A meta-analysis of the efficacy of anti-viral therapy was reported by Wong *et al.* who analyzed nine cohort studies with a total of 551 patients. The risk of HCC recurrence was reduced by 41% by the anti-viral treatment and they concluded that anti-viral therapy has potentially beneficial effects after the curative treatment of HBV-related HCC in terms of tumor recurrence, liver-related mortality and overall survival.[38]

Antiviral treatment for hepatitis C virus

Regarding the patients with HCV-related HCC, the long-term outcome was investigated including more than 300 patients after surgical resection and survival was shown to have improved in the period from 2000 to 2006 compared with the period from 1990 to 1999. This improvement in survival is attributable to antiviral therapy with interferon.[39] Viral mutations were investigated and postoperative recurrence of HCC was found to be associated with amino acid (aa) substitutions in the HCV core region, such as aa residue 91. The core mutations were shown to be associated with postoperative recurrence or survival in patients infected with HCV genotype 1b and treated by surgical resection.[40]

Interferon was first shown to be effective for the prevention of recurrence by a randomized study using interferon-β (IFN-β).[41] Thereafter, several reports of the preventive effects of interferon on the recurrence of HCC have been published; interferon did not affect overall prevention of HCC recurrence after resection[42] or RFA[42] but, if the HCV infection had been cured, interferon was effective for preventing the development of HCC and improving survival.[43] A meta-analysis has been reported and IFN-α treatment after curative treatment of primary tumors within the Milan criteria may be effective for the prevention of HCC recurrence, and a higher rate of sustained virological response (SVR) may be associated with a better preventive effect of IFN-α treatment on HCC recurrence.[44,45] To improve the SVR rate, peginterferon treatment after curative treatment of HCC was reported to be closely correlated with the prevention of recurrence.[46]

Branched chain amino-acid supplementation

The backgroud liver dysfunction has been shown to correlate with HCC recurrence, and even after curative resection with small HCC less than 2 cm, postoperative hepatic reserve influences HCC recurrence.[47] Recently, supplementation by branched chain amino acid (BCAA)-enrichment for patients with HCC after RFA has been shown to be effective for the improvement of serum albumin and quality of life[48] and a positive effect on serum albumin by BCAA was noted in patients with Child–Pugh B grade.[49]

Whether BCAA supplementation inhibits HCC recurrence or not is an important issue to be investigated, and recently, the mechanism whereby BCAA is effective for the prevention of the development of HCC has been precisely discussed in detail.[50]

Vitamin K2

In 2004, Habu *et al.*[51] reported that the incidence of development of HCC was reduced among cirrhotic women assigned to receive oral vitamin K2. The incidence of HCC recurrence was clearly shown to be lower than the control group in prospective studies by Mizuta *et al.*[52] and Kakizaki *et al.*;[53] however, conflicting results that HCC recurrence was not reduced by administration of vitamin K2 were reported by Hotta *et al.*[54] Therefore, a large scale multicenter prospective randomized study was conducted in Japan to investigate the preventive effects of vitamin K2 on HCC recurrence. The administration of vitamin K2 at 45 mg per day was not effective in preventing HCC recurrence and, moreover, in the patient group treated with a high dose of vitamin K2 of 90 mg per day, the incidence of HCC was rather higher than the control group.[55] Fortunately enough, severe adverse events were not observed.

Acyclic retinoid

Oral polyprenic acid of an acyclic retinoid was shown to inhibit the development of second primary HCC in a prospective randomized study with a median follow-up of 38 months, reported by Muto *et al.*[56] The overall survival of those receiving the acyclic retinoid was shown to be better than the control group.[57] A large scale multicenter, prospective randomized study has been carried out and oral administration of 600 mg per day of acyclic retinoid was shown to be preventive.[58]

Chemotherapeutic agent and molecular targeted agent

Although adjuvant chemotherapy has been considered for other solid malignancies with a high risk of recurrence, this is difficult in the case of HCC because few conventional chemotherapeutic agents are effective and hepatotoxicity can be of critical significance, because liver function often is already impaired. A randomized trial was performed with uracil-tegaful as postoperative adjuvant therapy, but did not improve the recurrence-free survival, and the overall survival appeared to be reduced.[59]

Whether sofarenib is effective for the prevention of recurrence is now under investigation, including in distinguished centers for treating HCC worldwide, in the so-called STORM trial.[60] A phase III study was conducted to determine whether sorafenib is effective for the prolongation of time to progression after transarterial chemoembolization (TACE), and sorafenib did not significantly prolong the time to progression in patients who responded to TACE.[61]

CONCLUSION

TO IMPROVE THE overall survival of patients with HCC, an important issue is to prevent intrahepatic recurrence. Many significant findings regarding gene expression in the liver and adjacent liver tissue, which relate to intrahepatic recurrence have been reported recently. Following such investigations, there is an urgent need for improved methods of prediction and prevention of intrahepatic recurrence of HCC.

REFERENCES

1 Kudo M, Izumi N, Kokudo N *et al.* HCC expert panel of Japan society of hepatology. *Dig Dis* 2011; **29**: 339–64.
2 Poon RT. Prevention of recurrence after resection of hepatocellular carcinoma: a daunting challenge. *Hepatology* 2011; **54**: 757–9.
3 Villanueva A, Hoshida Y, Toffanin S *et al.* New strategies in hepatocellular carcinoma: genomic prognostic markers. *Clin Cancer Res* 2010; **16**: 4688–94.
4 Murakata A, Tanaka S, Mogushi K *et al.* Gene expression signature of the gross morphology in hepatocellular carcinoma. *Ann Surg* 2011; **253**: 94–100.
5 Kimura O, Takahashi T, Ishii N *et al.* Characterization of the epithelial cell adhesion molecule (EpCAM)+ cell population in hepatocellular carcinoma cell lines. *Cancer Sci* 2010; **101**: 2145–55.
6 Yamashita T, Ji J, Brudhu A *et al.* EpCAM-positive hepatocellular carcinoma cells are tumor-initiating cells with stem/progenitor cell features. *Gastroenterology* 2009; **136**: 1012–24.
7 Komuta M, Spee B, Vander Borght S *et al.* Clinicopathological study on cholangiocellular carcinoma suggesting hepatic progenitor cell origin. *Hepatology* 2008; **47**: 1544–56.
8 Ziol M, Nault JC, Aout M *et al.* Intermediate hepatobiliary cells predict an increased risk of hepatocarcinogenesis in patients with hepatitis C virus – related cirrhosis. *Gastroenterology* 2010; **139**: 335–43.
9 Yang XR, Xu Y, Shi GM *et al.* Cytokeratin 10 and cytokeratin 19: predictive markers for poor prognosis in hepatocellular carcinoma patients after curative resection. *Clin Cancer Res* 2008; **14**: 3850–9.
10 Zhuang PY, Zhang JB, Zhu XD *et al.* Two pathologic types of hepatocellular carcinoma with lymph node metastasis with distinct prognosis on the basis of CK 19 expression in tumor. *Cancer* 2008; **112**: 2740–8.
11 Uenishi T, Kubo S, Yamamoto T *et al.* Cytokeratin 19 expression in hepatocellular carcinoma predicts early postoperative recurrence. *Cancer Sci* 2003; **94**: 851–7.
12 Durnez A, Verslype C, Nevens F *et al.* The clinicopathological and prognostic relevance of cytokeratin 7 and 19 expression in hepatocellular carcinoma. A possible progenitor cell origin. *Histopathology* 2006; **49**: 138–51.
13 Tsuchiya K, Komuta M, Yasui Y *et al.* Expression of keratin 19 is related to high recurrence of hepatocellular carcinoma after radiofrequency ablation. *Oncology* 2011; **80**: 278–88.
14 Sasaki A, Kamiyama T, Yokoo H *et al.* Cytoplasmic expression of CD133 is an important risk factor for overall survival in hepatocellular carcinoma. *Oncol Res* 2010; **24**: 537–46.
15 Vasuri F, Golifieri R, Fiorentino M *et al.* OATP 1B1/1B3 expression in hepatocellular carcinomas treated with orthotopic liver transplantation. *Virchows Arch* 2011; **459**: 141–6.
16 Nakamura Y, Mizuguchi T, Kawamoto M *et al.* Cluster analysis of indicators of liver functional and preoperative low branched-chain amino acid tyrosine ration indicate a high risk of early recurrence in analysis of 165 hepatocellular carcinoma patients after initial hepatectomy. *Surgery* 2011; **150**: 250–62.
17 Hoshida Y, Villanueva A, Kobayashi M *et al.* Gene expression in fixed tissues and outcome in hepatocellular carcinoma. *N Engl J Med* 2008; **359**: 1995–2004.
18 Villanueva A, Hoshida Y, Battiston C *et al.* Combining clinical, pathology, and gene expression data predict recurrence of hepatocellular carcinoma. *Gastroenterology* 2011; **140**: 1501–12.
19 Teufel A, Marquardt JU, Galle PR. Novel insight in the genetics of HCC recurrence and advances in transcriptomic data integration. *J Hepatol* 2011 E pub July 23.
20 Amaoka N, Osada S, Kanematsu M *et al.* Clinicopathological features of hepatocellular carcinoma evaluated by vascular endothelial growth factor expression. *J Gastroenterol Hepatol* 2007; **22**: 2202–7.
21 Toyoda H, Kumada T, Kaneoka Y *et al.* Prognostic value of pretreatment levels of tumor markers for hepatocellular carcinoma on survival after curative treatment of patients with HCC. *J Hepatol* 2008; **49**: 223–32.
22 Nobuoka D, Kato Y, Gotohda N *et al.* Postoperative serum alpha-fetoprotein level is a useful predictor of recurrence after hepatectomy for hepatocellular carcinoma. *Oncol Rep* 2010; **24**: 521–8.
23 Yamamoto K, Imamura H, Matsuyama Y *et al.* Significance of alpha-fetoprotein and des-gamma-carboxy prothrombin in patients with hepatocellular carcinoma undergoing hepatectomy *Ann Surg Oncol* 2009; **16**: 2795–804.

