Table 4. Risk ratios for death in interferon and control groups

	All deaths			Liver-related deaths		
	Risk ratio	95% CI	*P* value	Risk ratio	95% CI	*P* value
Control group	1.00			1.00		
IFN group	0.37	0.13–1.05	0.06	0.80	0.25–2.53	0.71
Sustained virological response	0.15	0.04–0.59	0.01	0.12	0.01–1.16	0.07
Virological non-response	0.44	0.16–1.23	0.12	0.97	0.31–3.05	0.96
Sustained biochemical response	0.18	0.05–0.65	0.01	0.10	0.01–0.95	0.05
Transient biochemical response	0.24	0.07–0.87	0.03	0.50	0.11–2.21	0.36
Biochemical non-response	0.54	0.19–1.53	0.24	1.26	0.40–4.03	0.69

Age, sex, time of liver biopsy (until 1992/after 1993) and histologic staging score were adjusted in the Cox proportional hazard analysis

SMR

The SMRs in the IFN and control groups are shown in Table 5 and Fig. 3. In the control group, overall mortality was slightly higher than that in the sex- and age-matched general population (SMR, 1.40; 95% CI, 0.76–2.45). On the other hand, overall mortality in the IFN group was significantly lower compared with that of the general population (SMR, 0.73; 95% CI, 0.52–0.98). Liver-related mortality was high in the control group (SMR, 10.70; 95% CI, 4.29–22.05), and it was also high in the IFN group (SMR, 5.05; 95% CI, 3.38–7.26), although it was half of that in the control group. In the patients with sustained virological response, liver-related mortality (SMR, 0.65; 95% CI, 0.01–3.61) was very low compared with that in the control group, and it was similar to that for the general population. On the contrary, liver-related mortality was high in virological non-responders (SMR, 6.71; 95% CI, 4.46–9.70).

In terms of biochemical response, the SMRs for liver-related death of sustained and transient biochemical responders in the IFN groups were low compared with that in the control group (SMR, 0.53; 95% CI, 0.01–2.97 and SMR, 3.25; 95% CI, 0.87–8.32, respectively). In the patients with biochemical non-response, liver-related mortality was high, and was equal to that in the control group (SMR, 9.12; 95% CI, 5.84–13.57).

The IFN group showed lower liver-unrelated mortality than the general population (SMR, 0.25; 95% CI, 0.13–0.43), whereas the control group had liver-unrelated mortality similar to the general population (SMR, 0.71; 95% CI, 0.26–1.55).

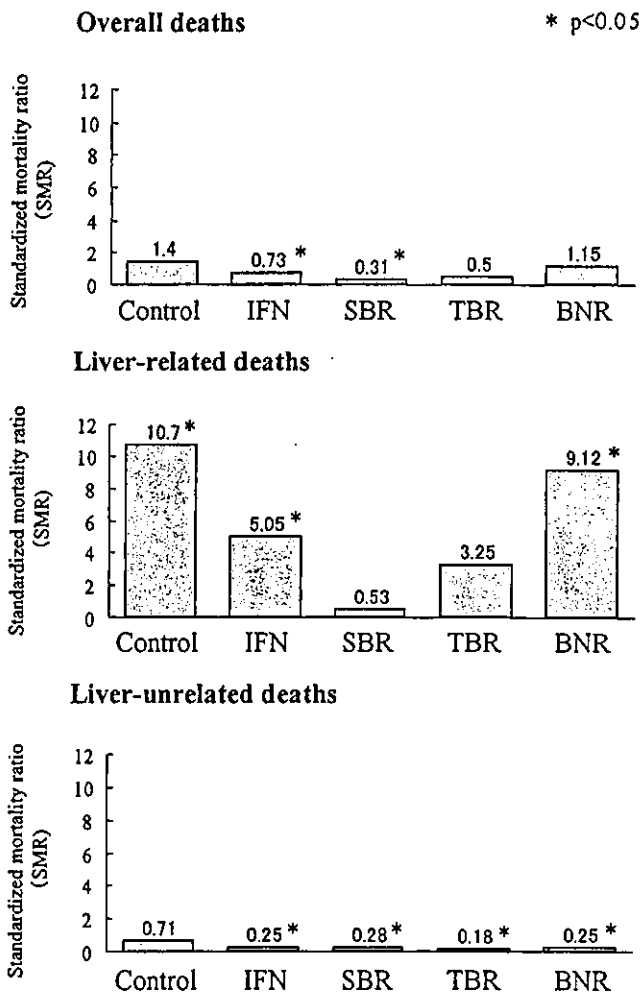

Fig. 3. Standardized mortality ratios (*SMRs*) for overall, liver-related, and liver-unrelated deaths. *SBR*, sustained biochemical response; *TBR*, transient biochemical response; *BNR*, biochemical non-response. When the SMR did not include unity, we considered the difference from the expected number of deaths to be significant

Discussion

There have been a few reports regarding the effect of IFN therapy on survival in chronic hepatitis C patients.[10,16–19] Yoshida et al.[17] reported that IFN therapy had a preventive effect on liver-related death, bringing

Table 5. Standardized mortality ratios (SMRs) in interferon and control groups

	All deaths			Liver-related deaths			Liver-unrelated deaths		
	Observed	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)
Control group	13	9.1	1.40 (0.76–2.45)	7	0.7	10.70 (4.29–22.05)	6	8.4	0.71 (0.26–1.55)
Interferon group	42	57.8	0.73 (0.52–0.98)	29	5.7	5.05 (3.38–7.26)	13	52.0	0.25 (0.13–0.43)
Sustained virological response	4	15.8	0.25 (0.07–0.65)	1	1.5	0.65 (0.01–3.61)	3	14.3	0.21 (0.04–0.61)
Virological non-response	38	41.7	0.91 (0.64–1.25)	28	4.2	6.71 (4.46–9.70)	10	37.6	0.27 (0.13–0.49)
Sustained biochemical response	6	19.5	0.31 (0.11–0.67)	1	1.9	0.53 (0.01–2.97)	5	17.6	0.28 (0.09–0.66)
Transient biochemical response	6	12.1	0.50 (0.18–1.08)	4	1.2	3.25 (0.87–8.32)	2	10.9	0.18 (0.02–0.66)
Biochemical non-response	30	26.2	1.15 (0.77–1.64)	24	2.6	9.12 (5.84–13.57)	6	23.5	0.25 (0.09–0.55)

A difference from the expected number of deaths was considered significant when the 95% confidence interval (CI) of SMR did not include unity

about improved survival of chronic hepatitis C patients, as assessed by multivariate analysis and SMR. Recently, we also reported that IFN therapy improved survival by preventing liver-related deaths in patients with chronic hepatitis C, in a multicenter, large-scale, retrospective cohort study.[20] In that study, we showed that liver-related mortality, as well as overall mortality, was much higher in untreated patients than in IFN-treated patients, as assessed by SMR. Furthermore, we found that patients showing sustained and transient biochemical responses to IFN therapy had a very low risk of death compared with untreated patients.

In this study, we evaluated the effect of IFN therapy on survival in patients over 60 years of age with histologically proven chronic hepatitis C, by SMR and by risk ratio calculated by Cox proportional hazard regression analysis. Compared with the general population, liver-related mortality was high in the IFN-treated patients (SMR, 5.05), but it was much lower than that in the control group (SMR, 10.70). Yoshida et al.[17] also examined the effect of IFN therapy on liver-related mortality in chronic hepatitis C patients over 60 years of age in their large-scale retrospective cohort study, and reported that the SMR for liver-related death in IFN-treated patients was much lower than that in the untreated patients, which was consistent with our result. In our IFN group, sustained virological responders and sustained biochemical responders had very low liver-related mortality (SMR, 0.65 and 0.53, respectively), which was equal to that in the sex- and age-matched general population. Multivariate regression analysis also showed that IFN therapy reduced the risk of liver-related death in sustained virological responders by 88% and in sustained biochemical responders by 90%. The overall mortality in the control group was not high (SMR, 1.40), whereas that in the IFN group was significantly lower in comparison with the sex- and age-matched general population (SMR, 0.73). These results may reflect a selection bias due to the nature of the liver biopsy procedure, which was undergone by all of the patients in our study. This kind of selection bias may occur, as aged patients sometimes have illnesses other than liver disease, which make a liver biopsy difficult. Furthermore, IFN-treated patients had a significantly lower risk of liver-unrelated mortality compared with the untreated patients. It seems likely that this may be attributed not to the beneficial effect of IFN therapy on liver-unrelated mortality but to a selection bias in using IFN; only the patients who had no serious diseases, such as cardiovascular disease, received IFN therapy. However, our study indicated that IFN therapy could reduce liver-related mortality, particularly in patients with sustained virological or biochemical response.

In the patients with a transient biochemical response, liver-related mortality was low when compared with the

control group, as assessed by SMR. The SMR of the transient biochemical responders (3.25; 95% CI, 0.87–8.32), which included unity, was lower than that in the control patients (10.70; 95% CI, 4.29–22.05). Similarly, the risk ratio for liver-related death in transient biochemical responders was 0.50, although this was not significant. On the other hand, SMR, as well as the risk of liver-related death estimated by multivariate analysis in the biochemical non-responders (SMR, 9.12; adjusted risk ratio, 1.26), was similar to that in the control patients. These data suggest that a reduction in liver-related mortality by IFN therapy can be expected in patients showing a transient biochemical response. Retreatment or long-term treatment with IFN might lead to an improved survival rate in transient biochemical responders, although such treatment may not be easy with some aged patients.

There was no difference between the baseline characteristics of the IFN and control groups, except for the age distribution. However, because our study was a retrospective cohort study, it had some limitations. Because the time at liver biopsy in the control group was earlier than that in the IFN group, lead-time bias may have existed. The survival of the IFN group could be higher than that of the control group. To minimize this bias, 5-year time-specific mortality rates for the general population were prepared in the SMR analysis. Furthermore, the time at liver biopsy was included as a variable for the multivariate analysis. Another limitation of our study is the small number of patients in the control group compared with the IFN group. This limitation may also be overcome by calculating the SMRs of the IFN and control groups, representing the ratio of the observed number of deaths to the expected number of deaths, calculated after taking sex-, calendar time-, and cause-specific mortality rates for the general population into consideration. The beneficial effect of IFN therapy on survival in the aged patients with chronic hepatitis C resulting from the SMR analysis was consistent with that of the Cox proportional hazard regression analysis.

In conclusion, we showed in this study that IFN therapy reduced liver-related mortality in aged patients with chronic hepatitis C, especially in those exhibiting a biochemical response and in those showing a sustained virological response. IFN therapy is recommended for aged patients with chronic hepatitis C in whom a biochemical response or a sustained virological response can be expected, after screening for diseases other than chronic hepatitis C.

