Comparison of HCC rates between the long-term PegIFNα-2a administration group ($n = 59$) and non-administration group ($n = 59$) in the propensity-matched control study (Kaplan–Meier log-rank test, $p = 0.019$)

Table 5 Risk factors for HCC in the propensity-matched control study (Cox proportional hazard model)

Variables	Risk ratio	95 % CI	p value
PegIFN versus control	0.17	0.03–0.75	<0.05
Age (every 1 year)	1.12	1.02–1.25	<0.05
Fibrosis (F3, 4 vs. F0, 1, 2)	1.70	0.75–4.16	n.s.
Platelet count (every 10 × 10^3/μL)	0.89	0.73–1.09	n.s.
Albumin (every 1.0 g/dL)	0.80	0.10–6.68	n.s.
On-treatment AFP (<10 vs. ≥10 ng/L)	4.07	0.59–40.12	n.s.

the PegIFNα-2a group and the control group (patients who did not agree to receive IFN treatment), because this was a retrospective and non-randomized study. However, concordant with the findings of the HALT-C study [14], the present results show that PegIFNα-2a inhibits the development of HCC in patients with advanced fibrosis of the liver.

Recent studies show that polymorphisms in the host *IL28B* gene are important factors in the response to Peg-IFNα and ribavirin combination therapy [20, 21]. However, the mechanism of IL28B involvement in the response to PegIFNα and ribavirin has not been elucidated completely. A recent report has shown that IL28B is a significant factor in the development of HCC as well as in the response to IFN therapy [22]. Further studies are warranted to analyze the relationship between IL28B and inhibition of the development of HCC by PegIFNα in chronic hepatitis C.

Risk factors for the development of HCC have been discussed previously. Increased intrahepatic fat is involved in the development of HCC in chronic hepatitis C patients [23, 24]. In addition, diabetes-associated fat disorder [25,

26], hepatic iron overload [27], advanced fibrosis, older age, and fatty deposits in the liver are risk factors for HCC development [4]. Therefore, it is important to establish strategies to mitigate these risk factors to prevent the development of HCC and thus improve the outcomes of hepatitis C patients.

IFN therapy after HCC treatment is reported to inhibit the recurrence of tumors [28, 29], and a meta-analysis has revealed a trend toward inhibition of the recurrence of HCC [30, 31]. The prevention of HCC is an important issue that needs to be addressed to improve the survival of chronic hepatitis C patients. The findings of the present study and the HALT-C trial [14] indicate the effectiveness of long-term administration of maintenance IFN for preventing the development of HCC in chronic hepatitis C patients without an SVR. Improvement in ALT levels is also known to be an important predictor for the prevention of HCC [32]. A low AFP value during IFN administration is also recognized as a significant indicator of a lower risk of HCC [33, 34]. Recently, Osaki et al. [35] reported that a decrease of serum AFP during treatment with IFN was associated with a reduced incidence of HCC. Taking these findings and our own together, we conclude that maintenance administration of low-dose PegIFNα-2a weekly or biweekly to non-SVR patients with chronic hepatitis C decreases the incidence of HCC, especially in patients whose serum ALT and AFP levels are within the normal range 24 weeks after the start of treatment. The preventive effects of IFN against the development of HCC without elimination of the virus may be associated with its anti-carcinogenic effects [16, 35]; however, the precise mechanism should be investigated.

The limitations of the present study are that it is retrospective and multicentric; therefore, potentially there may have been a selection bias. However, the reduction of the rate of development of HCC by maintenance administration of PegIFNα-2a in the patients in whom serum ALT and AFP levels were within the normal ranges 24 weeks after the start of treatment may be attributable to the anticarcinogenic effects of IFN without elimination of the virus.

Conclusion

The incidence of HCC was lower in non-SVR patients with chronic hepatitis C who were administered with maintenance low-dose PegIFNα-2a; especially in those whose serum ALT and AFP levels were within the normal ranges 24 weeks after the start of treatment.