24 Zhang XF, Lai EC, Kang XY *et al.* Lens culinaris agglutinin-reactive fraction of alpha-fetoprotein as a marker of prognosis and a monitor of recurrence of hepatocellular carcinoma after curative liver resection. *Ann Surg Oncol* 2011; 18: 2218–23.
25 Beppu T, Sugimoto K, Shiraki K *et al.* Clinical significance of tumor markers in detection of recurrent hepatocellular carcinoma after radiofrequency ablation. *Int J Mol Med* 2010; 26: 425–33.
26 Morimoto M, Numata K, Nozaki A *et al.* Novel lens culinaris agglutinin-reactive fraction of α-fetoprotein: a biomarker of hepatocellular carcinoma recurrence in patients with low α-fetoprotein concentrations. *Int J Clin Oncol* 2011 E pub Aug 26.
27 Kobayashi M, Hosaka T, Ikeda K *et al.* Highly sensitive AFP-L3% assay is useful for predicting recurrence of hepatocellular carcinoma after curative treatment pre-and postoperatively. *Hepatol Res* 2011 E pub Aug 26.
28 Komuta T, Mizukoshi E, Kita Y *et al.* Impact of diabetes on recurrence of hepatocellular carcinoma after surgical treatment in patients with viral hepatitis. *Am J Gastroenterol* 2007; 102: 1939–46.
29 Imai K, Takai K, Nishigaki Y *et al.* Insulin resistance raises the risk for recurrence of stage 1 hepatocellular carcinoma after curative ablation in hepatitis C virus-positive patients: a prospective, case series study. *Hepatol Res* 2010; 40: 376–82.
30 Huo TI, Wu JC, Lui WY *et al.* Differential mechanism and prognostic impact of diabetes mellitus on patients with hepatocellular carcinoma undergoing surgical treatment. *Am J Gastroenterol* 2004; 99: 1479–87.
31 Chen WT, Macatula TC, Lin CC, Lin CJ, Lin SM. Diabetes may not affect outcomes in hepatocellular carcinoma after radio-frequency ablation. *Hepatogastroenterology* 2011; 58: 551–7.
32 Wang WM, Xu Y, Yang XR, Wang YH, Sun HX, Fan J. Prognostic role of diabetes mellitus in hepatocellular carcinoma patients after curative treatments: a meta-analysis. *Hepatobiliary Pancreat Dis Int* 2011; 10: 346–55.
33 Ohki T, Tateishi R, Shiina S *et al.* Visceral fat accumulation is an independent risk factor for hepatocellular carcinoma recurrence after curative treatment in patients with suspected NASH. *Gut* 2009; 58: 839–44.
34 Tokushige K, Hashimoto E, Yatsuji S *et al.* Prospective study of hepatocellular carcinoma in non-alcoholic steatohepatitis in comparison with hepatocellular carcinoma caused by chronic hepatitis C. *J Gastroenterol* 2101; 45: 960–7.
35 Goto T, Yoshida H, Tateishi R *et al.* Influence of serum HBVDNA load on recurrence of hepatocellular carcinoma after treatment with percutaneous radiofrequency ablation. *Hepatol Int* 2011 E pub Jan 25.
36 Yoshida H, Goto E, Sato T *et al.* Safety and efficacy of lamivudine after radiofrequency ablation in patients with hepatitis B virus-related hepatocellular carcinoma. *Hepatol Int* 2008; 2: 89–94.
37 Chan AC, Chok KS, Yuen WK, Chan RT, Lo CM, Fan ST. Impact of antiviral therapy on the survival of patients after major hepatectomy for hepatitis B virus-related hepatocellular carcinoma. *Arch Surg* 2011; 146: 675–81.
38 Wong JS, Wong GL, Tsoi KK *et al.* Meta-analysis: the efficacy of anti-viral therapy in prevention of recurrence after curative treatment of chronic hepatitis B-related hepatocellular carcinoma. *Aliment Pharmacol Ther* 2011; 33: 1104–12.
39 Shirabe K, Takeishi K, Taketomi A, Uchiyama H, Kayashima H, Maehara Y. Improvement of long-term outcomes in hepatitis C virus antibody-positive patients with hepatocellular carcinoma after hepatectomy in the modern era. *World J Surg* 2011; 35: 1072–84.
40 Toyoda H, Kumada T, Kaneoka Y, Maeda A. Amino acid substitutions in the hepatitis C virus core region are associated with postoperative recurrence and survival of patients with genotype 1b-associated hepatocellular carcinoma. *Ann Surg* 2011; 254: 326–32.
41 Ikeda K, Arase Y, Saitoh S *et al.* Interferon beta prevents recurrence of hepatocellular carcinoma after complete resection or ablation of the primary tumor- A prospective randomized study of hepatitis C virus-related cancer. *Hepatology* 2000; 32: 228–32.
42 Mazzaferro V, Romito R, Schiavo M *et al.* HCC Italian Task Force. Prevention of hepatocellular carcinoma recurrence with alpha-interferon after liver resection in HCV cirrhosis. *Hepatology* 2006; 44: 1543–54.
43 Shiratori Y, Ito Y, Yokosuka O *et al.* Tokyo-Chiba Hepatitis Research Group. Antiviral therapy for cirrhotic hepatitis C: association with hepatocellular carcinoma development and improved survival. *Ann Intern Med* 2005; 18: 105–14.
44 Miyake Y, Takaki A, Iwasaki Y, Yamamoto K. Meta-analysis: interferon-alpha prevents the recurrence after curative treatment of hepatitis C virus-related hepatocellular carcinoma. *J Viral Hepat* 2010; 17: 287–92.
45 Shen YC, Hsu C, Chen LT, Cheng CC, Hu FC, Cheng AL. Adjuvant interferon therapy after curative therapy for hepatocellular carcinoma (HCC): a meta-regression approach. *J Hepatol* 2010; 52: 889–94.
46 Hagihara H, Nouso K, Kobayashi Y *et al.* Effect of pegylated interferon therapy on intrahepatic recurrence after curative treatment of hepatitis C virus-related hepatocellular carcinoma. *Int J Clin Oncol* 2011; 16: 210–20.
47 Kaibori M, Ishizaki M, Saito T, Matsui K, Kwon AH, Kamiyama Y. Risk factors and outcome of early recurrence after resection of small hepatocellular carcinomas. *Am J Surg* 2009; 198: 39–45.
48 Kuroda H, Ushio A, Miyamoto Y *et al.* Effects of branched-chain amino acid-enriched nutrient for patients with hepatocellular carcinoma following radiofrequency ablation: a one-year prospective trial. *J Gastroenterol Hepatol* 2010; 25: 1550–5.