References

1. Di Bisceglie AM. Hepatitis C and hepatocellular carcinoma. Semin Liver Dis 1995;15:64–9.
2. Nishioka K, Watanabe J, Furuta S, Tanaka E, Iino S, Suzuki H, et al. A prevalence of antibody to the hepatitis C virus in patients with hepatocellular carcinoma in Japan. Cancer 1991;67:429–33.
3. Tsukuma H, Hiyama T, Tanaka S, Nakao M, Yabuuchi T, Kitamura T, et al. Risk factors for hepatocellular carcinoma among patients with chronic liver disease. N Engl J Med 1993; 328:1797–801.
4. Ikeda K, Saitoh S, Koida I, Arase Y, Tsubota A, Chayama K, et al. A multivariate analysis of risk factors for hepatocellular carcinogenesis: a prospective observation of 795 patients with viral and alcoholic cirrhosis. Hepatology 1993;18:47–53.
5. Kasahara A, Hayashi N, Mochizuki K, Takayanagi M, Yoshioka K, Kakumu S, et al. Risk factors for hepatocellular carcinoma and its incidence after interferon treatment in patients with chronic hepatitis C. Hepatology 1998;27:1394–402.
6. Imai Y, Kawata S, Tamura S, Yabuuchi I, Noda S, Inada M, et al. Relation of interferon therapy and hepatocellular carcinoma in patients with chronic hepatitis C. Ann Intern Med 1998;129:94–9.
7. Yoshida H, Shiratori Y, Moriyama M, Arakawa Y, Ide T, Sata M, et al. Interferon therapy reduces the risk for hepatocellular carcinoma: national surveillance program of cirrhotic and noncirrhotic patients with chronic hepatitis C in Japan. Ann Intern Med 1999; 131:174–81.
8. Okanoue T, Itoh Y, Minami M, Sakamoto S, Yasui K, Sakamoto M, et al. Interferon therapy lowers the rate of progression to hepatocellular carcinoma in chronic hepatitis C but not significantly in an advanced stage; a retrospective study of 1146 patients. J Hepatol 1999;30:653–9.
9. Ikeda K, Saitoh S, Arase Y, Chayama K, Suzuki Y, Kobayashi M, et al. Effect of interferon therapy on hepatocellular carcinogenesis in patients with chronic hepatitis type C: a long-term observation study of 1643 patients using statistical bias correction with proportional hazard analysis. Hepatology 1999;29:1124–30.
10. Tanaka H, Tsukuma H, Kasahara A, Hayashi N, Yoshihara H, Masuzawa M, et al. Effect of interferon therapy on the incidence of hepatocellular carcinoma and mortality of patients with chronic hepatitis C: a retrospective cohort study of 738 patients. Int J Cancer 2000;87:741–9.
11. Benvegnu L, Chemello L, Noventa F, Fattovich G, Pontisso P, Alberti A. Retrospective analysis of the effect of interferon therapy on the clinical outcome of patients with viral cirrhosis. Cancer 1998;83:901–9.
12. Valla DC, Chevallier M, Marcellin P, Payen JL, Trepo C, Fonck M, et al. Treatment of hepatitis C virus-related cirrhosis: a randomized, controlled trial of interferon alfa-2b versus no treatment. Hepatology 1999;29:1870–5.
13. Serfaty L, Aumaitre H, Chazouilleres O, Bonnand AM, Rosmorduc O, Poupon RE, et al. Determinants of outcome of compensated hepatitis C virus-related cirrhosis. Hepatology 1998; 27:1435–40.
14. Nishiguchi S, Shiomi S, Nakatani S, Takeda T, Fukuda K, Tamori A, et al. Prevention of hepatocellular carcinoma in patients with chronic active hepatitis C and cirrhosis. Lancet 2001;357:196–7.
15. Fattovich G, Giustina G, Degos F, Tremolada F, Diodati G, Almasio P, et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. Gastroenterology 1997;112:463–72.
16. Niederau C, Lange S, Heintges T, Erhardt A, Buschkamp M, Hurter D, et al. Prognosis of chronic hepatitis C: results of a large prospective cohort study. Hepatology 1998;28:1687–95.
17. Yoshida H, Arakawa Y, Sata M, Nishiguchi S, Yano M, Fujiyama S, et al. Interferon therapy prolonged life expectancy among chronic hepatitis C patients. Gastroenterology 2002;123:483–91.
18. Okanoue T, Itoh Y, Kirishima T, Daimon Y, Toyama T, Morita A, et al. Transient biochemical response in interferon therapy decreases the development of hepatocellular carcinoma and improves the long-term survival of chronic hepatitis C patients. Hepatology Res 2002;23:62–77.

19. Imazeki F, Yokosuka O, Fukai K, Saisho H. Favorable prognosis of chronic hepatitis C after interferon therapy by long-term cohort study. Hepatology 2003;38:493–502.
20. Kasahara A, Tanaka H, Okanoue T, Imai Y, Tsubouchi H, Yoshioka K, et al. Interferon treatment improves survival in chronic hepatitis C patients showing biochemical as well as virological responses by preventing liver-related death. J Viral Hepat 2004;11:148–56.
21. Davis GL, Balart LA, Schiff ER, Lindsay K, Bodenheimer HC, Perrillo RP, et al. Treatment of chronic hepatitis C with recombinant interferon alpha. A multicenter randomized controlled trial. N Engl J Med 1989;321:1501–6.
22. Di Bisceglie AM, Martin P, Kassianides C, Lisker-Melman M, Murray L, Waggoner J, et al. Recombinant interferon alpha therapy for chronic hepatitis C. A randomized, double blind placebo-controlled trial. N Engl J Med 1989;321:1506–10.
23. Hagiwara H, Hayashi N, Mita E, Hiramatsu N, Ueda K, Takehara T, et al. Quantitative analysis of hepatitis C virus RNA in serum during interferon alfa therapy. Gastroenterology 1993;104:877–83.
24. Kasahara A, Hayashi N, Hiramatsu N, Oshita M, Hagiwara H, Katayama K, et al. Ability of prolonged interferon treatment to suppress relapse after cessation of therapy in patients with chronic hepatitis C: a multicenter randomized controlled trial. Hepatology 1995;21:291–7.
25. Shiratori Y, Kato N, Yokosuka O, Imazeki F, Hashimoto E, Hayashi N, et al. Predictors of the efficacy of interferon therapy in chronic hepatitis C virus infection. Gastroenterology 1997;113:558–66.
26. McHutchison JG, Gordon SC, Schiff ER, Schiffman ML, Lee WM, Rustgi VK, et al. Interferon alpha 2b alone or combination with ribavirin as initial treatment for chronic hepatitis C. N Engl J Med 1998;339:1485–92.
27. Poynard T, Marcellin P, Lee SS, Niederau C, Minuk GS, Ideo G, et al. Randomized trial of interferon alpha 2b plus ribavirin for 48 weeks or for 24 weeks versus interferon alpha 2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. Lancet 1998;352:1426–32.
28. Fried MW, Schiffman ML, Reddy KR, Smith C, Marinos G, Goncales FL. Peginterferon alpha-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002;347:975–82.
29. Tanaka H, Tsukuma H. Hepatitis C virus. In: J Tooze, editor. Cancer survey, vol. 33. New York: Cold Spring Harbor Laboratory Press; 1999. p. 213–35.
30. Yoshizawa H. Trends of hepatitis virus carriers. Hepatology Res 2002;24:S28–39.
31. Tanaka H, Tsukuma H. Characteristics of Japanese patients with liver cancer—epidemiological study based on a comparison between male and female patients. Hepatology Res 2002;24:S11–20.
32. Okanoue T, Yasui K, Sakamoto S, Minami M, Nagao Y, Itoh Y, et al. Side effects of high-dose interferon therapy for chronic hepatitis C. J Hepatol 1996;25:283–91.
33. Desmet VJ, Gerber M, Hoofnagle JH, Manns M, Sheuer PJ. Classification of chronic hepatitis: grading and staging. Hepatology 1994;19:1513–20.
34. Statistics and Information Department, Japan Ministry of Health and Welfare. Vital statistics in Japan (in Japanese). Tokyo: Health and Welfare Statistics Association; 2002.

Journal of Viral Hepatitis, 2004, 11, 148–156

Interferon treatment improves survival in chronic hepatitis C patients showing biochemical as well as virological responses by preventing liver-related death

A. Kasahara,[1] H. Tanaka,[2] T. Okanoue,[3] Y. Imai,[4] H. Tsubouchi,[5] K. Yoshioka,[6] S. Kawata,[7] E. Tanaka,[8] K. Hino,[9] K. Hayashi,[5] S. Tamura,[7] Y. Itoh,[3] K. Kiyosawa,[8] S. Kakumu,[10] K. Okita[9] and N. Hayashi[11] [1]*Department of General Medicine, Osaka University Graduate School of Medicine;* [2]*Department of Cancer Control and Statistics, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka;* [3]*Third Department of Internal Medicine, Kyoto Prefectural University of Medicine, Kyoto;* [4]*Department of Internal Medicine, Ikeda Municipal Hospital, Ikeda;* [5]*Second Department of Internal Medicine, Miyazaki Medical College, Miyazaki;* [6]*Third Department of Medicine, Nagoya University Graduate School of Medicine, Nagoya;* [7]*Department of Internal Medicine and Molecular Science, Osaka University Graduate School of Medicine, Osaka;* [8]*Second Department of Medicine, Shinshu University School of Medicine, Shinshu;* [9]*First Department of Medicine, Yamaguchi University School of Medicine, Yamaguchi;* [10]*Department of Internal Medicine, Division of Gastroenterology, Aichi Medical University School of Medicine, Aichi; and* [11]*Department of Molecular Therapeutics, Osaka University Graduate School of Medicine, Osaka, Japan*

Received June 2003; accepted for publication June 2003

SUMMARY. Interferon therapy for chronic hepatitis C reduces the risk of hepatocellular carcinoma, especially among virological and biochemical responders. However, little is known about the effect of interferon therapy on mortality. We studied the long-term effect of interferon therapy on mortality in patients with chronic hepatitis C. For this retrospective cohort study, 2954 patients with chronic hepatitis C were recruited, of whom 2698 received interferon therapy and 256 did not. The effect of interferon therapy on survival was assessed by standardized mortality ratio (SMR) based on published mortality data for the general Japanese population and by risk ratio calculated by proportional hazard regression. Over 6.0 ± 2.2 years follow-up, death from liver-related diseases was observed in 69 (68%) of 101 deaths among interferon-treated patients and in 42 (81%) of 52 deaths among untreated patients. Compared with the general population, overall mortality was high among untreated patients (SMR: 2.7; 95% CI: 2.0–3.6) but not among interferon-treated patients (SMR: 0.9; 95% CI: 0.7–1.1). Liver-related mortality was extremely high among untreated patients (SMR: 22.2; 95% CI: 16.0–30.0) and less among interferon-treated patients (SMR: 5.5; 95% CI: 4.3–6.9). The risk of death from all causes was lower for interferon-treated than untreated patients (risk ratio: 0.47; 95% CI: 0.261–0.836; $P = 0.01$). The risk of death from liver-related diseases was significantly lower for sustained virological responders (risk ratio: 0.04; 95% CI: 0.005–0.301; $P = 0.002$) compared with untreated patients, but not for nonsustained virological responders. Sustained biochemical responders (risk ratio: 0.03; 95% CI: 0.004–0.230; $P < 0.001$) and transient biochemical responders (risk ratio: 0.18; 95% CI: 0.063–0.532; $P = 0.002$) showed a significantly reduced risk of death from liver-related death, whereas biochemical nonresponders did not. Hence interferon treatment improved survival in chronic hepatitis C patients showing a biochemical as well as a virological response by preventing liver-related deaths.

Keywords: chronic hepatitis C, interferon, liver-related mortality, multivariate analysis, standardized mortality ratio.

Abbreviations: HCC, hepatocellular carcinoma; SMR, standardized mortality ratio.