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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Waiting list mortality of patients with primary biliary cirrhosis in the Japanese transplant allocation system

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Hiroyuki Furukawa · Seiji Kawasaki · Yukihiro Inomata

Abstract

Background The present study aimed to evaluate etiology-based differences in the risk of waiting list mortality, and to compare the current Japanese transplant allocation system with the Child–Turcotte–Pugh (CTP) and the Model for End-Stage Liver Disease (MELD) scoring systems with regard to the risk of waiting list mortality in patients with primary biliary cirrhosis (PBC).

Methods Using data derived from all adult candidates for deceased donor liver transplantation in Japan from 1997 to 2011, we assessed factors associated with waiting list mortality by the Cox proportional hazards model. The waiting list mortality risk of PBC patients was further estimated with adjustment for each scoring system.

Results Of the 1056 patients meeting the inclusion criteria, 743 were not on the list at the end of study period; waiting list mortality was 58.1 % in this group. In multivariate analysis, increasing age and PBC were significantly associated with an increased risk of waiting list mortality. In comparison with patients with hepatitis C virus (HCV) infection, PBC patients were at 79 % increased risk and had a shorter median survival time by approximately 8 months. The relative hazard of PBC patients was statistically significant with adjustment for CTP score and medical point score, which was the priority for ranking candidates in the Japanese allocation system. However, it lost significance with adjustment for MELD score. Stratification by MELD score indicated a comparable waiting list survival time between patients with PBC and HCV.

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Conclusions PBC patients are at high risk of waiting list mortality in the current allocation system. MELD-based allocation could reduce this risk.

Keywords: Child–Turcotte–Pugh · Liver transplantation · Model for End-Stage Liver Disease

Introduction

Liver transplantation is the only curative treatment option with excellent long-term results in patients with end-stage liver diseases. At present, the number of patients waiting to undergo liver transplantation is increasing in Japan, as well as in both Europe and the United States. However, many patients are dying on the waiting list because of the donor organ shortage. For example, recent waiting list mortality was reported as being 22.8 % in the United States [1]. Management of liver transplant waiting lists is aimed at minimizing waiting list deaths by prioritization of those with a higher mortality risk, and by ensuring allocation of available organs to these patients. Therefore, prioritization and allocation decisions require the accurate prediction of the survival probability of patients.

The indications for liver transplantation include a wide variety of liver diseases, including viral hepatitis, autoimmune hepatitis, cholestatic disease, metabolic disorders, and hepatic neoplasms. Because each type of liver disease has disease-specific therapeutic options and associated risk of complications, liver disease etiology can influence the patient's natural disease course and risk of death. Moreover, disease-specific clinical tools are widely used to determine prognosis in patients with primary biliary cirrhosis (PBC) [2, 3] and primary sclerosing cholangitis [4]. However, it is uncertain whether patients waiting for liver transplantation have a disease-specific risk for waiting list mortality, and whether the ability of the currently used allocation system to assess the urgency of transplantation could be generalized to every patient with heterogeneous etiology.

By consensus, a disease severity index used to allocate liver donor organs should be able to predict the probability of death in patients with end-stage liver diseases of heterogeneous etiology. In the United States, where a large number of patients are registered for liver transplantation, the Child–Turcotte–Pugh (CTP) score [5] was initially applied to assess the severity of liver disease in the United Network for Organ Sharing (UNOS) allocation algorithms, because of its simplicity and recognized ability to assess prognosis in patients with heterogeneous chronic liver disease. Subsequently, a number of studies have demonstrated the accuracy of the Model of End-Stage Liver Disease (MELD) score [6] in predicting short-term

mortality risk in patients with end-stage liver disease [7–9]. Since February 2002, the MELD score has therefore been used as a UNOS criterion for allocating organs to patients waiting for liver transplantation [10].

On the other hand, in the countries with a small number of registrations for liver transplantation, a system of prioritization based on a detailed clinical review, which includes CTP score, MELD score, and other disease-specific prognostic scores, as well as patients' demographics, laboratory data, and disease histories, by a small number of expert clinicians is likely to be used to judge disease severity and potential mortality accurately. This clinical judgment-based prioritization of patients awaiting liver transplantation was initiated in October 1997 in Japan and, at present, little information is available concerning the prognostic ability of this allocation system.

The aims of the present retrospective study were: (1) to clarify the disease-specific risk for waiting list mortality in patients waiting for liver transplantation; and (2) to compare the current system of waiting list prioritization and organ allocation in Japan with the MELD and CTP scoring systems with regard to the risk in PBC patients, who have the highest risk of waiting list mortality.