49 Ishikawa T, Michitaka I, Kamimura H *et al.* Oral branched-chain amino acids administration improves impaired liver dysfunction after radiofrequency ablation therapy for hepatocellular carcinoma. *Hepatogastroneterology* 2009; **56**: 1491–5.
50 Kawaguchi T, Izumi N, Charlton MR, Sata M. Branched-chain amino acids as pharmacological nutrients in chronic liver disease. *Hepatology* 2011; **54**: 1063–70.
51 Habu D, Shiomi S, Tamori A *et al.* Role of vitamin Ks in the development of hepatocellular carcinoma in women with viral cirrhosis of the liver. *JAMA* 2004; **292**: 358–61.
52 Mizuta T, Ozaki I, Eguchi Y *et al.* The effect of menatetteone, a vitamin K2 analogue, on disease recurrence and survival in patients with hepatocellular carcinoma after curative treatment. *Cancer* 2006; **106**: 867–72.
53 Kakizaki S, Sohara N, Sato K *et al.* Preventive effects of vitamin K on recurrence disease in patients with hepatocellular carcinoma arising from hepatitis C viral infection. *J Gastroenterol Hepatol* 2007; **22**: 518–22.
54 Hotta N, Ayada M, Sato K *et al.* Effect of vitamin K2 on the recurrence in patients with hepatocellular carcinoma. *Hepatogastroenterology* 2007; **54**: 2073–77.
55 Yoshida H, Shiratori Y, Kudo M *et al.* Effect of vitamin K2 on the recurrence of hepatocellular carcinoma. *Hepatology* 2011; **54**: 532–40.
56 Muto Y, Moriwaki H, Nonomiya M *et al.* Prevention of second primary tumors by an acyclic retionid, polyprenoic acid, in patients with hepatocellular carcinoma. Hepatoma Prevention Study Group. *N Engl J Med* 1996; **13**: 1561–7.
57 Muto Y, Moriwaki H, Saito A. Prevention of second primary tumors by an acyclic retinoid in patients with hepatocellular carcinoma. *N Engl J Med* 1999; **340**: 1046–7.
58 Okita K, Matsui O, Kumada H *et al.* Effect of peretinoin on recurrence of hepatocellular carcinoma (HCC): results of a phase II/III randomized placebo-controlled trial. *Am Soc Clin Oncol* 2011. ASCO Annual Meeting. Abstract No. 4024.
59 Hasegawa K, Takayama T, Ijichi M *et al.* Uracil-tegaful as an adjuvant for hepatocellular carcinoma: a randomized trial. *Hepatology* 2006; **44**: 891–95.
60 Prints C. Clinical trials of note. Sorafenib as adjuvant treatment for the prevention of disease recurrence in patients with hepatocellular carcinoma (HCC) (STORM). *Cancer* 2009; **115**: 4646.
61 Kudo M, Imanaka K, Chida N *et al.* Phase III study of sorafenib after transarterial chemoembolization in Japanese and Korean patients with unresectable hepatocellular carcinoma. *Eur J Cancer* 2011; **47**: 2117–27.

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Noninvasive estimation of fibrosis progression overtime using the FIB-4 index in chronic hepatitis C

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SUMMARY. The FIB-4 index is a simple formula to predict liver fibrosis based on the standard biochemical values (AST, ALT and platelet count) and age. We here investigated the utility of the index for noninvasive prediction of progression in liver fibrosis. The time-course alteration in the liver fibrosis stage between paired liver biopsies and the FIB-4 index was examined in 314 patients with chronic hepatitis C. The average interval between liver biopsies was 4.9 years. The cases that showed a time-course improvement in the fibrosis stage exhibited a decrease in the FIB-4 index, and those that showed deterioration in the fibrosis stage exhibited an increase in the FIB-4 index with a significant correlation ($P < 0.001$). Increase in the ΔFIB-4 index per year was an independent predictive factor for the progression in liver fibrosis with an odds ratio of 3.90 ($P = 0.03$). The area under the receiver operating characteristic curve of the ΔFIB-4 index/year for the prediction of advancement to cirrhosis was 0.910. Using a cut-off value of the ΔFIB-4 index/year <0.4 or ≥0.4, the cumulative incidence of fibrosis progression to cirrhosis at 5 and 10 years was 34% and 59%, respectively in patients with the ΔFIB-4 index/year ≥0.4, whereas it was 0% and 3% in those with the ΔFIB-4 index/year <0.4 ($P < 0.001$). In conclusion, measurement of the time-course changes in the FIB-4 index is useful for the noninvasive and real-time estimation of the progression in liver fibrosis.

Keywords: FIB-4, fibrosis, HCV, noninvasive.

INTRODUCTION

Advanced stage of liver fibrosis in chronic hepatitis C is associated with failure of interferon therapy or development of major concomitant disease such as variceal bleeding, liver failure and hepatocellular carcinoma [1–3]. Therefore, evaluation of the stage of liver fibrosis is essential in clinical practice. Liver biopsy is the gold standard for diagnosis of liver fibrosis [4,5], but inaccuracy in evaluation of fibrosis because of sampling errors [6–8] or by the inter-observer variation has been reported [9]. Real-time assessment of liver fibrosis may be clinically useful, but the invasiveness of liver biopsy precludes repeated examinations.

A variety of noninvasive methods to diagnose liver fibrosis have been proposed. Recently, transient elastography [10–13] and real-time tissue elastography [14] using ultrasonography have been developed, but these modalities are not widely available. For blood tests, the aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio [15], the AST/platelet ratio index (APRI) [16,17] and the Fibrotest [18,19] have been reported to be useful. The FIB-4 index is another prediction value of liver fibrosis in chronic hepatitis C based on the standard biochemical values and age. The FIB-4 index has been reported to be markedly useful for the prediction of advanced liver fibrosis [20,21]. Given its noninvasiveness and simplicity, the FIB-4 index has the advantage of an easy follow-up of the time-course changes by repeated measurements.

In the present study, we investigated the utility of the real-time assessment of the FIB-4 index for the prediction of time-course progression in liver fibrosis.

Abbreviations: ALT, alanine aminotransferase; AST, aspirate aminotransferase; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

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PATIENTS AND METHODS

Patients

A total of 421 patients with chronic hepatitis C who had repeated liver biopsies between 1991 and 2010 at the Musashino Red Cross hospital were consecutively investigated. All patients received interferon therapy after the first biopsy and had nonsustained virological response. A second

biopsy was performed at least 6 months after the completion of interferon therapy. Exclusion criteria were as follows: (i) co-infection with HBV or HIV (n = 1), (ii) alcohol abuse (intake of alcohol equivalent to pure alcohol 40 g/day or more) (n = 8), (iii) the presence of nonalcoholic steatohepatitis (n = 14), (iv) the presence of hepatocellular carcinoma (n = 15), (v) interval between paired biopsies was <1.5 years (n = 41) and (vi) length of biopsy sample <15 mm (n = 28). The demographic characteristics of the 314 patients enrolled are shown in Table 1.

Assessment of liver fibrosis stage

Liver biopsy was carried out under laparoscopic or ultrasonographic guidance. A sample 15 mm or larger was collected and evaluated. The fibrosis stage was categorized according to the METAVIR score: F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with few septa; F3, numerous septa without cirrhosis; and F4, cirrhosis. Two pathologists examined all samples and determined the fibrosis stage. When staging was inconsistent between the two pathologists, an appropriate stage was determined by discussion between the two.

Calculation of FIB-4 index

The FIB-4 index at the time of each liver biopsy was calculated based on the blood test results within 1 month before liver biopsy according to the following formula: The FIB-4 index = (age [years] × AST [IU/L])/(platelet count [10^9/L] × (ALT [IU/L])$^{1/2}$). Change in the FIB-4 index per year (ΔFIB-4 index/year) was calculated by the following formula: ΔFIB-4 index/year = (the FIB-4 index at the second liver biopsy − the FIB-4 index at the first liver biopsy)/interval between paired biopsies (years). Change in AST, ALT, platelet counts per year (ΔAST/year, ΔALT/year, ΔPlatelet counts/year) and the degree of changes in the fibrosis stage per year were calculated similarly.

Table 1 Clinical background of patients

	First biopsy	Second biopsy
Age (years)	53.7 ± 9.8	58.7 ± 9.4
Gender (male/female)	149/165	
AST (IU/L)	64.5 ± 36.7	58.5 ± 37.7
ALT (IU/L)	87.7 ± 58.9	69.9 ± 53.9
Platelet counts (× 10^9/L)	165 ± 48	159 ± 48
Histological findings		
Activity: 0/1/2/3	38/143/117/16	10/147/131/26
Fibrosis: 0–1/2/3/4	139/107/61/7	134/101/63/16
Interval of between biopsies (years)	4.9 ± 2.9	–

AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Statistical analysis

The SPSS software package 15.0 (SPSS Inc, Chicago, IL, USA) was used for statistical analysis. Categorical data were analysed using Fisher's exact test. Continuous variables were compared with Student's t-test. Factors associated with the progression in liver fibrosis were analysed by multivariate logistic regression analysis. Association between progression in fibrosis stage and changes in the FIB-4 was analysed by Spearman's rank correlation test. Kaplan–Meier method and log-rank test were used to analyse time to occurrence of fibrosis progression to cirrhosis. A P-value of < 0.05 was considered statistically significant.

RESULTS

Changes in liver fibrosis stage overtime

The clinical backgrounds of patients at the first and second biopsies are shown in Table 1. The average interval was 4.9 years between the two liver biopsies. The fibrosis stage progressed over time in 23%, regressed in 17% and remained unchanged in 60%. Changes of fibrosis stage stratified by the fibrosis stage at the first liver biopsy are shown in Table 2.

Comparison of FIB-4 index and liver fibrosis stage

For the prediction of advanced liver fibrosis (F3–4), a FIB-4 index <1.45 had a negative predictive value of 97%, whereas a FIB-4 > 3.25 had a positive predictive value of 49% at first biopsy. Similarly, a FIB-4 < 1.45 had a negative predictive value of 98%, and a FIB-4 > 3.25 had a positive predictive value of 54% at second biopsy (Fig. 1).