Correspondence: Akinori Kasahara MD, PhD, Department of General Medicine, Osaka University Graduate School of Medicine, 2-15, Yamadaoka, Suita, Osaka 565-0871, Japan. E-mail: kasahara@hp-gm.med.osaka-u.ac.jp

INTRODUCTION

Hepatitis C virus (HCV) infection rarely resolves spontaneously once it becomes chronic [1]. Consequently, most patients in Japan with chronic HCV infection are likely to progress steadily to liver cirrhosis and hepatocellular carcinoma (HCC), which develops approximately 30 years after blood transfusion [2–4]. HCC is one of the most common malignancies, especially in Southeast Asia, and a major cause of death for patients with chronic HCV infection. In the early 1990s, interferon was introduced worldwide as a therapy for patients with chronic hepatitis C and was effective in inducing normalization of serum alanine aminotransferase (ALT) [5,6], eliminating HCV RNA [7,8], and improving liver histological findings [9–11] in patients with chronic hepatitis C.

To evaluate the effect of interferon therapy on the incidence of HCC and the risk of mortality for chronic hepatitis C patients, a randomized controlled trial is needed. However, a prospective randomized trial with untreated control patients is ethically impossible, because interferon therapy has already been established as a standard treatment for patients with chronic hepatitis C. Therefore, almost all chronic hepatitis C patients, except for cases with medical conditions such as depression, autoimmune disease and severe diabetes mellitus, have been treated with interferon in Japan. Recently, several investigators have reported this therapy as being effective for reducing the incidence of HCC among patients who showed normalization of ALT during and after interferon therapy, as well as among those in whom HCV was eradicated [12–17]. However, a reduced risk of HCC does not necessarily lead to improvement in survival. Indeed, little is known about the effects of interferon therapy on the mortality of patients with chronic hepatitis C. Several investigators [14, 18–23] have tried to evaluate the impact of interferon therapy on mortality. Four of these studies indicated that interferon therapy significantly reduced the mortality of compensated HCV-related cirrhotic patients [18,20] or of chronic hepatitis C patients including patients with compensated cirrhosis [21,23]. However, lack of analysis on response to interferon [18,20–23] or lack of information on disease-specific mortality [20,21] has made it difficult to evaluate the benefits of interferon for survival. Recently, Yoshida *et al.* [24] demonstrated that interferon therapy improved survival by preventing liver-related deaths of chronic hepatitis C patients showing a sustained virological response. However, whether a biochemical response to interferon therapy results in a reduced risk of mortality has not been investigated.

We conducted a multi-centre, large-scale, retrospective cohort study of patients with chronic hepatitis C, who had been enrolled at the end of 1997 at participating hospitals in order to analyse the effect of interferon therapy on the incidence of HCC. The aim of the present study was to examine the effect of interferon therapy on the mortality and causes of death among chronic hepatitis C patients.

PATIENTS AND METHODS

Patients

We recruited chronic hepatitis C patients from four previous studies which were conducted to assess the effect of interferon therapy on the incidence of HCC [12,14,15,17]. All patients meeting the following criteria were included in this study: (i) histological diagnosis of chronic hepatitis or cirrhosis; (ii) no history of clinical signs at entry into the study of complications of cirrhosis, i.e. ascites, jaundice, encephalopathy, or variceal bleeding; (iii) no evidence of HCC at entry into the study as assessed by ultrasonography and/or computed tomography; (iv) absence of serum hepatitis B surface antigen; (v) absence of co-existing liver diseases such as autoimmune hepatitis or primary biliary cirrhosis; (vi) absence of excessive alcohol consumption (>80 g/day); and (vii) absence of human immunodeficiency virus antibodies, as described previously [12,14,15,17]. A total of 3025 patients who met these criteria and whose initial sera tested positive for anti-HCV as determined by either first- or second-generation ELISA (Ortho Diagnostics, Tokyo, Japan) and HCV RNA were included in the study. The sera of patients who had been diagnosed as non-A, non-B hepatitis before anti-HCV testing became available (i.e. before 1989) had been frozen at −80 °C and were retrospectively assayed.

Of the 3025 chronic hepatitis C patients, 2762 had received interferon after 1987, when interferon became available in Japan. Interferon-treated patients received a 4–12-month course of interferon therapy, which was initiated within 1 month of liver biopsy. The remaining 263 patients did not undergo interferon therapy or any other antiviral therapy, including almost all patients with biopsy-proven chronic hepatitis who had refused interferon treatment due to adverse effects, lack of time for therapy, or their inability to undergo treatment as a consequence of depression, severe diabetes mellitus or other medical conditions.

Criteria for biochemical and virological responses to interferon therapy

The biochemical response during the follow-up up to 6 months after the completion of interferon therapy was defined according to previously described criteria with minor modifications [8,9]. In the sustained response group, ALT levels decreased to the normal range during therapy and remained within that range up to 24 weeks after therapy without any abnormal elevation. In the transient response group, ALT levels decreased to the normal range by the end of therapy, remained normal during therapy but returned to abnormal levels during the 24 weeks following interferon therapy. In the no-response group, ALT levels did not decrease to the normal range, or fluctuated during therapy and the subsequent 24 weeks. Both biochemical transient

and nonresponders were designated as nonsustained biochemical responders.

A sustained virological response was defined as HCV RNA negativity at more than 6 months after the cessation of interferon therapy. Patients showing positive HCV RNA at the same time were designated as nonsustained virological responders.

Histological evaluation

Liver biopsy was carried out before interferon therapy in all cases. Specimens were fixed in formaldehyde and embedded in paraffin. The sections were stained with haematoxylin-eosin and Azan-Mallory and analysed by two pathologists without any knowledge of the clinical and laboratory data. Histological findings were scored according to the classification of Desmet *et al.* [25].

Follow-up

The starting date of the follow-up for both the interferon-treated and untreated groups was defined as the date of liver biopsy. Biochemical examinations including α-fetoprotein and abdominal ultrasonography were carried out before interferon therapy and every 3–6 months thereafter at the outpatient clinic of the respective hospitals. The end of the follow-up was the date of death or the latest confirmation of survival. Follow-up data on the patients were obtained from the participating hospitals. Follow-up data that were not available from the hospitals were collected from the resident registry of the local municipal office. Death from liver-related disease was defined as death from HCC, liver failure determined by the presence of one or more of ascites, jaundice and hepatic encephalopathy, or variceal bleeding diagnosed on the basis of endoscopic findings of patients presenting with upper gastrointestinal haemorrhage.

Five untreated patients were observed for over 162 months, which corresponded to the longest period of observation of those treated with interferon. In these subjects, only the follow-up data up to 162 months were considered. Seventy-one patients whose follow-up period was shorter than 12 months were excluded from the study. The final numbers of study subjects were 2698 for the interferon-treated group and 256 for the untreated group.

Informed consent was obtained from each patient included in the study. The study protocol was in accordance with the Helsinki Declaration of 1975 (revised in 1983) and approved by the Ethical Committee of the Osaka University Graduate School of Medicine.

Statistical analysis

The chi-square test was used to compare the frequency of gender between the interferon-treated and untreated groups. The difference in age at liver biopsy and ALT between the two groups, expressed as median, was assessed for significance with the Student's *t*-test. The Wilcoxon rank-sum test was used to compare the distribution of age at liver biopsy and histological staging. Cumulative survival curves were determined with the Kaplan–Meier method, and the log-rank test was used to compare the cumulative survival rates.

The observed number of deaths was compared with the expected number, which was calculated by applying sex, 5-year age, 5-year calendar time, and cause-specific mortality rates for the general population in Japan, as prepared by the Statistics and Information Department, Japan Ministry of Health and Welfare [26]. The standardized mortality ratio (SMR) was expressed by dividing the observed number of deaths by the expected number of deaths. The standard error and the 95% CI of SMR were estimated by assuming Poisson's distribution, and differences in mortality between the study cohort and the general population were considered to be significant if the CI did not include unity.

Survival was also analysed by using Cox proportional hazards regression controlling for age (continuous variable), gender, stages of liver fibrosis (stage: 0/1/2/3/4) and time at liver biopsy (1991/1992). Risk ratios attributable to biochemical sustained, transient and no responses and to virological sustained and nonsustained responses were calculated in comparison with no treatment by using dummy variables.

Data analysis was performed with the SAS/PC statistical package (SAS Institute, Cary, NC, USA). All reported *P*-values were two-sided and $P < 0.05$ was considered to be significant.

RESULTS

Patient characteristics at entry

Of the 2698 patients treated with interferon, 901 (33.3%) had a sustained biochemical response, 701 (26.0%) a transient biochemical response and the remaining 1096 patients (40.6%) were classified as biochemical nonresponders. Serum HCV RNA remained negative at more than 6 months after cessation of interferon therapy in 738 (81.9%) of the sustained biochemical responders, designated as sustained virological responders, whereas serum HCV RNA remained positive in 133 (14.8%). Serum HCV RNA was not examined after the termination of interferon therapy in 30 sustained biochemical responders, who were excluded from the analysis according to virological responses to interferon. Positive HCV RNA after interferon therapy was detected in all of the biochemical transient and nonresponders.

The demographic and clinical features of interferon-treated patients according to virological and biochemical responses to interferon and of untreated patients at the time of enrolment are summarized in Table 1. Untreated patients were significantly older than interferon-treated patients ($P = 0.04$), but frequency distribution of age at liver biopsy

Table 1 Characteristics of interferon-treated patients according to virological and biochemical responses to interferon and of untreated patients

	Interferon-treated							
	Virological response		Biochemical response					
	SVR (n = 738)	non-SVR (n = 1930)	SBR (n = 901)	TBR (n = 701)	BNR (n = 1096)	Total (n = 2698)	Untreated (n = 256)	P-value
Median age (range)	51 (20–72)	54 (20–76)	52 (20–73)	53 (20–75)	54 (20–76)	53 (20–76)	54 (21–72)	0.04
Age at biopsy (%)								
≤49	337 (45.7)	687 (35.6)	392 (43.5)	277 (39.5)	369 (33.7)	1038 (38.5)	75 (29.3)	0.12
50–59	240 (32.5)	759 (39.3)	303 (33.6)	280 (39.9)	428 (39.1)	1011 (37.5)	123 (48.9)	
≥60	161 (21.8)	484 (25.1)	206 (22.9)	144 (20.5)	299 (27.3)	649 (24.1)	58 (22.7)	
Sex (M/F)	507/231	1210/720	595/306	440/261	703/393	1738/960	157/99	0.32
Median ALT (U/L), SD (range)	91 (7–1110)	92 (11–1195)	87 (7–1110)	79 (13–1195)	103 (13–828)	92 (7–1195)	98 (9–563)	0.57
Stage of fibrosis (%)								
0	5 (0.7)	11 (0.6)	7 (0.8)	4 (0.6)	5 (0.9)	16 (0.6)	9 (3.5)	0.34
1	259 (35.1)	476 (24.7)	337 (37.4)	228 (32.5)	190 (17.3)	755 (28.0)	84 (32.8)	
2	263 (35.6)	614 (31.8)	297 (33.0)	238 (34.0)	349 (31.8)	884 (32.8)	40 (15.6)	
3	189 (25.6)	725 (37.6)	235 (26.1)	209 (29.8)	471 (43.0)	915 (33.9)	93 (36.3)	
4	22 (3.0)	104 (5.4)	25 (2.8)	22 (3.1)	81 (7.4)	128 (4.7)	30 (11.7)	

SVR, sustained virological responders; SBR, sustained biochemical responders; TBR, transient biochemical responders; BNR, biochemical nonresponders; ALT, alanine aminotransferase.

and the stages of liver fibrosis, gender and ALT did not differ significantly. In sustained biochemical responders, the ratio of male patients and median ALT levels were significantly higher for patients with HCV eradication than for those without it ($P < 0.001$, each), whereas median age and the frequency distribution of the stages of liver fibrosis were not significantly different between the two groups.