Patients and methods

Patients and liver allocation policy in Japan

This was a nationwide retrospective cohort study. We used the Japan Organ Transplant Network (JOT)/the Assessment Committee of Indication for Transplantation database to identify all patients listed for deceased donor liver transplantation in Japan between October 15, 1997 and August 31, 2011. We excluded patients who were less than 18 years of age because they had a spectrum of primary diagnoses substantially different from those of patients older than 18 years. We also excluded patients listed for retransplantation to ensure that all observations represented unique individuals. Finally, we excluded patients who were diagnosed with acute liver failure because these patients rarely have chronic liver disease and are assigned the highest priority.

For JOT registration, the demographic, clinical, and laboratory data including CTP score, MELD score, or disease-specific prognostic score of all candidates are reviewed, and each candidate is assigned a clinical priority by the Assessment Committee of Indication for Transplantation (four physicians, five surgeons, and one pediatrician). The priority of candidates is represented by a medical point system, in which points are awarded according to estimated survival: 9 points for estimated survival <30 days, 6 points for <180 days, 3 points for

<360 days, and 1 point for ≥360 days. In patients with hepatocellular carcinoma, the points were determined only by the degree of hepatic decompensation. Additional points are awarded according to ABO blood group compatibility: 1.5 points for an identical blood group and 1 point for a compatible blood group. Patients with higher total points have a higher priority for donor liver allocation. For patients with identical points, waiting time is a liver allocation measure.

Age of the patient, blood type, etiology of liver disease, and medical point at listing were available for all the patients. Detailed demographic, clinical, laboratory data, including CTP score and MELD score at the time of listing, were available only in patients registered since June 22, 2006. The CTP score uses two clinical variables (ascites and encephalopathy), and three laboratory parameters (serum bilirubin and albumin levels and prothrombin time). Each variable is assigned a score from 1 to 3, with the aggregate score representing the CTP score [5]. Although the original CTP score used different criteria for total bilirubin level between patients with cholestatic disease and those with other etiologies, the criteria for the CTP score in the current Japanese allocation system did not change according to the etiology of liver disease. The MELD score was calculated using the most recent version of the formula documented on the UNOS website [11]: $9.57 \times \log_e(\text{creatinine mg/dL}) + 3.78 \times \log_e(\text{bilirubin mg/dL}) + 11.2 \times \log_e(\text{international normalized ratio [INR]}) + 6.43$, rounded to the nearest integer. Liver disease etiology was not incorporated in this version of the formula. Laboratory values less than 1.0 were set to 1.0 and the maximum serum creatinine was set to 4.0 mg/dL. The serum creatinine was set to 4.0 mg/dL if the patients had received dialysis at least twice within the week prior to the serum creatinine test. The MELD score was not capped at a score of 40. In PBC patients, the spontaneous survival predicted by the updated Mayo model was calculated as described previously [3].

Outcome

The patients' follow-up ended on 30 September 2011. The primary endpoint "waiting list mortality" or "waiting list death" was a combination of death and removal from the waiting list because the patient became too sick for transplantation or was otherwise medically unsuitable. We considered patients who were removed from the transplant list on account of clinical deterioration to be equivalent to patients who died, because these chronic liver diseases are almost uniformly fatal in the short term without transplantation. All other outcomes were censored, with the most common censoring events being transplantation or list removal due to an improvement in the patient's condition resulting in the patient no longer requiring transplantation.

Statistical analysis

Cox proportional hazards ratios (HRs) with 95 % confidence intervals (CI) for waiting list mortality were estimated with univariate models using age, gender, blood type, etiology of liver disease, as well as multivariate models using age and etiology of liver disease. To compare patients' characteristics between chronic hepatitis C virus (HCV) infection and PBC, we used the Mann–Whitney U test for numerical variables or the chi-square test for categorical variables. The HRs with 95 % CI for waiting list mortality of PBC patients were adjusted for each disease severity index, such as medical point, CTP score, and MELD score by bivariate Cox proportional hazards models. The rates of survival were estimated by the Kaplan–Meier method, and compared by log-rank test. All analyses were conducted using IBM SPSS version 19 (IBM SPSS, Chicago, IL, USA). A P value below 0.05 was considered to be statistically significant.