Table 2 Changes of fibrosis stage over time

	Fibrosis stage at second biopsy				
Fibrosis stage at first biopsy	F0–1 (%)	F2 (%)	F3 (%)	F4 (%)	Total
F0–1	98 (71)	33 (24)	8 (5)	–	139
F2	33 (31)	50 (47)	21 (20)	3 (2)	107
F3	3 (5)	18 (29)	33 (55)	7 (11)	61
F4	–	–	1 (14)	6 (86)	7

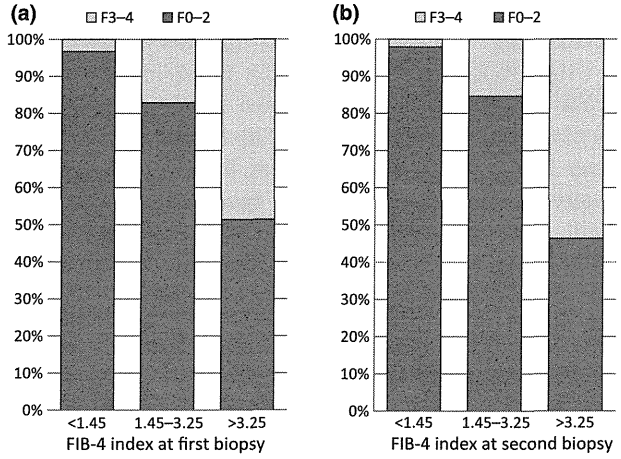

Fig. 1 Comparison of the FIB-4 index and liver fibrosis stage. Patients were categorized into three groups according to the FIB-4 index using cut-off values of < 1.45, 1.45–3.25, > 3.25 at liver biopsy. The lower bar chart (dark grey) indicates patients with F0–2, while the upper bar chart (light grey) indicates patients with F3–4. (a) comparison of the FIB-4 index and liver fibrosis stage at first biopsy and (b) at second biopsy.

Predictive factors for the progression of fibrosis

Higher level of ΔAST/year, lower level of ΔALT/year, lower level of ΔPlatelet counts/year and higher level of the ΔFIB-4/year were significantly associated with the progression of fibrosis overtime (Table 3). Multivariate analysis demonstrated that only the ΔFIB-4 index/year was an independent predictive factor for the progression of fibrosis stage ($P = 0.03$) with an odds ratio of 3.70 (95% CI:1.07–12.5).

Correlation between the degree of changes in the fibrosis stage and the ΔFIB-4 index per year

When the patients were categorized into five groups according to the degree of changes in the fibrosis stage per year (< −0.2, −0.2 – < 0, 0, > 0 – 0.2 and > 0.2), median value of the ΔFIB-4 index/year was −0.29, −0.02, 0.04, 0.16 and 0.47, respectively. The FIB-4 index reduced along the regression of the fibrosis stage, while the FIB-4 index increased along the progression of the fibrosis stage, which showed a significant correlation ($P < 0.001$) (Fig. 2).

Prediction of progression to cirrhosis by the changes in the FIB-4 index per year

The area under the receiver operating characteristic curve of the ΔFIB-4 index/year for the prediction of advancement to cirrhosis was 0.910. By the ΔFIB-4 index/year of 0.4, the sensitivity and specificity for the prediction of advancement to cirrhosis was 80% and 91%. The cumulative incidence of fibrosis progression to cirrhosis, at 5 and 10 years, was 34% and 59%, respectively, in patients with the ΔFIB-4 index/year ≥0.4, whereas it was 0% and 3% in those with the ΔFIB-4 index/year <0.4 ($P < 0.001$) (Fig. 3).

DISCUSSION

Recently, noninvasive markers of liver fibrosis have been used as a predictive factor of liver-related outcome such as

Table 3 Factors associated with the progression of liver fibrosis

	Progression of Liver fibrosis	Nonprogression of Liver fibrosis	*P*-value
Gender (male/female)	31/42	118/123	0.33
Age at first biopsy (years)	54.4 ± 8.7	53.5 ± 10.2	0.50
AST at first biopsy (IU/L)	63.9 ± 35.0	64.8 ± 37.3	0.85
ALT at first biopsy (IU/L)	86.5 ± 58.4	88.1 ± 59.2	0.84
Platelet counts at first biopsy (10^9/L)	15.8 ± 4.6	16.7 ± 4.8	0.16
Change between biopsies			
ΔAST (IU/L)/year	3.8 ± 19.5	−4.1 ± 14.8	<0.001
ΔALT (IU/L)/year	−1.9 ± 28.4	7.2 ± 22.6	0.005
ΔPlatelet counts (10^9/L)/year	−4.1 ± 9.5	−0.002 ± 9.5	0.001
ΔFIB-4 index/year	0.31 ± 0.52	−0.005 ± 0.37	<0.001

ΔAST/year: (AST at the second liver biopsy – AST at the first liver biopsy) /interval between paired biopsies (years); ΔALT/year: (ALT at the second liver biopsy – ALT at the first liver biopsy) /interval between paired biopsies (years); ΔPlatelet counts/year: (platelet counts at the second liver biopsy –platelet counts at the first liver biopsy) /interval between paired biopsies (years); ΔFIB-4 index /year: (the FIB-4 index at the second liver biopsy – the FIB-4 index at the first liver biopsy) /interval between paired biopsies (years).

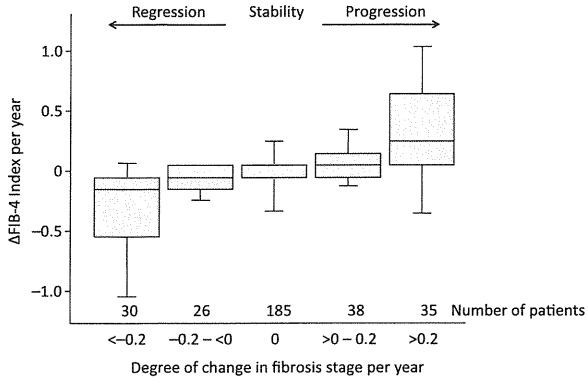

Fig. 2 Correlation between the degree of changes in the fibrosis stage and the ΔFIB-4 index per year. Boxplot of the ΔFIB-4 index/year is shown according to the degree of changes in the fibrosis stage per year. The bottom and top of each box represent the 25 and 75th percentiles, giving the interquartile range. The line through the box indicates the median value, and the error bar indicates the 5 and 95th percentiles.

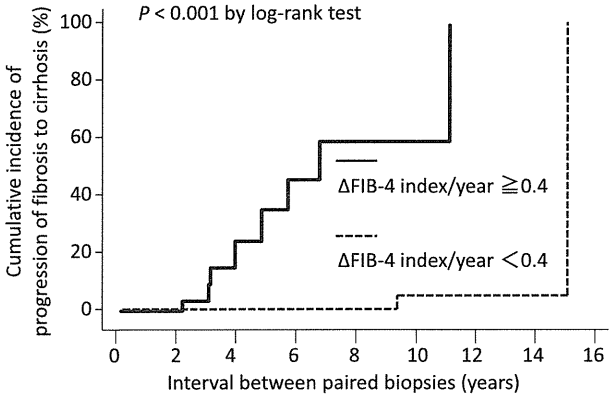

Fig. 3 Cumulative incidence of fibrosis progression to cirrhosis. Patients were categorized into two groups according to the ΔFIB-4 index/year using cut-off value of < 0.4 or ≥ 0.4.

mortality [22–24] or HCC development [24–26] in patients with chronic liver disease. There have been few studies that investigated the association between changes of noninvasive markers and liver-related outcome [27–29]. However, it is still unclear whether there is a relation between the time-course changes in the value of noninvasive markers and progression of liver fibrosis.

The aim of the study was to evaluate the utility of the real-time assessment of the FIB-4 index for the prediction of time-course progression in liver fibrosis. We have shown that the FIB-4 index reduced along the regression of the fibrosis stage, while the FIB-4 index increased along the progression of the fibrosis stage. These results indicate that the measurement of the time-course changes in the FIB-4 index may be useful for the noninvasive and real-time estimation of the progression in liver fibrosis overtime.

Although the gold standard for diagnosis of liver fibrosis is liver biopsy, there are a variety of problems including invasiveness and sampling errors [6]. Diagnostic methods of liver fibrosis by measurement of elasticity of the liver by ultrasonography [10–14] have been developed, but these modalities are not widely available.

The FIB-4 index has an advantage among these noninvasive liver fibrosis diagnostic methods. Firstly, it is quite easily calculated. The parameters required for calculation are only age, AST, ALT and platelet counts, which are measured at the routine examination of patients with liver disease. Therefore, additional blood collection is unnecessary, and the index can be calculated at no cost. Secondly, because of its simple calculation, it is possible to evaluate the clinical conditions in a real-time manner. Repeated measurements of the FIB-4 index make it possible to predict deterioration in liver fibrosis continuously over time. Because no special equipment or system is necessary, and objective data on the clinical conditions are provided in a real-time manner, the FIB-4 index is simple and convenient compared with other noninvasive liver fibrosis diagnostic methods.