Follow-up data

The mean period of observation (total cases: 6.0 ± 2.2 years) of the interferon-treated and untreated patients was 5.8 and 8.0 years, respectively, with the former being significantly shorter than the latter ($P = 0.0001$) because interferon therapy was not introduced in Japan until 1987.

Table 2 Follow-up data for interferon-treated patients according to virological and biochemical responses to interferon and for untreated patients

	Interferon-treated						
	Virological response		Biochemical response				
	SVR (n = 738)	non-SVR (n = 1930)	SBR (n = 901)	TBR (n = 701)	BNR (n = 1096)	Total (n = 2698)	Untreated (n = 256)
Mean period of observation, year (SD)	5.7 (2.0)	5.8 (1.9)	5.6 (2.0)	5.7 (1.8)	5.9 (1.9)	5.8 (1.9)	8.0 (3.4)
No. of deaths	7	94	10	10	81	101	52
Liver-related deaths	1	68	1	5	63	69	42
Death from HCC	1	57	1	4	53	58	31
Death from other liver diseases	0	11	0	1	10	11	11
Liver-unrelated deaths	9	26	9	5	18	32	10

SVR, sustained virological responders; SBR, sustained biochemical responders; TBR, transient biochemical responders; BNR, biochemical nonresponders; HCC, hepatocellular carcinoma.

The sustained virological responders, nonsustained virological responders, sustained biochemical responders, transient biochemical responders and biochemical nonresponders were observed for a mean of 5.7, 5.8, 5.6, 5.7 and 5.9 years, respectively (Table 2).

We identified 153 deaths from all causes during the follow-up. The 153 patients who died consisted of 10 sustained biochemical responders (seven of whom were sustained virological responders and three of whom were sustained biochemical responders without HCV eradication), 10 transient biochemical responders, 81 biochemical nonresponders and 52 cases without interferon treatment. Death from all causes did not occur in 30 sustained biochemical responders whose serum HCV RNA was not examined after cessation of interferon therapy. Death from liver-related disease was identified in 111 (73%) of the 153 patients who died: only one death (10%) from liver-related disease (death from HCC) was found among sustained responders with HCV eradication, five (50%) among transient biochemical responders (death from HCC in four cases), 63 (78%) among biochemical nonresponders (death from HCC in 53 cases) and 42 (81%) among untreated patients (death from HCC in 31 cases) (Table 2).

Cumulative survival

The cumulative survival rates from all causes of death were found to be significantly higher for interferon-treated than for untreated patients ($P < 0.001$) (Fig. 1a) The respective 5-year survival rates of interferon-treated and untreated groups were 97.8 and 95.3%, and the 10-year survival rates 87.2 and 77.1%. The cumulative survival rates for sustained virological responders were significantly higher than for nonsustained virological responders ($P < 0.001$) (Fig. 1b), with 5-year survival rates of 99.5 and 97.1%, and 10-year survival rates of 97.8 and 81.9%, respectively. The cumulative survival rates for sustained biochemical responders were significantly higher than for nonsustained biochemical responders ($P < 0.001$). When nonsustained biochemical responders were divided into transient biochemical responders and biochemical nonresponders, the cumulative survival rates for the transient biochemical responders were significantly higher than for the biochemical nonresponders ($P < 0.001$) (Fig. 1c). The respective cumulative survival rates for sustained biochemical responders, transient biochemical responders and biochemical nonresponders were 99.2, 99.1 and 95.8% at the end of the fifth year and 97.8, 97.6 and 72.6% at the end of the 10th year. Among sustained biochemical responders, the cumulative survival rates for sustained virological responders and sustained biochemical responders without HCV eradication were 99.5 and 99.2% at the end of fifth year and 97.8 and 99.2% at the end of the 10th year, showing no statistical significance ($P = 0.18$).

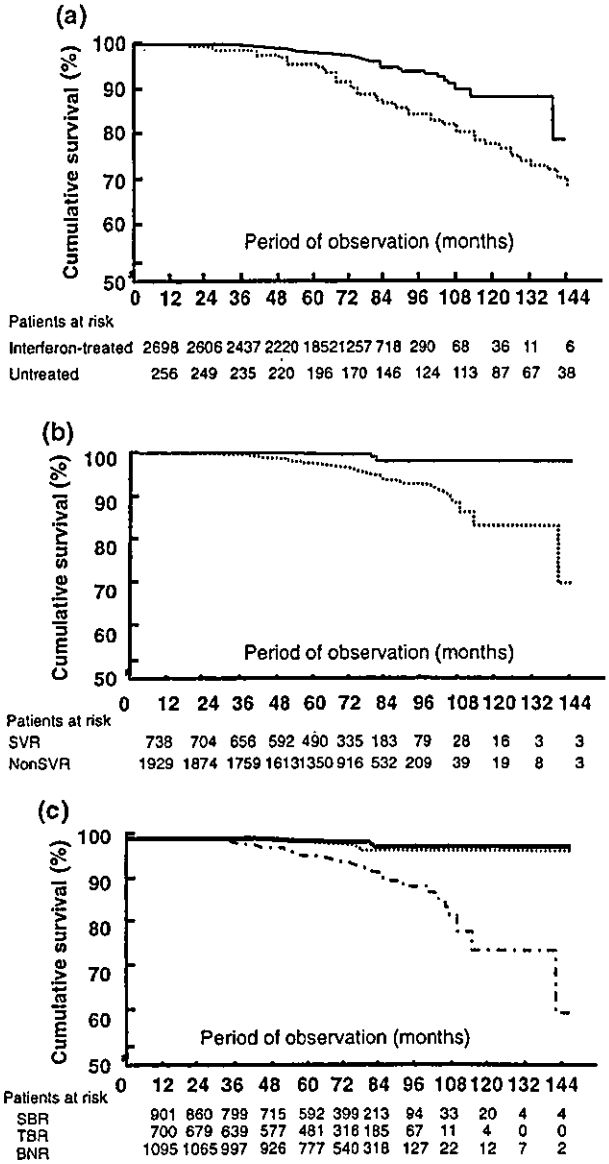

Fig. 1 Cumulative survival rates from all causes of death for patients with chronic hepatitis C. (a) For interferon-treated patients (solid line) and untreated patients (dotted line). (b) According to the virological response to interferon therapy; sustained virological responders (SVR) (solid line) and nonsustained virological responders (non-SVR) (dotted line). (c) In terms of the biochemical responses to interferon, sustained biochemical responders (SBR) (solid line), transient biochemical responders (TBR) (dotted line) and biochemical nonresponders (BNR) (dash-and-dot line).

Standardized mortality ratio

Differences in mortality among interferon-treated and untreated patients from the general population were further assessed by calculating SMR, the ratio of the observed number of deaths to the expected number. Overall mortality

Table 3 Standardized mortality ratios (SMR) in patients with chronic hepatitis C according to virological and biochemical responses to interferon

	Overall deaths			Liver-related deaths			Liver-unrelated deaths		
	Observed	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)
Untreated	52	19.2	2.7 (2.0–3.6)	42	1.9	22.2 (16.0–30.0)	10	17.3	0.6 (0.3–1.1)
Interferon-treated	101	112.7	0.9 (0.7–1.1)	69	12.6	5.5 (4.3–6.9)	32	100.0	0.3 (0.2–0.5)
Virological response									
Sustained (HCV RNA negative)	7	29.8	0.2 (0.1–0.5)	1	3.3	0.3 (0.0–1.7)	6	26.5	0.2 (0.1–0.5)
Nonsustained (HCV RNA positive)	94	82.2	1.1 (0.9–1.4)	68	9.2	7.4 (5.8–9.4)	26	73.0	0.4 (0.2–0.5)
Biochemical response									
Sustained response	10	36.5	0.3 (0.1–0.5)	1	4.0	0.3 (0.0–1.4)	9	32.5	0.3 (0.1–0.5)
Transient response	10	27.5	0.4 (0.2–0.7)	5	3.2	1.6 (0.5–3.7)	5	24.3	0.2 (0.1–0.5)
No response	81	48.8	1.7 (1.3–2.1)	63	5.4	11.6 (8.9–14.9)	18	43.3	0.4 (0.3–0.7)

Difference from the expected number of deaths was considered significant if 95% CI of SMR did not include unity.

for untreated patients (SMR: 2.7; 95% CI: 2.0–3.6) but not for the interferon-treated patients (SMR: 0.9; 95% CI: 0.7–1.1) was significantly higher than for the general population. Liver-related mortality was high for untreated patients (SMR: 22.2; 95% CI: 16.0–30.0) and also for interferon-treated patients, although to a lesser degree (SMR: 5.5; 95% CI: 4.3–6.9) (Table 3). For sustained virological responders overall mortality was low (SMR: 0.2; 95% CI: 0.1–0.5), and liver-related mortality (SMR: 0.3; 95% CI: 0.0–1.7) was equivalent to that for the general population. In contrast, liver-related mortality was high for nonsustained virological responders (SMR: 7.4; 95% CI: 5.8–9.4).

Sustained and transient biochemical responders showed a low overall mortality compared with that for the general population (SMR: 0.3; 95% CI: 0.1–0.5, and SMR: 0.4; 95% CI: 0.2–0.7, respectively), whereas overall mortality was high for biochemical nonresponders (SMR: 1.7; 95% CI: 1.3–2.1). Liver-related mortality was not high for sustained and transient biochemical responders (SMR: 0.3; 95% CI: 0.0–1.4, and SMR: 1.6; 95% CI: 0.5–3.7, respectively) compared with that for the general population, but it was high for biochemical nonresponders (SMR: 11.6; 95% CI: 8.9–14.9) (Table 3). Overall and liver-related mortality for sustained biochemical responders without HCV eradication was equivalent to that for the general population (SMR: 0.5; 95% CI: 0.1–1.5, and SMR: 0.0; 95% CI: 0.0–6.1, respectively).

Interferon-treated patients had a statistically lower risk of liver-unrelated death than the general population (SMR: 0.3; 95% CI: 0.2–0.5), whereas untreated patients did not (SMR: 0.6; 95% CI: 0.3–1.1).