Results

Patient characteristics and outcome

A total of 1,407 patients were listed for deceased donor liver transplantation through the JOT registry during the study period. Of these patients, 1,295 (92.0 %) were aged ≥18 years. The etiology of liver disease in these subjects is shown in Table 1. The most prevalent diagnoses in patients ≥18 years were HCV infection (254 of 1,295, 19.6 %), hepatitis B virus infection (157 of 1,295, 12.1 %), and PBC (156 of 1,295, 12.0 %), and these accounted for 43.7 % of all patients ≥18 years. Of 1,295 patients, 239 were excluded from the study: 142 for acute liver failure and 97 for repeat liver transplant. Thus, a total of 1,056 patients formed the study cohort. In the study cohort, 64 % of patients were men and the median age of all patients was 51 years (range, 18–69 years). At listing, 78 patients were registered at medical point 1, 297 at point 3, 682 at point 6, and 29 at point 9. A flow diagram of the patient outcomes is shown in Fig. 1. At the end of study period, 313 patients were still listed and 743 had been removed from the list, with 267 removed for liver transplantation, 378 for death, and 98 for other reasons, including 54 who were too sick, 11 for improvement in their condition, and 33 for an unknown reason. Of the 267 patients who received liver transplantation, only 81 cases were able to receive deceased donation in Japan, and this accounted for 10.9 % of all patients removed from the list. Waiting list mortality, a combination of death and becoming too sick for transplantation, accounted for 58.1 % of all the patients removed from the list.

Factors associated with waiting list mortality

In univariate analysis, age, biliary atresia, PBC, hepatocellular carcinoma, metabolic diseases, polycystic diseases,

Table 1 Etiology of liver disease

	Total (n = 1,407)	≥18 years (n = 1,295)	<18 years (n = 112)
Cholestatic diseases	381	325	56
BA	93	48	46
PBC	156	156	0
PSC	105	99	6
Caroli disease	8	7	1
Others	18	15	3
Hepatocellular diseases	567	565	2
HCV	254	254	0
HBV	157	157	0
HCV and HBV	8	8	0
Alcoholic	48	48	0
AIH	22	22	0
NASH	25	25	0
Cryptogenic cirrhosis	53	51	2
HCC	76	76	0
Acute liver failure	163	142	21
Graft failure	121	97	24
Vascular disease	12	12	0
Metabolic disease	62	53	9
Polycystic disease	24	24	0
Others	1	1	0

AIH autoimmune hepatitis, *BA* biliary atresia, *HBV* hepatitis B virus, *HCC* hepatocellular carcinoma, *HCV* hepatitis C virus, *NASH* nonalcoholic steatohepatitis, *PBC* primary biliary cirrhosis, *PSC* primary sclerosing cholangitis

and vascular diseases showed statistically significant association with waiting-list mortality. In multivariate analysis, age (HR 1.04; 95 % CI 1.03–1.05, $P < 0.001$), PBC (HR 1.79; 95 % CI 1.34–2.39, $P < 0.001$), and polycystic diseases (HR 0.27; 95 % CI 0.10–0.73, $P = 0.01$) were independently associated with waiting list mortality (Table 2). Hence, PBC patients had a 79 % higher risk of waiting list mortality compared with HCV patients with adjustment for age.

Waiting list mortality of PBC patients

The Kaplan–Meier waiting list survival curves for all PBC and HCV patients are shown in Fig. 2. The 1- and 2-year survival probabilities in HCV patients were 63 and 49 %, respectively (median 631 days, 95 % CI 355–907 days), whereas those in PBC patients were 51 and 33 %, respectively (median 392 days, 95 % CI 283–500 days); the differences between them represented a statistically significant difference (log-rank test, $P < 0.001$). Detailed demographic and clinical characteristics were available in 189 of 254 HCV patients and 81 of 156 PBC patients who were registered after June 2006. A comparison of the characteristics of patients with PBC and HCV is shown in Table 3. In comparison with HCV patients, PBC patients were younger and predominantly female. Patients with PBC had significantly higher platelet counts and serum bilirubin values, and lower INR and serum creatinine values. Neither the CTP score nor the medical point at listing was different between the groups. Conversely, the MELD score at listing was significantly higher in patients with PBC than in those with HCV. In addition, the median of the updated Mayo risk score was 9.4 in the PBC patients, and this predicted 1- and 2-year spontaneous survival rates of 74 and 54 %, respectively.