It is widely known that a decrease in platelet counts is useful for the prediction of the progression of fibrosis stage [30]. We have reported that elevated AST or ALT is also associated with the progression of liver fibrosis [31]. However, the results of this study showed that a change in the FIB-4 index over time was a more useful factor for the prediction of the progression of fibrosis stage than AST, ALT and changes in platelet counts.

Liver biopsy is still an important examination as the gold standard for diagnosis of liver fibrosis, but time-course changes cannot be readily observed by repeated biopsies because of its invasiveness. On the other hand, it is possible to estimate the progression of liver fibrosis by repeated measurement of the FIB-4 index. Therefore, two examinations should be combined: liver biopsy may be utilized to determine the baseline of fibrosis stage, and the serial measurement of the FIB-4 index may be utilized to predict changes of fibrosis stages overtime in a real-time manner.

In conclusion, we believe that measurement of the time-course changes in the FIB-4 index is useful for the noninvasive and real-time estimation of the progression in liver fibrosis.

ACKNOWLEDGEMENTS

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CONFLICT OF INTEREST

No conflicts of interest exist for all authors.

REFERENCES

1 Dienstag JL. The role of liver biopsy in chronic hepatitis C. *Hepatology* 2002; 5(Suppl 1): S152–S160.
2 Benvegnu L, Gios M, Boccato S, Alberti A. Natural history of compensated viral cirrhosis: a prospective study on the incidence and hierarchy of major complications. *Gut* 2004; 53(5): 744–749.
3 Serfaty L, Aumaitre H, Chazouilleres O *et al.* Determinants of outcome of compensated hepatitis C virus-related cirrhosis. *Hepatology* 1998; 27(5): 1435–1440.
4 Gebo KA, Herlong HF, Torbenson MS *et al.* Role of liver biopsy in management of chronic hepatitis C: a systematic review. *Hepatology* 2002; 5(Suppl 1): S161–S172.
5 Saadeh S, Cammell G, Carey WD, Younossi Z, Barnes D, Easley K. The role of liver biopsy in chronic hepatitis C. *Hepatology* 2001; 33(1): 196–200.
6 Bravo AA, Sheth SG, Chopra S. Liver biopsy. *N Engl J Med* 2001; 344(7): 495–500.
7 Bedossa P, Dargere D, Paradis V. Sampling variability of liver fibrosis in chronic hepatitis C. *Hepatology* 2003; 38(6): 1449–1457.
8 Colloredo G, Guido M, Sonzogni A, Leandro G. Impact of liver biopsy size on histological evaluation of chronic viral hepatitis: the smaller the sample, the milder the disease. *J Hepatol* 2003; 39(2): 239–244.
9 The French METAVIR Cooperative Study Group. Intraobserver and interobserver variations in liver biopsy interpretation in patients with chronic hepatitis C. *Hepatology* 1994; 20(1 Pt 1): 15–20.
10 Sandrin L, Fourquet B, Hasquenoph JM *et al.* Transient elastography: a new noninvasive method for assessment of hepatic fibrosis. *Ultrasound Med Biol* 2003; 29(12): 1705–1713.
11 Ganne-Carrie N, Ziol M, de Ledinghen V *et al.* Accuracy of liver stiffness measurement for the diagnosis of cirrhosis in patients with chronic liver diseases. *Hepatology* 2006; 44(6): 1511–1517.
12 Foucher J, Chanteloup E, Vergniol J *et al.* Diagnosis of cirrhosis by transient elastography (FibroScan): a prospective study. *Gut* 2006; 55(3): 403–408.
13 Castera L, Vergniol J, Foucher J *et al.* Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. *Gastroenterology* 2005; 128(2): 343–350.
14 Tatsumi C, Kudo M, Ueshima K *et al.* Noninvasive evaluation of hepatic fibrosis using serum fibrotic markers, transient elastography (FibroScan) and real-time tissue elastography. *Intervirology* 2008; 51(Suppl 1): 27–33.
15 Williams AL, Hoofnagle JH. Ratio of serum aspartate to alanine aminotransferase in chronic hepatitis. Relationship to cirrhosis. *Gastroenterology* 1988; 95(3): 734–739.
16 Wai CT, Greenson JK, Fontana RJ *et al.* A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Hepatology* 2003; 38(2): 518–526.
17 Lin ZH, Xin YN, Dong QJ *et al.* Performance of the aspartate aminotransferase-to-platelet ratio index for the staging of hepatitis C-related fibrosis: an updated meta-analysis. *Hepatology* 2011; 53(3): 726–736.
18 Imbert-Bismut F, Ratziu V, Pieroni L, Charlotte F, Benhamou Y, Poynard T. Biochemical markers of liver fibrosis in patients with hepatitis C virus infection: a prospective study. *Lancet* 2001; 357(9262): 1069–1075.
19 Sebastiani G, Vario A, Guido M *et al.* Stepwise combination algorithms of non-invasive markers to diagnose significant fibrosis in chronic hepatitis C. *J Hepatol* 2006; 44(4): 686–693.
20 Sterling RK, Lissen E, Clumeck N *et al.* Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. *Hepatology* 2006; 43(6): 1317–1325.
21 Vallet-Pichard A, Mallet V, Nalpas B *et al.* FIB-4: An inexpensive and accurate marker of fibrosis in HCV infection. Comparison with liver biopsy and fibrotest. *Hepatology* 2007; 46(1): 32–36.
22 Vergniol J, Foucher J, Terrebonne E *et al.* Noninvasive tests for fibrosis and liver stiffness predict 5-year outcomes of patients with chronic hepatitis C. *Gastroenterology* 2011; 140(7): 1970–1979. 1979 e1971-1973.
23 Nunes D, Fleming C, Offner G *et al.* Noninvasive markers of liver fibrosis are highly predictive of liver-related death in a cohort of HCV-infected individuals with and without HIV infection. *Am J Gastroenterol* 2010; 105(6): 1346–1353.
24 Fung J, Lai CL, Seto WK, Wong DK, Yuen MF. Prognostic significance of liver stiffness for hepatocellular carcinoma and mortality in HBeAg-negative chronic hepatitis B. *J Viral Hepat* 2011; 18(10): 738–744.
25 Masuzaki R, Tateishi R, Yoshida H *et al.* Prospective risk assessment for hepatocellular carcinoma development in patients with chronic hepatitis C by transient elastography. *Hepatology* 2009; 49(6): 1954–1961.
26 Jung KS, Kim SU, Ahn SH *et al.* Risk assessment of hepatitis B virus-related hepatocellular carcinoma development using liver stiffness measurement (FibroScan). *Hepatology* 2011; 53(3): 885–894.
27 Vergniol J, Foucher J, Castera L *et al.* Changes of non-invasive markers and FibroScan values during HCV treatment. *J Viral Hepat* 2009; 16(2): 132–140.
28 Mummadi RR, Petersen JR, Xiao SY, Snyder N. Role of simple biomarkers in predicting fibrosis progression in HCV infection. *World J Gastroenterol* 2010; 16(45): 5710–5715.
29 Jain MK, Seremba E, Bhore R *et al.* Change in fibrosis score as a predictor of mortality among HIV-infected patients with viral hepatitis. *AIDS Patient Care STDS* 2012; 26(2): 73–80.
30 Poynard T, Bedossa P. Age and platelet count: a simple index for predicting the presence of histological lesions in patients with antibodies to hepatitis C virus. METAVIR and CLINIVIR Cooperative Study Groups. *J Viral Hepat* 1997; 4(3): 199–208.
31 Kurosaki M, Matsunaga K, Hirayama I *et al.* The presence of steatosis and elevation of alanine aminotransferase levels are associated with fibrosis progression in chronic hepatitis C with non-response to interferon therapy. *J Hepatol* 2008; 48(5): 736–742.

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Guidelines

2011 Japanese Society for Dialysis Therapy Guidelines for the Treatment of Hepatitis C Virus Infection in Dialysis Patients

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[1]Working Group for the Preparation of Guidelines for the Treatment of Hepatitis C Virus Infection in Dialysis Patients, [2]Chairman, Subcommittee for the Preparation of Guidelines, [3]Chairman, Scientific Committee, and [4]Chairman, Board of Directors, Japanese Society for Dialysis, Tokyo, Japan

INTRODUCTION

Objectives of the preparation of the guidelines

The prevention, diagnosis, and treatment of hepatitis C Virus (HCV) infection are clearly important for the management of patients undergoing chronic hemodialysis, because (i) the HCV infection rate is high in dialysis patients; (ii) the outcome is poorer in HCV-infected than non-infected dialysis patients; and (iii) an improvement in the outcome can be expected by the prevention or diagnosis and treatment of HCV infection. Therefore, it was decided to prepare "guidelines for the treatment and management of hepatitis C at dialysis facilities by dialysis physicians and nephrologists in cooperation with hepatologists" by the instruction of Tadao Akizawa, Chairman of the Board of Directors of the Japanese Society for Dialysis Therapy, and Hideki Hirakata, Chairman of the Scientific Committee, and under the leadership of Tadashi Tomo, Chairman of the Committee for the Preparation of the Guidelines. In preparing the guidelines, it was agreed (i) that they would be applied to chronic dialysis patients; and (ii) that they would be used by physicians at dialysis facilities. They would also be prepared to inform hepatologists about the dose of interferon and the criteria for the introduction and reduction of interferon administration in dialysis patients. Their preparation was initiated at the first meeting of the Committee for the Preparation of Guidelines for the Treatment of Hepatitis C Virus Infection in Dialysis Patients on 6 January 2009.