Multivariate analysis

The effect of interferon on the risk of death was assessed by Cox proportional hazards regression controlling for age, gender, score of liver fibrosis and time at liver biopsy. Interferon therapy significantly reduced the risk of overall death to a ratio of only 0.47, in comparison with no treatment. When patients were classified according to virological responses to interferon, sustained virological responders showed reduced risks of overall death (risk ratio: 0.14; 95% CI: 0.056–0.352; $P < 0.001$) and liver-related death (risk ratio: 0.04; 95% CI: 0.005–0.301; $P = 0.002$) compared with untreated patients, whereas nonsustained virological responders did not. Similarly, sustained biochemical responders showed a lower risk of death from all causes (risk ratio: 0.16; 95% CI: 0.069–0.354; $P < 0.001$) and liver-related diseases (risk ratio: 0.03; 95% CI: 0.004–0.230; $P < 0.001$). Transient biochemical responders had a high, but still significantly reduced risk of overall death (risk ratio: 0.19; 95% CI: 0.083–0.445; $P < 0.001$) and liver-related death (risk ratio: 0.18; 95% CI: 0.063–0.532; $P = 0.002$), whereas the risk for nonresponders and untreated patients did not

Table 4 Risk of death in patients with chronic hepatitis C according to virological and biochemical responses to interferon

	All causes of deaths			Liver-related deaths		
	Risk ratio	95% CI	*P*-value	Risk ratio	95% CI	*P*-value
Untreated	1.00			1.00		
Interferon-treated	0.47	0.261–0.836	0.010	0.59	0.312–1.097	0.095
Virological response						
Sustained (HCV RNA negative)	0.14	0.056–0.352	<0.001	0.04	0.005–0.301	0.002
Nonsustained (HCV RNA positive)	0.59	0.327–1.057	0.08	0.76	0.402–1.417	0.380
Biochemical response						
Sustained response	0.16	0.069–0.354	<0.001	0.03	0.004–0.230	<0.001
Transient response	0.19	0.083–0.445	<0.001	0.18	0.063–0.532	0.002
No response	0.78	0.432–1.393	0.394	1.02	0.543–1.900	0.962

Adjusted for age, sex, score of liver fibrosis and period at liver biopsy.

change (Table 4). The risk of overall death for sustained biochemical responders without HCV eradication was lower than for untreated patients, although it did not reach a statistical significance (risk ratio: 0.31; 95% CI: 0.09–1.07; $P = 0.06$).

DISCUSSION

We previously demonstrated that interferon treatment could reduce the risk of HCC development in patients with chronic hepatitis C [12]. Following this, five retrospective studies [13–17] showed a similar effect of interferon on the risk of HCC, especially for virological and biochemical responders. These results suggest that interferon therapy for chronic hepatitis C can prevent the development of HCC, possibly leading to improvement in long-term survival. However, only a few previous studies have assessed the effects of interferon therapy on survival [18–24], and whether interferon therapy also reduces mortality from liver-related disease in patients with chronic HCV infection has not been thoroughly investigated. It is also still unclear what type of response to interferon results in the improvement of long-term survival.

To evaluate the effect of interferon therapy on the risk of mortality for chronic hepatitis C patients, a randomized controlled trial should be carried out. However, a prospective randomized trial with untreated control patients is ethically impossible, because interferon therapy has already been established as the standard modality for patients with chronic hepatitis C. Only two randomized controlled trials of a small number of HCV-related cirrhotic cases have evaluated the effect of interferon therapy on mortality [19,21], but with discrepant results. In contrast, large-scale prospective and retrospective cohort studies [23,24] indicate that interferon therapy for HCV-related cirrhosis or chronic hepatitis C improves long-term survival. In particular, Yoshida *et al.* [24] demonstrated in their recent retrospective cohort study that interferon therapy improved survival of chronic hepatitis C patients by preventing liver-related deaths. However, its beneficial effect was considered to be limited to patients with a sustained virological response.

As ours is a retrospective cohort study, it may be subject to several biases. The interferon-treated and untreated groups had different demographic characteristics, including age and gender. These factors were adjusted for multivariate regression analysis and considered when calculating SMR by applying the corresponding mortality for the general population. Severity of chronic liver disease was adjusted by using the stage of liver fibrosis for multivariate analysis. As the time of liver biopsy of untreated patients was earlier than for interferon-treated patients, mortality for untreated patients may be generally higher than for interferon-treated patients. To avoid this bias, we adjusted the time at liver biopsy for multivariate analysis, and 5-year time-specific mortality rates for the general population were prepared in the SMR analysis. Moreover, the number of untreated patients was small, because most Japanese chronic hepatitis C patients, except for cases with medical problems, have been treated with interferon. However, the relatively small number of untreated patients in comparison with the large number of interferon-treated patients is not likely to have resulted in a substantial overestimation of the effect of interferon therapy on survival as several of the biases already mentioned were controlled in the analyses.

When we compared the observed mortality with the expected mortality for the matched general population by calculating SMR, we were able to demonstrate that chronic hepatitis C patients had higher overall and liver-related mortality than the general population, and that the majority of deaths were liver-related. However, interferon-treated patients had a significantly lower risk of liver-unrelated mortality, whereas untreated patients did not. This may represent a selection bias in the use of interferon therapy, which included patients with no medical problems

except for having chronic liver diseases. However, our multivariate regression analysis clearly showed that interferon therapy reduced the risk of liver-related death in virological responders by 96% and in biochemical responders by 82–97%. These findings indicate that a significant reduction in the risk of death from all causes for patients treated with interferon, shown in the analysis of SMR, was not caused by a selection bias but is mainly attributable to the prevention of liver-related death by interferon therapy.

Our multivariate analysis made it clear that the risks of overall and liver-related deaths for chronic hepatitis C patients displaying a sustained virological response were 86 and 96% lower than for untreated patients. The risk reduction for sustained biochemical responders was almost equal to that for sustained virological responders. Similarly, the SMR analyses showed that liver-related mortality for these patients was equivalent to that for the general population. Thus, and as expected, when patients treated with interferon belong to the sustained virological or biochemical response group, they appear to have the highest long-term survival rate.

Of nonsustained virological responders, the risk of death from all causes and liver-related diseases for transient biochemical responders was significantly lower than for untreated patients, but higher than for sustained biochemical and virological responders. The same effects of interferon therapy on survival were observed in the SMR analyses. Although the follow-up period was not sufficiently long for a reliable and accurate examination of mortality, we would like to emphasize that the risk of death from all causes and liver-related diseases was significantly lower for chronic hepatitis C patients for whom interferon was effective in normalizing ALT than for patients who did not receive interferon, even when HCV was not eradicated. However, the risk of death from all causes and liver-related diseases was not reduced in biochemical nonresponders.

In conclusion, the findings reported here indicate that interferon therapy improves long-term survival in chronic hepatitis C patients showing a biochemical as well as a virological response by preventing liver-related deaths.

REFERENCES

1 Yokosuka O, Kato N, Hosoda K *et al.* Efficacy of long-term interferon treatment in chronic liver disease evaluated by sensitive polymerase chain reaction assay for hepatitis C virus RNA. *Gut* 1995; 37: 721–726.

2 Kiyosawa K, Sodeyama T, Tanaka E *et al.* Interrelationship of blood transfusion, non-A, non-B hepatitis and hepatocellular carcinoma. Analysis by detection of antibody to hepatitis C virus. *Hepatology* 1990; 12: 671–675.

3 Yano M, Kumada H, Kage M *et al.* The long-term pathological evolution of chronic hepatitis C. *Hepatology* 1996; 23: 1334–1340.

4 Ikeda K, Saitoh S, Suzuki Y *et al.* Disease progression and hepatocellular carcinogenesis in patients with chronic viral hepatitis: a prospective observation of 2215 patients. *J Hepatol* 1998; 28: 930–938.

5 Davis GL, Balart LA, Schiff ER *et al.* Treatment of chronic hepatitis C with recombinant interferon alpha. A multicenter randomized controlled trial. *N Engl J Med* 1989; 321: 1501–1506.

6 Di Bisceglie AM, Martin P, Kassianides C *et al.* Recombinant interferon alpha therapy for chronic hepatitis C. A randomized, double blind placebo-controlled trial. *N Engl J Med* 1989; 321: 1506–1510.

7 Hagiwara H, Hayashi N, Mita E *et al.* Detection of hepatitis C virus RNA in serum of patients with chronic hepatitis C treated with interferon-α. *Hepatology* 1992; 15: 37–41.

8 Hagiwara H, Hayashi N, Mita E *et al.* Quantitative analysis of hepatitis C virus RNA in serum during interferon alfa therapy. *Gastroenterology* 1993; 104: 877–883.

9 Kasahara A, Hayashi N, Hiramatsu N *et al.* Ability of prolonged interferon treatment to suppress relapse after cessation of therapy in patients with chronic hepatitis C: a multicenter randomized controlled trial. *Hepatology* 1995; 21: 291–297.

10 Shiratori Y, Imazeki F, Moriyama M *et al.* Histologic improvement of fibrosis in patients with hepatitis C who have showed sustained response to interferon therapy. *Ann Intern Med* 2000; 132: 517–524.

11 Hiramatsu N, Hayashi N, Kasahara A *et al.* Improvement of liver fibrosis in chronic hepatitis C patients treated with natural interferon alpha. *J Hepatol* 1995; 22: 135–142.

12 Kasahara A, Hayashi N, Mochizuki K *et al.* Risk factors for hepatocellular carcinoma and its incidence after interferon treatment in patients with chronic hepatitis C. *Hepatology* 1998; 27: 1394–1402.

13 Yoshida H, Shiratori Y, Moriyama M *et al.* Interferon therapy reduces the risk for hepatocellular carcinoma: national surveillance program of cirrhotic and noncirrhotic patients with chronic hepatitis C in Japan. *Ann Intern Med* 1999; 131: 174–181.

14 Tanaka H, Tsukuma H, Kasahara A *et al.* Effect of interferon therapy on the incidence of hepatocellular carcinoma and mortality of patients with chronic hepatitis C: a retrospective cohort study of 738 patients. *Int J Cancer* 2000; 87: 741–749.

15 Imai Y, Kawata S, Tamura S *et al.* Relation of interferon therapy and hepatocellular carcinoma in patients with chronic hepatitis C. *Ann Intern Med* 1998; 129: 94–99.

16 Ikeda K, Satoh S, Arase Y *et al.* Effect of interferon therapy on hepatocellular carcinogenesis in patients with chronic hepatitis type C: a long-term observation study of 1643 patients using statistical bias correction with proportional hazard analysis. *Hepatology* 1999; 29: 1124–1130.

17 Okanoue T, Itoh Y, Minami M *et al.* Interferon therapy lowers the rate of progression to hepatocellular carcinoma in chronic hepatitis C but not significantly in an advanced stage: a retrospective study of 1146 patients. *J Hepatol* 1999; 30: 653–659.

18 Benvegnu L, Chemello L, Noventa F, Fattovich G, Pontisso P, Alberti A. Retrospective analysis of the effect of interferon therapy on the clinical outcome of patients with viral cirrhosis. *Cancer* 1998; 83: 901–909.
19 Valla DC, Chevallier M, Marcellin P *et al.* Treatment of hepatitis C virus-related cirrhosis: a randomized, controlled trial of interferon alfa-2b versus no treatment. *Hepatology* 1999; 29: 1870–1875.
20 Serfaty L, Aumaitre H, Chazouilleres O *et al.* Determinants of outcome of compensated hepatitis C virus-related cirrhosis. *Hepatology* 1998; 27: 1435–1440.
21 Nishiguchi S, Shiomi S, Nakatani S *et al.* Prevention of hepatocellular carcinoma in patients with chronic active hepatitis C and cirrhosis. *Lancet* 2001; 357: 196–197.
22 Fattovich G, Giustina G, Degos F *et al.* Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. *Gastroenterology* 1997; 112: 463–472.
23 Niederau C, Lange S, Heintges T *et al.* Prognosis of chronic hepatitis C: results of a large prospective cohort study. *Hepatology* 1998; 28: 1687–1695.
24 Yoshida H, Arakawa Y, Sata M *et al.* Interferon therapy prolonged life expectancy among chronic hepatitis C patients. *Gastroenterology* 2002; 123: 483–491.
25 Desmet VJ, Gerber M, Hoofnagle JH, Manns M, Sheuer PJ. Classification of chronic hepatitis: grading and staging. *Hepatology* 1994; 19: 1513–1520.
26 Statistics and Information Department, Japan Ministry of Health and Welfare. *Vital Statistics in Japan* (in Japanese). Tokyo: Health and Welfare Statistics Association, 2002.