Fig. 1 Flow diagram of patient outcomes. *DDLT* deceased donor liver transplantation, *LDLT* living donor liver transplantation, *LT* liver transplantation
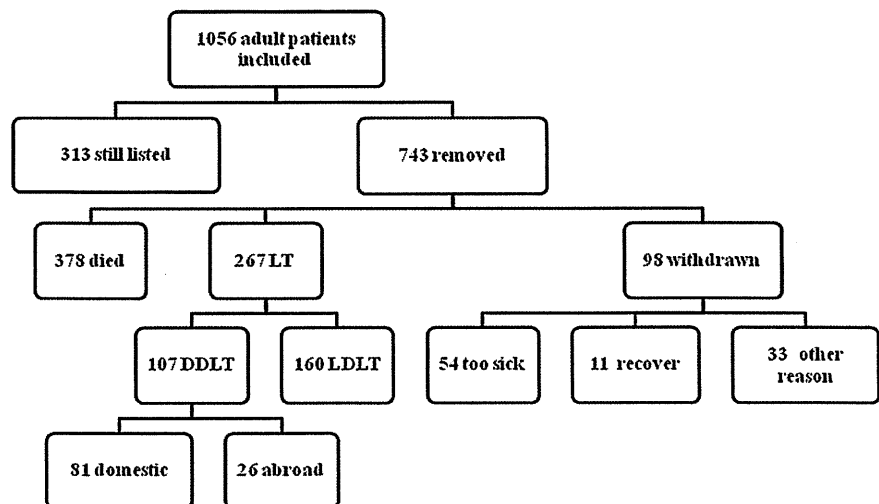
Table 2 Univariate and multivariate analysis of variables associated with waiting list mortality

Variables	Univariate			Multivariate		
	HR	95 % CI	P value	HR	95 % CI	P value
Age (per year of age)	1.04	1.03–1.05	<0.001	1.04	1.03–1.05	<0.001
Male gender	0.93	0.77–1.13	0.48			
Blood type						
A	1.00	Reference				
B	1.07	0.83–1.43	0.61			
O	1.13	0.90–1.43	0.29			
AB	1.26	0.90–1.77	0.17			
Etiology						
HCV	1.00	Reference				
BA	0.40	0.22–0.72	0.002			
PBC	1.62	1.21–2.16	0.001	1.79	1.34–2.39	<0.001
PSC	0.79	0.54–1.17	0.24			
HBV	0.77	0.56–1.05	0.10			
Alcohol	0.95	0.59–1.53	0.83			
AIH	0.77	0.34–1.74	0.52			
NASH	1.11	0.76–1.63	0.59			
HCC	1.46	1.05–2.05	0.003			
Metabolic disease	0.40	0.22–0.75	0.004			
Polycystic disease	0.26	0.10–0.70	0.008	0.27	0.10–0.73	0.01
Vascular disease	0.009	0.01–0.67	0.002			
Others	0.70	0.34–1.43	0.33			

AIH autoimmune hepatitis, *BA* biliary atresia, *HBV* hepatitis B virus, *HCC* hepatocellular carcinoma, *HCV* hepatitis C virus, *HR* hazard ratio, *NASH* non-alcoholic steatohepatitis, *PBC* primary biliary cirrhosis, *PSC* primary sclerosing cholangitis