Environment and history of the preparation of the guidelines

Prior to this, in April 2008, the Kidney Disease: Improving Global Outcomes (KDIGO) group presented the "KDIGO Clinical Practice Guidelines for the Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C in Chronic Kidney Disease" as the first guidelines by the KDIGO itself in *Kidney International* (1). The guidelines were a 107-page tour de force consisting of five chapters dealing with (i) detection and evaluation of HCV in CKD patients; (ii) treatment of HCV-infected CKD patients; (iii) prevention of HCV infection in the dialysis room; (iv) treatment of HCV infected patients before and after kidney transplantation; and (v) diagnosis and treatment of HCV-related retinopathy, were compiled under the supervision of Michel Jadoul and David Roth, and described the diagnosis, treatment, and prevention of HCV infection in patients with CKD in the maintenance period, dialysis patients, and patients undergoing kidney transplantation. The ISN informed its members of these guidelines and recommended to apply them in consideration of the state of each country, region, and facility (implantation), because

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they contained provisions not necessarily based on strong evidence.

Thus, the Working Group for the Preparation of the Guidelines for the Treatment of Hepatitis C Virus Infection decided to make the guidelines cover the (i) diagnosis, (ii) treatment, and (iii) prevention of HCV infection in dialysis patients, and (iv) their management before and after transplantation on the basis of the items of the KDIGO guidelines by securing the cooperation of experts in dialysis and HCV hepatitis. In addition, as the aminotransferase levels are low in dialysis patients, and as the method for the assessment of fibrosis was not established, some members considered it necessary to include test methods and diagnostic criteria, and the guidelines were decided to comprise five chapters dealing with (i) screening, (ii) management (methods and frequencies of blood tests and imaging studies), (iii) indications of antiviral therapies, (iv) treatment by antiviral therapies (including patients expected to receive kidney transplantation), and (v) prevention of HCV infection at hemodialysis facilities.

The references consisted primarily of English and Japanese literature published by the end of 2008, but domestic and overseas guidelines were also included.

Committee members involved in the preparation of the guidelines

Tadao Akizawa, Chairman, Board of Directors, Japanese Society for Dialysis Therapy
Hideki Hirakata, Chairman, Scientific Committee, Japanese Society for Dialysis Therapy
Tadashi Tomo, Chairman, Subcommittee for the Preparation of Guidelines of the Japanese Society for Dialysis Therapy
Working Group for the Preparation of Guidelines for the Treatment of Hepatitis C Virus Infection in Dialysis Patients

Chairman	Takashi Akiba (Tokyo Women's Medical University)
Vice-chairman	Kazuhiko Hora (Hokushin General Hospital)
Members	Michio Imawari (Showa University)
	Chifumi Sato (Tokyo Medical and Dental University)
	Eiji Tanaka (Shinshu University)
	Namiki Izumi (Musashino Red Cross Hospital)
	Takashi Harada (Nagasaki Kidney Hospital)
	Ryoichi Ando (Musashino Red Cross Hospital)
	Kan Kikuchi (Tokyo Women's Medical University)

All members listed above have submitted a conflict of interest disclosure report to the General Affairs Committee.

Times and dates of meetings of the Committee for the Preparation of Guidelines for the treatment of hepatitis C virus infection in dialysis patients

1st Meeting	6 January 2009	18:00–20:00	Seiyoken, Nihonbashi
2nd Meeting	17 June 2009	18:00–20:00	Seiyoken, Nihonbashi
3rd Meeting	30 September 2009	18:00–20:00	Seiyoken, Nihonbashi
4th Meeting	25 December 2009	18:00–20:00	Seiyoken, Nihonbashi
5th Meeting	5 February 2010	18:00–20:00	Seiyoken, Nihonbashi
6th Meeting	4 June 2010	18:00–20:00	Seiyoken, Nihonbashi
55th Consensus Conference on Hepatitis C, Scientific Committee, Japanese Society for Dialysis Therapy	20 June 2010	13:30–16:30	Kobe International Conference Center, 1st Conference Room
7th Meeting	6 August 2010	18:00–20:00	Seiyoken, Nihonbashi
Public Hearing	16 January 2011	13:00–15:00	Clinical Lecture Hall, Tokyo Women's Medical University
8th Meeting	4 February 2011	18:00–20:00	Office Tokyo, 4F, Meeting Room A4

Evaluation of the evidence and recommendation levels

The evidence and recommendation levels were prepared on the basis of the position paper "Grading evidence and recommendations for clinical practice guidelines in nephrology" (2) issued by KDIGO in 2006 and the Working Group Report on the Grading of Evidence Levels and Degrees of Recommendation disclosed by the Japanese Society for Dialysis Therapy on 16 November 2009 (Table 1) (later published in the *Journal of the Japanese Society for Dialysis Therapy* with modifications) (3).

TABLE 1. *Working Group Report on the grading of evidence levels and degrees of recommendation, 16 November 2009*

Chairman of WG: Masashi Fukagawa
Members of WG: Kazutaka Kukita, Yusuke Tsukamoto, Tsubakihara Yoshiharu, Yoshizo Kaizu, Eiji Kusano, Masaaki Nakayama
Chairman, Subcommittee for the Preparation of Guidelines: Tadashi Tomo
Chairman, Scientific Committee: Hideki Hirakata

General Principles
(1) Considering the situation that various global and local guidelines have been issued, the following general principles are observed.
(2) The consistency of the style of the text of the guidelines will be evaluated in the future.
(3) After the report is submitted to and approved by the Board of Directors, its details will be published formally as a WG Report in the Journal of Japanese Society for Dialysis Therapy.

On the evaluation of evidence levels
(1) Basically, the current evidence grading method of KDIGO is followed (Kidney International, 2006, see the attached table).
(2) The following may be decided by the responsibility of the working group for each guideline. However, the criteria and reasons must be stated clearly.
  (a) Restriction of conditions for the adoption of research papers (size, period, etc.)
  (b) Upgrading and downgrading of evidence (depending on the situation, that the data are about Japanese subjects may be regarded as a condition of upgrading).
(3) Papers in Japanese may be adopted by the judgment of the WG if the evidence level can be evaluated.
  (a) If they are adopted, the reason for the adoption and the evaluation of the evidence level must be stated clearly.
  (b) Maximum support for publication in English must be provided until the Guidelines are published in English.
(4) Abstracts are not adopted, in principle.

On the recommendation level
(1) Graded into 2 levels (strong, weak)
(2) The following expressions are used.
  (a) It is recommended to . . . , It is recommended not to . . . (strong)
  (b) It is desirable to . . . , It is desirable not to . . . (weak)
  (c) Since negative sentences such as "It is disrecommended to . . . or it is undesirable to . . ." is a strong expression, "It is recommended not to . . . or it is desirable not to . . ." is used by attaching conditioning modifications such as "as a routine procedure".
(3) Ungraded expert opinions may be attached to items lacking evidence. In this instance, only those agreed on by two thirds or more of the WG members are adopted.

Table of abbreviations

AFP	α-fetoprotein
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration time curve
Ccr	creatinine clearance
Cmax	peak serum concentration of a therapeutic drug
EIA	enzyme-linked immunosorbent assay
EOB-MRI	EOB-magnetic resonance imaging
EPO	erythropoietin
ESA	erythropoiesis stimulating agent
HA	hyaluronate
HCV	hepatitis C virus
IFN	interferon
KDIGO	Kidney Disease: Improving Global Outcomes
NIDDM	non-insulin-dependent diabetes mellitus
PCR	polymerase chain reaction
PEG-IFN	pegylated interferon
PIVKA-II	proteins induced by vitamin K absence-II
PLP	pyridoxal-5′-phosphate
PNALT	persistent normal ALT
ROC curve	receiver operating characteristic curve
RT-PCR	reverse transcriptase PCR
RVR	rapid virological response
SNMC	stronger neo-minophagen C
SVR	sustained virological response
Tmax	maximum drug concentration time
TRX	thioredoxin
UDCA	ursodeoxycholic acid
VRAD	virus removal and eradication by double filtration plasma pheresis

REFERENCES

1. Kidney Disease: Improving Global Outcomes. KDIGO clinical practice guidelines for the prevention, diagnosis, evaluation, and treatment of Hepatitis C in chronic kidney disease. *Kidney Int* 2008;73(Suppl 109):S1–99.
2. Uhlig K, MacLeod A, Craig J et al. Grading evidence and recommendations for clinical practice guidelines in nephrology. A position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2006;70:2058–65.
3. Fukagawa M, Tsukamoto Y, Tsubakihara Y et al. On the evaluation of evidence levels and degrees of guideline recommendation. *J Jpn Soc Dial Ther* 2010;43:347–9.