0041-1337/04/7706-880/0
TRANSPLANTATION

Vol. 77, 880–885, No. 6, March 27, 2004
Printed in U.S.A.

REHOSPITALIZATION AFTER PEDIATRIC LIVING-DONOR LIVER TRANSPLANTATION

TAKASHI ORII,[1,2,4] NOBUHIRO OHKOHCHI,[3] AND SUSUMU SATOMI[2]

Background. **Although rehospitalization is one of the factors affecting quality of life after successful liver transplantation, the effects of rehospitalization have not been assessed to date.**

Patients and Methods. **Of 40 consecutive cases of pediatric living-donor liver transplantation (LDLT) performed between April 1994 and October 2000, 28 patients with a graft survival of more than 1 year were enrolled in this study to examine rehospitalization after successful LDLT. The rate and cause of rehospitalization were analyzed retrospectively on the basis of medical records.**

Results. **A total of 23 of the 28 patients were rehospitalized. There were 84 episodes of rehospitalization. The mean number of rehospitalization days per episode per patient was 21.06±21.02 days. The rate of total rehospitalization days to the days after the hospitalization for LDLT was 6.56%±8.73%. Rehospitalization episodes were attributable to the following: cholangitis (21.4%), viral infection (16.7%), and portal stenosis (PS) (13.1%). Rehospitalization as the result of rejection accounted for 9.5% of the episodes. The period of rehospitalization was long in the case of cholangitis (49.7±62.4 days), PS (13.8±13.4 days), and rejection (52.9±45.4 days). Although there were a lot of rehospitalization episodes as the result of viral infection subsequent to cholangitis, each rehospitalization period lasted 4.4±6.6 days.**

Conclusion. **It is suggested that prevention of cholangitis and PS, which were the causes of frequent and long rehospitalization periods, would result in a reduction of rehospitalization and therefore a better quality of life after pediatric LDLT.**

The number of pediatric patients requiring living-donor liver transplantation (LDLT) is increasing year after year in Japan and Western countries. There is a shortage of brain-dead donors in Japan and Western countries, where cadaveric-donor liver transplantation (CDLT) is infrequently performed. The long-term prognosis of patients who undergo LDLT is good (*1*), and LDLT has already become an important procedure supporting liver transplantation. However, because a more highly advanced technique is used in LDLT than in CDLT, vascular and biliary complications are bound to occur, and because various other complications that are common in transplantation (e.g., rejection and infection) may also occur, frequent rehospitalization is inevitable after successful LDLT. Because the patient's communication with his or her family is interrupted, social participation is delayed as the result of long absences from kindergarten or school. Medical expenses are also increased by rehospitalization. An improvement in quality of life, which should be obtained after liver transplantation, is not necessarily acquired because of poor physical or social conditions. We investigated (1) rehospitalization as one of the determining factors of quality of life after pediatric LDLT, (2) the causes of rehospitalization, and (3) ways to reduce the frequency and duration of rehospitalization.

MATERIALS AND METHODS

Of 40 consecutive cases of pediatric LDLT performed between April 1994 and October 2000, 28 demonstrating a graft survival of more than 1 year were reviewed. The age at transplantation varied from 6 months to 17 years (mean 4.6 years±5.2 years). Thirteen patients were male, and 15 patients were female. The most frequent indication was biliary atresia (n=24, 85.7%) followed by Alagille syndrome (n=1), cryptogenic liver cirrhosis (n=1), primary sclerosing cholangitis (n=1), and hepatopulmonary syndrome as the result of patent ductus venosus (n=1). Three patients had incompatible blood types, and two patients had a positive lymphocyte cross-match (T cell, warm (TW)≥50%). No patients demonstrated an active infection requiring medical treatment, except for one patient whose native liver was the source of infection. Eight patients, who were

[1] Department of Surgery, Sendai Shakaihoken Hospital, Sendai, Japan.
[2] Division of Advanced Surgical Science and Technology, Department of Surgery, Graduate School of Medicine, Tohoku University, Sendai, Japan.
[3] Department of Surgery, Institute of Clinical Medicine, Tsukuba University, Tsukuba, Japan.
[4] Address correspondence to: Takashi Orii, M.D., Department of Surgery, Sendai Shakaihoken Hospital, 3-16-1 Tsutsumimachi, Aobaku, Sendai 981–8501, Japan. E-mail: orii-ltx@ya2.so-net.ne.jp.
Received 28 May 2003. Revised 10 July 2003. Accepted 22 October 2003.

DOI: 10.1097/01.TP.0000116566.98067.7E

seronegative for cytomegalovirus (CMV) infection, received liver grafts from seropositive donors. Epstein-Barr virus (EBV) capsid antigen (CA)-immunoglobulin G results were positive in 14 patients and negative in all of the other patients who had received liver grafts from positive donors. No patients demonstrated hepatitis B or C virus infections. The *z* score of height and weight, laboratory data at LDLT, and frequency of past operations before LDLT were analyzed from the medical records.

One of the two parents of each patient agreed to be the living donor; the parents' ages ranged from 24 to 50 years (mean 35.3±6.6 years). The left hepatic lobe or left lateral segment was resected to be used as a liver graft. LDLT was performed orthotopically after the whole native liver of the recipient was removed. A few designated surgeons performed the vascular and biliary reconstruction; a specialist with full training microscopically anastomosed the hepatic artery. In regard to biliary reconstruction, all patients underwent hepaticojejunostomy by the Roux-en-Y procedure. Biliary drainage was external or internal (lost tube). The graft weight (GW) to standard liver volume (SLV) was calculated from the body weight and computed tomography of the donor (2), and the procedure of abdominal closure was selected according to intra-abdominal pressure. A total of 9 of 13 patients with the unclosed muscle layer underwent the closure operation during the first hospital stay for LDLT.

Immunosuppression was begun with cyclosporine A (CsA), azathioprine, and methylprednisolone (MP), or FK506 and MP. MP was stopped 1 year after LDLT in patients treated with FK506 or after 2 years in patients treated with CsA and in patients with incompatible blood type or a positive T-lymphocyte cross-match.

Sulfamethoxazole-trimethoprim was administered to all patients for 6 months after LDLT to prevent *Pneumocystis carinii* infection, and acyclovir was administered for 3 months to prevent CMV infection.

The patients were discharged from the hospital when their liver function was stabilized, their blood level of CsA or FK506 reached the target level, and their general condition was stabilized. The mean hospitalization period after LDLT was 104.4 days (range 29–393 days). The patients were seen in the outpatient clinic every 2 weeks during the first year and every 1 month thereafter. In every visit to the outpatient clinic, they underwent hematologic and serologic examinations, blood concentration monitoring of immunosuppressive agents, and duplex Doppler ultrasonography. The examination of CMV antigenemia and serologic examination of EBV were performed every 3 months postoperatively. Patients were rehospitalized when liver function test results were abnormal or there was high fever, respiratory symptoms, nausea, vomiting, diarrhea, or unusual hepatic blood flow. Bacterial cultures of every specimen or hematoserologic examinations were performed at every rehospitalization episode. Whenever rejection was suspected, liver biopsy was performed.

The patient numbers were arranged from 1 to 28 in accordance with the frequency of rehospitalizations.

Observed proportions were compared by using the chi-square test and unpaired Student *t* test. Calculations were performed using StatView 4.51 software (Abacus Concepts Inc., Berkeley, CA), and differences with a *P* value of less than 0.05 were considered statistically significant.

RESULTS

The mean follow-up period was 3.94±2.21 years, and 23 of the 28 patients were rehospitalized. There were 84 episodes of rehospitalization. The duration of rehospitalization per episode was 0 to 76.7 days, with an average of 21.06±21.02 days. The rate of total rehospitalization days to the days after the first hospitalization for LDLT was 0% to 39.4%, with an average of 6.56%±8.73%.

The causes of rehospitalization are shown in Table 1. High fever accompanied by symptoms of upper respiratory tract infection, without a specific virus such as CMV or EBV or causative bacteria by bacterial cultures, was classified as viral infection (VI). The causes of rehospitalization were cholangitis in 18 episodes (21.4%), VI in 14 episodes (16.7%), and portal stenosis (PS) in 11 episodes (13.1%) (Fig. 1A). Cholangitis and PS repeatedly caused rehospitalization in the same patients. Rehospitalization as the result of rejection accounted for seven of the episodes (9.5%). The period of each rehospitalization (Fig. 1B) was long in cholangitis (1–194 days, 49.7±62.4 days on average), PS including gastrointestinal bleeding (2–48 days, 13.8±13.4 days), and rejection (7–117 days, 52.9±45.4 days). Although there were a lot of rehospitalization episodes because of VI subsequent to cholangitis, each rehospitalization period was short (1–26 days), with an average of 4.4±6.6 days.

Cholangitis: Patients 1, 7, 8, 11, and 13

Five patients who were rehospitalized because of cholangitis were classified into group C, and the other patients were classified into group NC (Table 2). There were no characteristic factors of those in group C in regard to age at transplant, gender, native liver disease, and blood type. There were no differences between patients in groups C and NC in general condition, hepatic and renal function, existence of hypersplenism, and existence of ascites. Donor age was 39.0±9.1 years and 34.7±6.1 years in groups C and NC, respectively, which was not significantly different. There were four males and one female in group C and seven males and 16 females in group NC, a significant difference in donor gender (P=0.039). The number of past operations, especially the Kasai operation in which the hepatic hilum is manipulated, as an index of the grade of adhesions, tended to be larger in group C (P=0.084). The *z* score of height at transplant was −2.15±1.29 in group C and −1.77±1.51 in group NC. The *z* score of weight at transplant was −1.15±0.94 in group C and −1.11±1.13 in group NC, with no significant difference between the two groups. There was no difference between the two groups in GW:SLV and the method of biliary drainage. There was no difference between the two groups in the procedure used to close the abdominal wall, but closure of the whole abdominal wall tended to be more frequent in group NC (P=0.063). Patients 1, 8, 11, and 13 experienced bile leakage from the hepaticojejunostomy, and patient 7 experienced stenosis of the intrahepatic bile duct (e.g., the withered branch) because of circulatory disturbance of the intrahepatic arterioles.

There were 18 episodes of rehospitalization as the result of infection: otitis media (one case), severe diarrhea as the result of rotavirus infection (one case), EBV infection (two cases), and VI (14 cases).