Table 3 Comparison of patient characteristics between HCV and PBC

Variable	HCV (n = 189)	PBC (n = 81)	P value
Age (years)	55 (29–69)	52 (27–69)	0.02[a]
Gender (male/female)	143/46	15/66	<0.001[b]
Platelet count (×10⁴/μL)	6.0 (1.7–49.0)	10.2 (2.2–42.3)	<0.001[a]
Albumin (g/dL)	2.8 (1.8–4.4)	2.8 (1.4–4.2)	0.96[a]
Total bilirubin (mg/dL)	2.7 (0.4–39.8)	7.2 (0.7–41.2)	<0.001[a]
Creatinine (mg/dL)	0.78 (0.4–7.4)	0.67 (0.37–2.83)	<0.001[a]
Prothrombin time (%)	54.7 (11.0–103.0)	62.2 (16.0–120.0)	0.001[a]
INR	1.51 (0.98–6.24)	1.32 (0.91–4.31)	0.001[a]
MELD score	15 (7–52)	17.5 (8–39)	0.002[a]
CTP score	10 (6–15)	10 (5–15)	0.27[a]
Medical point (1, 3/6, 9)	54/135	22/59	0.81[b]

Data are shown as median (range). Data were available for patients who were listed after June 22, 2006

CTP Child–Turcotte–Pugh, *HCV* hepatitis C virus, *INR* international normalized ratio, *MELD* model of end-stage liver disease, *PBC* primary biliary cirrhosis

[a] Mann–Whitney U test

[b] Chi-square test

Fig. 3 Adjusted risk of waiting list mortality for patients with primary biliary cirrhosis compared with patients with chronic hepatitis C
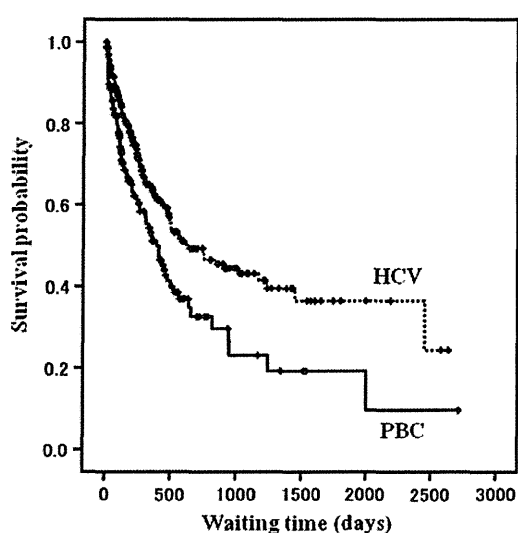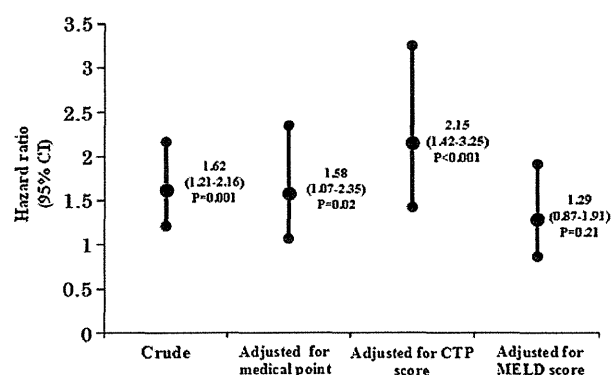

Fig. 2 Kaplan–Meier curves comparing the cumulative waiting list survival probability of patients with chronic hepatitis C (HCV, n = 254) and primary biliary cirrhosis (PBC, n = 156)

To examine which disease severity index was able to assess the risk of PBC patients accurately, we estimated their relative hazards with adjustment for each index. We did not estimate age-adjusted relative hazard because age was not included in the allocation measures. Figure 3 indicates the crude and disease severity index-adjusted HR for waiting list mortality of PBC patients with reference to HCV patients. In univariate analysis, PBC patients were at 62 % (HR 1.62; 95 % CI 1.21–2.16, P = 0.001) increased risk of waiting list mortality