SCREENING OF DIALYSIS PATIENTS FOR HEPATITIS C VIRUS INFECTION

[Statements]

1. The serum aminotransferase levels are lower in dialysis patients than in individuals with normal renal function. (Evidence level: High, Recommendation level: Strong)
2. The serum aminotransferase levels are higher in HCV-antibody-positive than in negative dialysis patients, but the criteria for the general population cannot be applied to dialysis patients. (Evidence level: High, Recommendation level: Strong)
3. In dialysis patients, it is desirable to measure the serum aminotransferase levels at least once a month even if they are asymptomatic. (Evidence level: Low, Recommendation level: Weak)
4. It is recommended to perform the HCV antibody test and, if necessary, the HCV-RNA test at the

introduction of dialysis and the acceptance of patients. (Evidence level: Low, Recommendation level: Strong)
5. In dialysis patients, it is desirable to perform the HCV antibody test at least once every 6 months even if HCV antibody is negative on the initial test. (Evidence level: Low, Recommendation level: Weak)
6. If the serum aminotransferase level increases with no clear cause, it is recommended to perform an ad hoc HCV-RNA or HCV core antigen test in addition to the HCV antibody test. (Evidence level: Low, Recommendation level: Strong)
7. If an HCV-positive patient considered to be due to nosocomial infection that has been detected, it is recommended to perform the HCV-RNA or HCV core antigen test in all dialysis patients who may have been exposed. (Evidence level: Very low, Recommendation level: Strong)

[Comments]

1. The serum aminotransferase level is lower in dialysis patients than in individuals with normal renal function. (Evidence level: High, Recommendation level: Strong)

Serum aminotransferase levels (AST, ALT) as indices of liver function have been reported to be lower in dialysis patients than in individuals with normal kidney function. There has been a report that the ALT level was 15.6 ± 12 IU/L in dialysis patients and 22.7 ± 18 IU/L in normal controls and that the upper limit of the normal range of ALT in dialysis patients was 27 IU/mL (1). Thus, if the upper limit of the normal range was set at 25 IU/L, then the ALT level was normal in 67% of dialysis patients (2). There is also a report that the AST levels in healthy individuals and dialysis patients were 22.3 (22.0 ± 22.7) and 20.6 (21.6 ± 23.6), respectively, that the ALT levels were 20.3 (19.9 ± 20.7) and 16.3 (15.3 ± 17.3), respectively, and that the cutoff values effective for the prediction of HCV infection were 18 for AST and 16 for ALT (3). Since the serum aminotransferase levels are lower in dialysis patients than the standards in the general population, their cutoff values for the prediction of HCV infection should be set at lower levels in these patients. It has been known that the serum aminotransferase levels in uremic patients are low and negatively correlate with the blood urea nitrogen level (4), and factors that inhibit the serum aminotransferase activities have been reported to accumulate in patients' serum with elevations of the serum aminotransferase levels due to dialysis (5). However, the level of pyridoxal-5'-phosphate (PLP) is positively correlated with the AST and ALT levels. Additionally, serum aminotransferase levels were significantly lower in the PLP-deficient group than in the normal group, being 9.2 ± 0.3 vs. 13.4 ± 0.7 for AST and 8.6 ± 0.6 vs. 11.4 ± 0.9 for ALT. Also, as the AST and ALT levels were elevated by supplementation of PLP only in the PLP-deficient group, deficiency of PLP, which acts as a coenzyme of aminotransferases, has been suggested to partly explain the low aminotransferase levels in dialysis patients (6). There is also a report that, in uremia, the enzyme activity of PLP is lost as its lysine-binding site is carbamylated by cyanogen salts formed by urea (7). In contrast, it has also been reported that the Vitamin B6 and PLP levels are normal in dialysis patients and thus, the low serum aminotransferase levels cannot be explained by Vitamin B6 deficiency (8,9).

Therefore, based on the clinical observations to date and abnormalities of enzyme activities in uremic patients, serum aminotransferase levels are considered to be lower in dialysis patients than in people with normal kidney function.

2. The serum aminotransferase levels are higher in HCV-antibody-positive than in negative dialysis patients, but the criteria for the general population cannot be applied to dialysis patients. (Evidence level: High, Recommendation level: Strong)

The serum aminotransferase levels are normal in dialysis patients regardless of whether they are negative or positive for HCV antibody. However, the ALT level is higher in HCV antibody positive dialysis patients than in HCV antibody negative dialysis patients (2.7 ± 20.0 and 12.5 ± 8.8, respectively) (10). Particularly, the simultaneous detection of HB antigen and HCV-RNA has been related to ALT elevation. Also, it has been reported that the ALT level was 32.4 ± 24.2 and 33.7 ± 27.2 in male and female HCV-antibody-positive dialysis patients, respectively, but 17.0 ± 11.4 and 13.9 ± 6.1 in male and female HCV-antibody-negative patients, respectively. The ALT level was also reported to be higher in HCV-RNA-positive than in HCV RNA negative patients. However, the ALT level was not related to the HCV genotype (11). In HCV-antibody-positive, HCV-antibody-negative, HCV-RNA-positive, and HCV-antibody-negative dialysis patients, the ratio of ALT/upper limit of the normal range was 0.77 ± 0.57, 0.38 ± 0.23, 0.81 ± 0.57, and 0.37 ± 0.23, respectively. The cutoff value of ALT for being HCV-antibody-positive as determined

from the receiver operating characteristic (ROC) curve was 50% of the upper limit of the normal range (sensitivity: 67%, specificity: 83%) and that for being HCV-RNA-positive was 45% (sensitivity: 71%, specificity 80%). Also, the observed value/upper limit of normal range of ALT was clearly higher in HCV-RNA-positive than in HCV-RNA-negative dialysis patients (12). Moreover, this value was reported not to differ in the group without hepatitis but to be higher in the group with hepatitis compared with the group without hepatitis, suggesting that the ALT level of HCV-RNA-positive dialysis patients may be useful as a marker of liver disorder obtained by liver biopsy (13). However, histological findings obtained by liver biopsy were reported to be milder, and the ALT level to be lower, in HCV-positive dialysis patients than in HCV-positive individuals with normal kidney function (14,15).

Therefore, the serum aminotransferase levels are considered to be higher in HCV-antibody-positive dialysis patients than in those negative, but the criteria for the general population are not considered to be applicable to dialysis patients.

3. In dialysis patients, it is desirable to measure the serum aminotransferase levels at least once a month even if they are asymptomatic. (Evidence level: Low, Recommendation level: Weak)

While there is no evidence concerning the frequency of measurement of the serum aminotransferase levels in dialysis patients, there have been reports that the serum aminotransferase levels and the ratio of ALT/upper limit of the normal range has been reported to be higher in HCV-antibody-positive and HCV-RNA-positive patients than in negative patients (10–12,16). Although the ALT level was elevated in only 51% of the HCV-RNA-positive patients after kidney transplantation, but that the ALT level was correlated with the degree of liver tissue damage evaluated by liver biopsy, and that ALT can serve as a marker of liver tissue damage in HCV-RNA-positive recipients of kidney transplantation (13). Therefore, observation of changes in ALT levels by regular examinations may lead to the early detection of HCV infection, and the possibility of HCV infection must always be considered even if the serum aminotransferase levels are within the normal ranges.

Liver function tests are usually performed once a month in dialysis patients. It is desirable to measure the serum aminotransferase levels at least once a month even in asymptomatic patients.