Viral Infection: Patients 2, 3, 4, 9, 12, 14, and 15

Seven patients who were rehospitalized because of VI were classified into group VI, and the other patients were classified into group NVI (Table 3). The age at transplantation was 2 years and 8 months on average in group VI and 5 years in group NVI, with no significant difference between the two groups (P=0.21). There was no difference in disturbance of growth or GW:SLV. Two of eight patients who received CsA and five of 20 patients who received FK506 were in group VI; there was no difference in the type of immunosuppressant between the two groups. Eight of 14 episodes of rehospital-

TABLE 1. Cause of rehospitalization in every patient

Patient number	Time of rehospitalization							
	1st	2nd	3rd	4th	5th	6th	7th	8th
1	CHOL	CHOL	CHOL	CHOL	CHOL	CHOL	CHOL	CHOL
2	DIA	ITP	GIB, PS	PS	PS	GIB, PS	GIB, PS	URVI
3	URVI	URVI	URVI	REJ	URVI	OM	DIA	
4	URVI	URVI	URVI	LD	URVI	URVI		
5	PS	PS	GIB, PS	PANC	HBI			
6	DIA	MLC	GIB, PS	GIB, PS	PS			
7	CHOL	CHOL	CHOL	CHOL				
8	CHOL	MLC	CHOL	CHOL				
9	URVI	LD	PTLD	AWC				
10	MLC	ITP	HG	HG				
11	CHOL	IH	SCA	SCA				
12	REJ	URVI	[a]					
13	CHOL	CHOL	MLC					
14	REJ	URVI	PTLD					
15	REJ	URVI	LD, CR					
16	REJ	DM						
17	REJ	IH						
18	ILEUS	ILEUS						
19	LD	REJ						
20	LD	DM						
21	Closure of ileostomy							
22	PTLD							
23	Splenomegaly							
24	None							
25	None							
26	None							
27	None							
28	None							

[a] Exchange of immunosuppression because of gingival hypertrophy.

CHOL, cholangitis; DIA, diarrhea; LD, liver dysfunction; PANC, pancreatitis; GIB, gastrointestinal bleeding; PS, portal stenosis; URVI, upper respiratory viral infection; REJ, acute rejection; OM, otitis media; ITP, idiopathic thrombocytopenic purpura; MLC, muscle layer closure; PTLD, posttransplant lymphoproliferative disease; AWC, abdominal wall closure; HG, hypoglycemia; HBI, hepatitis B virus infection; IH, incisional hernia; SCA, subcutaneous abscess; DM, diabetes mellitus.

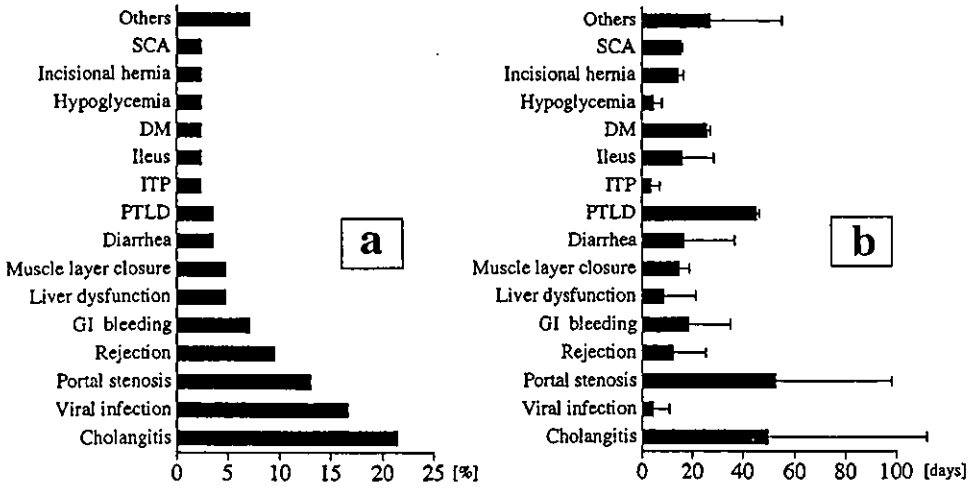

FIGURE 1. (A) Rate of cause of rehospitalization to total episodes of rehospitalization. (B) Average rehospitalization period for every cause of rehospitalization. GI, gastrointestinal; PTLD, posttransplant lymphoproliferative disease; ITP, idiopathic thrombocytopenic purpura; DM, diabetes mellitus; SCA, subcutaneous abscess.

ization occurred before the cessation of MP, so the frequency of rehospitalization because of VI had no relation to the administration of MP.

Late Portal Stenosis and Gastrointestinal Bleeding: Patients 2, 5, and 6

All patients with gastrointestinal bleeding were included in the group of patients with PS. Biliary atresia was the original liver disease in all three patients. Patient 2's abdominal wall had to remain open for a long time because of hepatic arterial thrombosis as the result of compression when the abdominal wall was closed. Because the lateral segment graft gradually moved to the right, the portal vein was considered to be extended excessively and stenosed. Patient 5 had recovered from various complications (i.e., peritoneal abscess, peritoneal bleeding, vanishing bile duct syn-

TABLE 2. Comparison of characteristics and features between patients with cholangitis (+) and cholangitis (−)

		Cholangitis (+)[a] (5)	Cholangitis (−)[b] (23)	P value
Age of recipient		7.1±8.6	4.0±4.3	0.237
Age of donor		39.0±9.1	34.7±6.1	0.693
Gender of recipient	Male	3	10	0.502
	Female	2	13	
Gender of donor	Male	4	7	0.039
	Female	1	16	
Frequency of Kasai operation		1.60±0.55	1.09±0.60	0.084
z score	Height	−2.15±1.29	−1.77±1.51	0.606
	Weight	−1.15±0.94	−1.11±1.13	0.945
GW:SLV		63.7±26.5	69.9±23.7	0.611
Biliary drainage	External	4	18	0.932
	Internal	1	5	
Closure of abdominal wall	Whole layer	2	13	0.064
	Skin	1	9	
	Prosthesis	2	1	
Posttransplant biliary complication		Bile leakage 4 Disturbance of arterial flow 1		

[a] Rehospitalization because of cholangitis.
[b] Rehospitalization with causes other than cholangitis.
GW, graft weight; SLV, standard liver volume.

TABLE 3. Comparison of characteristics and features between patients with viral infection and others

		Rehospitalization because of viral infection (7)	Others (21)	P value
Age		2.3±2.0	5.3±5.8	0.200
z score	Height	−1.40±2.35	−1.98±1.05	0.368
	Weight	−0.59±0.91	−1.29±1.09	0.141
GW:SLV (%)		71.1±20.6	68.0±23.6	0.769
Immunosuppressant	FK 506	5	15	
	CsA	2	6	

CsA, cyclosporine A.

drome, and others), and PS was diagnosed after hypersplenism. Patient 6 developed a biliary fistula and experienced episodes of frequent diarrhea caused by severe food allergy. The time of onset of PS was postoperative day (POD) 332 in patient 2, POD 496 in patient 5, and POD 499 in patient 6 (i.e., ~1 year or more). The age of the patients with PS at LDLT was 3.14±4.21 years, which was not significantly different from the age of patients without PS (4.72±5.40 years) (P=0.632). The z score of height at LDLT was −1.98±−0.99 in patients with PS and −1.82±1.52 in patients without PS. The z score of weight was −1.59±0.33 in patients with PS and −1.06±1.13 in patients without PS, with no significant difference between patients with and without PS (P=0.858 and 0.436, respectively). There was no patient with incompatible blood type. Before the operation, blood from the portal vein flowed into the liver. A vein graft from the donor was used only in patient 5. Because the diameter of the native portal vein was 4 mm in both patients 2 and 6, a branch patch of 10 mm formed from the right and left portal branches was used for anastomosis in the two patients. The stenotic portal vein in patients 5 and 6 was dilated using a balloon, but in patient 2 the portal vein failed to be released from portal hypertension because of PS.

Rejection: Patients 3, 12, 14, 15, 16, 17, and 19

Patient 15 was excluded because of poor compliance with the immunosuppressive therapy, which was closely related to the occurrence of rejection. Four of six patients experienced rejection within 1 year, at PODs 334, 279, 189, and 331, respectively (Table 4). Rejection in patient 3 occurred at POD 454 immediately after cessation of FK506 for the treatment of PTLD. There were 13 patients who experienced graft rejection within 1 month after LDLT, including three of the six patients who returned to the hospital because of rejection and 10 of 21 patients who did not return to the hospital because of rejection. No relation was recognized between early posttransplant rejection and rehospitalization because of rejection (P=0.92). ABO incompatibility and positive lymphocyte cross-match test were not related to the frequency of rehospitalization because of graft rejection (P=0.29). There was no significant difference in any combination of donor and recipient gender (P=0.71).

DISCUSSION

After receiving a new liver, a patient expects not only to acquire a healthy body but also to return to a healthy social life. In regard to health-related quality of life, it was reported by Midgley et al. (*3*) that 90% of pediatric liver transplant recipients showed functional deficits (although mild), and that most showed chronic medical disability related to liver transplantation (mild in 71% and moderate in 29% of the cases) and predominantly delayed growth. Orii et al. (*4*) and Asonuma et al. (*5*) reported that delayed growth was related to age at transplantation (>5 years) and long-term administration of steroids, but most pediatric liver transplant recip-

TABLE 4. Comparison of characteristics and features between patients with rejection and others

		Rehospitalization because of rejection (6)	Others (21)	*P* value
Posttransplant days of rehospitalization because of rejection		454[a], 334, 279, 189, 331, 1,268		
Rejection episode within 1 mo after LTx		3	10	0.92
Immunologic disadvantage		2	3	0.29
	Identical	4	10	
Gender of donor to recipient	Male to female	1	6	0.71
	Female to male	1	5	

[a] Patient 3.
Immunologic disadvantage: incompatible ABO blood type or positive T-cell cross-match.
LTx: liver transplantation.

ients have a good quality of life, and only 10% demonstrate significant morbidity (*6*).

Frequent or long rehospitalization makes a pediatric patient feel disconnected and alienated from the family, and afraid of morbidity and mortality. Although recognition and examination of the cause and consequences of rehospitalization are indispensable, there are few reports that focus on the quality of life of liver transplant recipients after rehospitalization.

A total of 23 (82.1%) of the 28 patients who underwent LDLT required rehospitalization, and when they returned to the hospital, they spent approximately 3 weeks in the hospital on average. Loinaz et al. (*7*) reported that the mean follow-up period for adult patients was 119.3 months and that the readmission rate was 56.2% after the first year, with a mean cumulative hospitalization stay of 3 weeks. Stone et al. (*8*) reported that of 20 pediatric patients who underwent liver transplantation, 11 were admitted for varicella, 6 were admitted various times for liver biopsy, and 1 was admitted for a partial hepatic resection, and that rehospitalization was frequent. The rate of days spent rehospitalized to the days elapsed after the first hospital stay for LDLT was 6.56% on average, that is, patients were rehospitalized 23.9 days in 1 year. The data on rehospitalization depend on the views of a doctor or an institution and the medical situation of a country and differ between a child and an adult. As mentioned, because there are few studies on rehospitalization, it is impossible to compare and access the data, but it is certain that a patient's quality of life will be affected by the fact that more than 6.56% of his or her remaining life must be spent in a hospital.

Cholangitis, virus infection, late PS, and rejection were the main causes of rehospitalization.