Fig. 4 Kaplan–Meier curves comparing the cumulative waiting list survival probability of patients with chronic hepatitis C (HCV) and primary biliary cirrhosis (PBC). Patients stratified medical point = 6 (a), and Child–Turcotte–Pugh score ≥10 (b), and Model of End-Stage Liver Disease (MELD) score ≥15 (c)
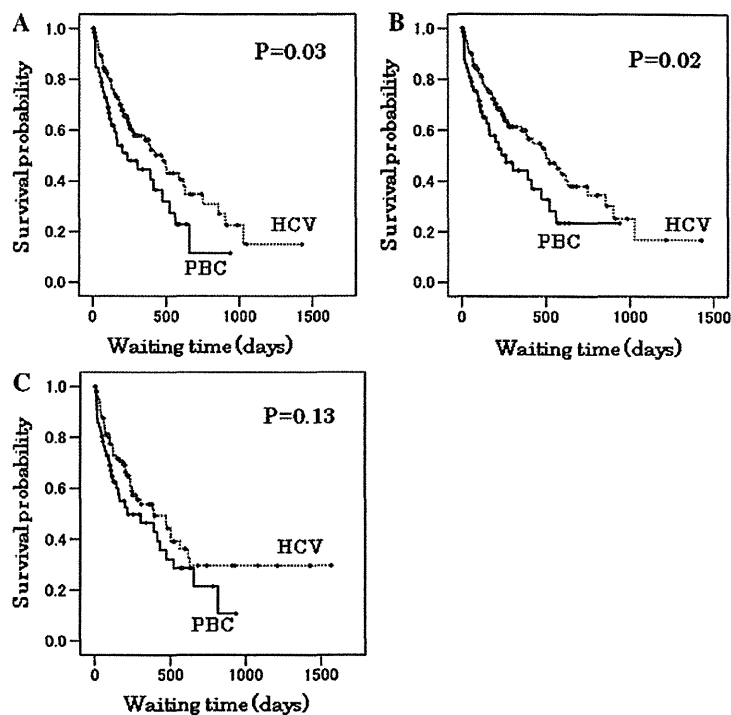
compared with HCV patients. In bivariate analysis, the medical point-adjusted HR of waiting list mortality of PBC patients was significantly higher than that of HCV patients (HR 1.58; 95 % CI 1.07–2.35, $P = 0.02$). The CTP score-adjusted HR also showed a significantly increased risk of waiting -list mortality in PBC patients (HR 2.15; 95 % CI 1.42–3.25, $P < 0.001$). However, the MELD score-adjusted HR did not show a statistically significant risk of waiting list mortality in PBC patients (HR 1.29; 95 % CI 0.87–1.91, $P = 0.21$).

Waiting list survival of patients with HCV and PBC was compared with stratification by each of the disease severity indices (Fig. 4). Patients with medical point 6, for which most PBC and HCV patients were registered, showed a significantly shorter waiting list survival for PBC patients than of HCV patients (median 261 vs. 503 days, $P = 0.02$). In patients with CTP score ≥10, the score classified as C, the shorter waiting list survival of PBC patients was also significant (median 235 vs. 475 days, $P = 0.03$). On the other hand, when they were selected by MELD ≥15, the score indicating patients who can be expected to achieve improved survival with liver transplantation [12], there was no significant difference in the waiting list survival rate between them ($P = 0.13$).

Discussion

The result of this study clearly indicated that the most common reason for removal from the waiting list in Japan was "waiting list death", which was a combination of

death and becoming too sick for transplantation. The waiting list death included 58.1 % of all the patients removed from the list. In the United States, a recent report indicated that waiting list death was the reason for removal from the list in 25.9 % of adult patients [1]. Although this report included patients with acute liver failure and re-transplantation, high waiting list mortality in Japan was evident. Thus, the high mortality rate on the liver transplant waiting list is a major challenge in Japan. Moreover, severe donor organ shortage in Japan should contribute to the high waiting list mortality [13]; an improved organ allocation policy will be necessary to cause a decrease in waiting list death.

In this study, we found that PBC patients had a significantly higher risk of waiting list mortality compared with patients with other etiologies in the JOT registry. Since PBC is currently the third most common diagnosis in the JOT registry for liver transplantation, poor waiting list survival of PBC patients would contribute to the high waiting list mortality in Japan. PBC is a cholestatic liver disease that causes bile duct deterioration and progresses slowly to a terminal phase characterized by hyperbilirubinemia, signs of decompensated cirrhosis, ascites, and variceal bleeding. Only one type of medical therapy, involving the use of ursodeoxycholic acid (UDCA), is now widely recognized to improve the prognosis of PBC patients. Many studies have shown that UDCA therapy not only improves biochemical indices, but also delays histologic progression and improves survival without transplantation [14–16]. However, evidence has also accumulated that the