There was no difference in general condition or liver function before LDLT between the patients who returned to the hospital with cholangitis and the other patients. The patients with many previous operations before LDLT and without complete closure of all layers of the abdominal wall at LDLT tended to be rehospitalized with cholangitis more frequently than other patients. It was not clear whether the patients who had received a liver from a male donor were rehospitalized because of cholangitis more frequently with a significant difference. Egawa et al. of Kyoto University (*9*) reported that the overall occurrence of biliary anastomotic complications was 18.2% in 400 patients undergoing LDLT, and that anastomotic leaks, CMV infection, hepatic artery complications, ABO incompatibility, and gender of recipients were significant risk factors for stricture. Schwarzenberg et al. (*10*) reported that 8 of 11 patients who underwent LDLT (72.7%) experienced one or more episodes of apparent biliary infection 5 to 9 months after successful transplantation, which is a high frequency. Although there are many disadvantages to LDLT compared with brain-dead donor liver transplantation, such as thinness and insufficient blood flow of the bile duct (*10*), all patients rehospitalized because of cholangitis experienced anastomotic leaks or hepatic artery complications, so hepatic arterial circulation and the surgical technique must be fully considered. In the donor operation, the surgeon must also ensure that the bile duct is not skeletonized beyond necessity and is dissected sharply without using electrocautery.

There are few reports about infection in pediatric liver transplant recipients after the hospital stay. Their et al. (*11*) reported that 56 pediatric liver and kidney transplant recipients had 126 episodes of rehospitalization as the result of infections, 18 of which involved urinary tract infections (the most common). Those 56 patients had only 13 episodes of rehospitalization as the result of upper respiratory tract infections (which we treated as VI and which accounted for almost all episodes of rehospitalization because of infection at our institution). Upper respiratory tract infection corresponds to the disease treated as the "common cold" or "flu," so whether this would be the cause of rehospitalization in patients receiving immunosuppression depends on the severity of the disease or the medical or political situation. As Mossad (*12*) reviewed, the common cold is a viral illness that affects children four to eight times per year. The disease rate of upper respiratory tract infection caused by viruses in our patients was not necessarily higher than that of the general public. The most common virus leading to the common cold was rhinovirus (*13–15*), and the frequency reached approximately 80% (the virus was detected in 104/138 patients). In our series, the period of rehospitalization because of VI was more than 4 days on average, even in patients receiving immunosuppression. It takes a few days to identify the virus by polymerase chain reaction and so forth. Furthermore, antiviral agents have no appreciable clinical benefit except against influenza virus (*12*), so VI does not largely affect the frequency of rehospitalization after LDLT.

Chardot et al. (*16*) reported that portal complications occurred in 16.5% of patients with biliary atresia as the original disease, approximately 80% of whom experienced it early (0–17 days posttransplantation). Significant risk factors of portal complications were young age and low weight at the time of transplantation, a small portal vein, and emergency transplantation (*16*). The portal vein commonly ranges from

2 to 4 mm in recipients with biliary atresia (*17*). There is also a report that pathologic changes of the recipient native portal vein were found in approximately 77% of the patients. The portal vein of the liver graft was anastomosed to the confluence of the recipient superior mesenteric vein and the splenic vein, and to a vein graft interposed between the confluence and the liver graft, by which postoperative Doppler ultrasonography showed excellent portal flow. PS did not occur thereafter (*18*). Because our review of the literature suggests that prevention of portal complications depends primarily on an appropriate surgical technique (*16*), it would be better to use a vein graft from the donor if it is thin and sclerotic, judging the pathology of the recipient portal vein.

It is said that LDLT has an immunologic advantage compared with CDLT in children. Toyoki et al. (*19*) reported that rejection episodes were diagnosed in 40 of 51 cadaveric first grafts (78.4%) and 25 of 37 living-related primary grafts (67.6%), in 37 of 51 cadaveric first grafts (72.5%) and 25 of 37 living-related primary grafts (67.6%) (not significant) within 1 year posttransplantation, and in 11 of 51 cadaveric first grafts (21.6%) and 0 of 37 living-related primary grafts (0%) ($P<0.05$) more than 1 year posttransplantation. In our study, five of six patients (83.3%), except for the patient with low compliance with the immunosuppressive therapy, who were rehospitalized because of rejection demonstrated rejection within 1 year after LDLT. D'Antiga et al. (*20*) reported that inadequate immunosuppression caused late cellular rejection in most cases. Wiesner and Menon (*21*) also mentioned that late acute rejection episodes were often related to a reduction or withdrawal of immunosuppressive agents or to poor compliance. Therefore, it is necessary to regularly monitor the blood level of an immunosuppressive agent within at least 1 year after LDLT and to always communicate the necessity of immunosuppression to the patients and their families.

CONCLUSION

During an approximate 3-year follow-up period, more than 80% of pediatric patients who underwent LDLT experienced three episodes of rehospitalization on average. It is suggested that prevention of cholangitis and portal PS, which caused frequent and long rehospitalization episodes, would result in a reduction of the frequency and length of rehospitalization episodes after pediatric LDLT.

REFERENCES

1. Chen CL, Fan ST, Lee SG, et al. Living-donor liver transplantation: 12 years of experience in Asia. Transplantation 2003; 75: S6-S11.
2. Kawasaki S, Makuuchi M, Ishizone H, et al. Liver regeneration in recipients and donor after transplantation. Lancet 1992; 339: 580–581.
3. Midgley DE, Bradlee TA, Donohoe C, et al. Health-related quality of life in long-term survivors of pediatric liver transplantation. Liver Transpl 2000; 6: 333–339.
4. Orii T, Ohkohchi N, Koyamada N, et al. Growth of pediatric patients with biliary atresia after liver transplantation: influence of age at transplantation and steroid administration. Transplant Proc 2000; 32: 2210–2212.
5. Asonuma K, Inomata Y, Uemoto S, et al. Growth and quality of life after living-related liver transplantation in children. Pediatr Transplant 1998; 1: 64–69.
6. Burdelski M, Nolkemper D, Ganschow R, et al. Liver transplantation in children: long-term outcome and quality of life. Eur J Pediatr 1999; 158(Suppl 2): S34–42.
7. Loinaz C, Marques E, Gomez R, et al. Clinical features of 32 patients after 8 years of a liver transplant. Transplant Proc 1999; 31: 2475–2476.
8. Stone RD, Beasley PJ, Treacy SJ, et al. Children and families can achieve normal psychological adjustment and a good quality of life following pediatric liver transplantation: a long time study. Transplant Proc 1997; 29: 1571–1572.
9. Egawa H, Inomata Y, Uemoto S, et al. Biliary anastomotic complications in 400 living related liver transplantations. World J Surg 2001; 25: 1300–1307.
10. Schwarzenberg SJ, Sharp HL, Payne WD, et al. Biliary stricture in living-related donor liver transplantation: management with balloon dilation. Pediatr Transplantation 2002; 6: 132–135.
11. Their M, Holmberg C, Lautenschlager I, et al. Infections in pediatric kidney and liver transplant patients after perioperative hospitalization. Transplantation 2000; 69: 1617–1623.
12. Mossad SB. Treatment of the common cold. BMJ 1998; 317: 33–36.
13. Makela MJ, Puhakka T, Ruuskanen O, et al. Viruses and bacteria in the etiology of the common cold. J Clin Microbiol 1998; 36: 539–542.
14. Kim MC, Lee NP. How to treat influenza and colds. West J Med 2000; 172: 260–264.
15. Monto AS. Epidemiology of viral respiratory infections. Am J Med 2002; 112(Suppl 6A): 4S-12S.
16. Chardot C, Herrera JM, Debray D, et al. Portal vein complications after liver transplantation for biliary atresia. Liver Transpl Surg 1997; 3: 351–358.
17. Millis JM, Seaman DS, Piper JB, et al. Portal vein thrombosis and stenosis in pediatric liver transplantation. Transplantation 1996; 62: 748–754.
18. Saad S, Tanaka K, Inomata Y, et al. Ann Surg 1998; 227: 275–281.
19. Toyoki Y, Renz JF, Mudge C, et al. Allograft rejection in pediatric liver transplantation: comparison between cadaveric and living related donors. Pediatr Transplantation 2002; 6: 301–307.
20. D'Antiga L, Dhawan A, Portmann B, et al. Late cellular rejection in paediatric liver transplantation: aetiology and outcome. Transplantation 2002; 73: 80–84.
21. Wiesner RH, Menon KVN. Late hepatic allograft dysfunction. Liver Transpl 2001; 7: S60–S73.

日本腹部救急医学会雑誌 24(1)：57～65，2004

特集：腹部救急疾患における深部真菌症への対策

生体肝移植における真菌感染症対策

東北大学大学院医学系研究科先進外科学分野
川岸直樹，藤盛啓成，里見　進

要旨：生体肝移植の周術期における真菌感染症対策について概説する。生体肝移植は脳死肝移植と違い基本的には待機手術であることより，術前からの真菌症対策が可能であることが多いため，さまざまな試みがなされてきた。術前では各種監視培養，血中抗原検査などにより上気道，腸管，尿路などの真菌を除菌しておく。術中は固有肝，吻合腸管の監視培養をし，術後においても予防的抗真菌薬の投与，監視培養，血中抗原検査などを行い厳重な感染管理を行う。起炎菌としては *Candida* が最も多く，*Aspergillus, Mucor, Cryptococcus* などもみられる。*Aspergillus* による髄膜炎は致死率が高く注意が必要である。移植後致死的となる重大な感染症の一つである深在性真菌症の診断には，発熱などの臨床所見，単純X線，CTなどの画像所見のほか，β-D glucan, *Aspergillus* 抗原，*Cryptococcus* 抗原，PCR法などによる補助診断が有用である。治療は fluconazole, amphotericin B, miconazole, micafungin などを用いる。

【索引用語】 肝移植，深在性真菌症，risk factor，臓器移植

はじめに

生体肝移植においては，肝不全状態の患者に対し手術を行うことが多いことから，易感染性の状態での手術となる。加えて，術中，術後早期においては大量の免疫抑制剤により拒絶反応を抑えなければならず，患者の感染症罹患率は他の一般外科手術に比べ高率となる。このようなことから，肝移植においては術前からの感染症対策が重要であり，各種監視培養検査，各種ウイルスに対する抗体価検査などを行い，移植後の感染症における治療の指標としている。移植後においては，二律背反である拒絶反応とのバランスを考慮に入れねばならず，特に免疫抑制剤の投与量が多い時期には，感染症の発症予防，早期診断，早期治療を常に念頭に置かなければならない。真菌感染症の中でも深在性真菌症においては，診断が困難であること，致死率が高いことなどから免疫抑制剤を服用している肝移植患者はとくに注意が必要である。

I. 生体肝移植における感染症対策

生体肝移植では術後初期においては大量に免疫抑制剤を使用することから，真菌感染症のみではなく，細菌，ウイルス，原虫などに対しても術前から対策を行っている[1]（表1）。細菌感染症の発症予防としては，術前には腸管処理，MRSAがでている場合はその除菌，小児で移植時に脾摘，またはすでに脾摘されている例では *Streptococcus pneumoniae* や *Hemophilus influenzae* に対する vaccine を考慮する。術後は最小限度の抗生剤投与にとどめ，週2回から3回程度の頻度で細菌培養検査をして適切な抗生剤の投与をする。また，長期間同じカテーテルを使用せず，長くても一週間を限度に交換する。当科では，MRSAが検出された時は，vancomycin(VCM)を投与直前と投与2時間後の血中濃度をモニターしながら点滴静注で投与している。ウイルス感染症に対しては，移植前に各種ウイルスに対する抗体価を測定しhigh risk（ドナーの抗体価が陽性でレシピエントの抗体価が陰性）かどうか把握する。小児の場合はなるべく各種ワクチンの接種を施行してから移植に臨む。ウイルス感染症の中で最も注意が必要なのはCMV感染症とEBV感染症である。CMV感染症の診断としては発熱，咳嗽，下痢，