4. It is recommended to perform the HCV antibody test and, if necessary, the HCV-RNA test at the introduction of dialysis and the acceptance of patients. (Evidence level: Low, Recommendation level: Strong)

In HCV-positive chronic nephritis, there has been a report that membranoproliferative glomerulonephritis was the most frequent, accounting for 54%, that cryoglobulinemia was noted in 54% of the patients, and that HCV-RNA was detected in 66% on cryoprecipitation and 22% of frozen sections (17). Immunocomplexes are noted in the glomeruli by kidney biopsy, and they have been shown to be a cause of chronic nephritis such as membranoproliferative glomerulonephritis in which factors such as cryoglobulin are involved (18–21). The HCV antibody-positive rate is 7.9% in patients with kidney diseases compared with 1.03% in healthy individuals and is particularly high (16.6%) in patients with glomerulonephritis. This rate is higher in those patients with a Ccr level of less than 30 mL/min than in patients with a Ccr level of 30 mL/min or higher (13% vs. 2.7%). Furthermore, HCV infection has been reported to be involved in the etiology of glomerulonephritis (22). There has also been a report that HCV was positive in 3.9% of the 1041 CKD patients, and that 95% of HCV-positive patients showed viremia, and that the HCV-positive rate is high in CKD patients (23). It has also been reported that HCV antibody was positive in 12.7% of dialysis patients, and that of the dialysis patients, the HCV-antibody-positive rate was higher in those with non-insulin dependent diabetes mellitus (NIDDM) (20.8%) than in those with no diabetes mellitus (DM) (10%) (24), and that the HCV-positive rate in NIDDM patients was high at 19.5% (25). Based on these reports, HCV infection is likely to be involved in the pathogenesis of chronic kidney diseases. Therefore, the HCV-antibody-positive rate has been reported to be high at 7.3% (26) or 14.4% (27) in dialysis patients at the introduction of dialysis therapy. Moreover, according to the Dialysis Outcomes and Practice Patterns Study (DOPPS), the HCV-positive rate varied from 2.6% to 22.9% among the participating countries, and its increases were related to the dialysis period, male gender, black race, diabetes status, HBV infection, kidney transplantation, and alcohol and drug dependence. Many other studies have clarified the wide differences in the HCV-antibody-positive rate and the HCV-antibody-positive-conversion rate among dialysis patients at different facilities (28,29). Particularly, the HCV-positive-conversion rate has been reported to be high at facilities with a high HCV-positive rate

(30). Therefore, it is recommended to perform HCV antibody or HCV-RNA test at the introduction of dialysis therapy or at transfer of patients to another hospital.

5. In dialysis patients, it is desirable to perform the HCV antibody test at least once every 6 months even if HCV antibody is negative on the initial test. (Evidence level: Low, Recommendation level: Weak)

While there is no evidence concerning the frequency of HCV antibody test in dialysis patients, HCV positivity was reported to be detected in 70 days (36–210 days) by second-generation enzyme immunoassay (EIA) and in 49 days (27–119 days) by the third generation EIA from the detection of abnormality of ALT. In patients with acute HCV hepatitis, HCV-RNA becomes detectable in 1–2 weeks after HCV infection, and chronic HCV hepatitis is diagnosed when HCV-RNA persists for 6 months or longer. The chronicity rate is 55–85%. In acute HCV hepatitis cases, the ALT level begins to increase 2–8 weeks after infection. Symptoms usually appear 3–12 weeks (mean 7 weeks) after infection, and HCV antibody become positive simultaneously or with a slight delay. If the infection takes a chronic course, the ALT level increases and changes. Some immune-deficient individuals remain HCV-antibody-negative even after HCV infection (31). In a previous study, the HCV-RNA-positive-rate increased from 12.9% to 15.7% after a 4-year follow-up, de novo HCV infection was observed in one patient during this period with an HCV-positive-conversion rate of 0.33%/year, and the initial examination is considered to have been made during the window period in five of the patients, so that it was concluded that the HCV-RNA test must be performed once a month to reduce nosocomial HCV infection (32).

Also, there is a report that the HCV-antibody positive conversion rate was 0.44%/year when examined at 6-month intervals while observing the CDC standard preventive measures (33). Therefore, the KDIGO guidelines recommend to perform the HCV antibody test in HCV-antibody-negative patients once every 6–12 months (intermediate recommendation level) (34). The KDIGO also recommends testing by the enzyme antibody method at facilities with a low HCV infection rate and by the nucleic acid amplification technique at those with a high HCV infection rate (intermediate recommendation level) (34).

Based on these observations, it is considered desirable to perform the HCV antibody test at least once every 6 months in dialysis patients even if the HCV antibody were negative on the initial test.

6. If the serum aminotransferase level increases with no clear cause, it is recommended to perform an ad hoc HCV-RNA test or HCV core antigen test in addition to the HCV antibody test. (Evidence level: Low, Recommendation level: Strong)

If the serum aminotransferase level has increased with no obvious reason, there is the possibility of HCV infection. It has been reported that 9% of dialysis patients were HCV-RNA-positive even if they were HCV-antibody-negative, and the viral level is considered to have been low in such patients. Caution is needed in immune-deficient individuals such as dialysis patients because of a low viral level (35). Therefore, HCV infection cannot be excluded on the basis of a negative HCV antibody test, the HCV-RNA test must be performed when considered necessary. For the HCV-RNA assay, real-time PCR is recommended because of its high sensitivity (36,37). It has also been reported that patients become positive for the HCV core antigen 2 days after HCV infection but do not become positive for the HCV antibody until 50.8 days after infection. Thus a high-sensitivity assay for the HCV core antigen that is an inexpensive and quick method for the judgment of HCV infection, is useful for the diagnosis of HCV infection and is used during the window period until HCV antibody becomes positive (38,39). KDIGO recommends that the HCV test by a nucleic acid amplification technique should be carried out if the serum aminotransferase level has increased with no clear reason (strong recommendation) (34). Also, the determination of the viral level and HCV genotype by the HCV-RNA assay contributes to the evaluation of responses to interferon therapy (36). Thus if the serum aminotransferase level has increased with no clear cause, it is recommended to perform the HCV-RNA or HCV core antigen test ad hoc in addition to the HCV antibody test.

7. If an HCV-positive patient considered to be due to nosocomial infection has been detected, it is recommended to perform the HCV-RNA or HCV core antigen test in all dialysis patients who may have been exposed. (Evidence level: Very low, Recommendation level: Strong)

If a patient is judged to be newly positive on the HCV antibody test, the possibility of a nosocomial outbreak of HCV infection must be examined. As mentioned in the comment for Statement 6, the possibility of HCV infection cannot be excluded in patients who may have been exposed even if they are HCV-antibody-negative. Also, to fill the window period of HCV infection, a test for HCV-RNA or HCV core antigen must be performed. KDIGO rec-

ommends that surveillance to examine whether nosocomial infection has not occurred by the HCV-RNA test using a nucleic acid amplification technique be carried out if an HCV-positive patient considered to be due to nosocomial infection has been detected (strong recommendation). In addition, KDIGO recommends re-examination within 2–12 weeks after an initial negative examination (weak recommendation) (34).

Therefore, if an HCV-positive patient considered to be due to nosocomial infection has been detected, it is recommended to carry out the HCV-RNA or HCV core antigen test in all dialysis patients who may have been exposed.

REFERENCES

1. Espinosa M, Martin-Malo A, Alvarez de Lara MA, Soriano S, Aljama P. High ALT levels predict viremia in anti-HCV-positive HD patients if a modified normal range of ALT is applied. *Clin Nephrol* 2000;54:151–6.
2. Yuki N, Ishida H, Inoue T et al. Reappraisal of biochemical hepatitis C activity in hemodialysis patients. *J Clin Gastroenterol* 2000;30:187–94.
3. Guh JY, Lai YH, Yang CY et al. Impact of decreased serum aminotransferase levels on the evaluation of viral hepatitis in hemodialysis patients. *Nephron* 1995;69:459–65.
4. Cohen GA, Goffinet JA, Donabedian RK, Conn HO. Observation on decreased serum glutamic oxalacetic aminotransferase(SGOT)activity in azotemic patients. *Ann Intern Med* 1976;84:275–80.
5. Crawford DR, Reyna RS, Weiner MW. Effect of in vivo and vitro dialysis on plasma transaninase activity. *Nephron* 1978; 22:418–22.
6. Ono K, Ono T, Matumata T. The pathogenesis of decreased aspartate aminotransferase and alaine aminotransferase activity in the plasma of hemodialysis patients: the role of vitamin B_6 deficiency. *Clin Nephrol* 1995;43:405–8.
7. Van Lente F, McHugh A, Pippenger CE. Carbomylation of Apo-Aspartete Amonitransferase: A possible mechanism for enzyme inactivation in uremic patients. *Clin Chem* 1986;32: 2107–8.
8. Heaf JG. Liver function tests and pyridoxine levels in uremia. *Nephron* 1982;30:131–6.
9. Yasuda K, Okuda K, Endo N et al. Hypoaminotransferasemia in patients undergoing long-term hemodialysis: clinical and biochemical appraisal. *Gastroenterology* 1995; 109:1295–300.
10. Nakayama E, Akiba T, Marumo F, Sato C. Prognosis of anti-hepatitis C virus antibody-positive patients on regular hemodialysis therapy. *J Am Soc Nephrol* 2000;11:1896–902.
11. Fabrizi F, Lunghi G, Audrulli S, Faranna P, Pagano A, Locatelli F. Influence of hepatitis C virus viremia upon serum aminotransferase activity in chronic hemodialysis patients. *Nephrol Dial Transplant* 1997;12:1394–8.
12. Lopes EP, Gouveia EC, Albuquerque ACC et al. Determination of the cut-off value of serum alanine aminotransferase in patients with hepatitis C viremia. *J Clin Virol* 2006;35:298–302.
13. Perez RM, Ferreira AS, Medina-Pestana JO, Lanzoni VP, Silva AE, Ferraz ML. Is alanine aminotransferase a good marker of histologic hepatic damage in renal transplant patients with hepatitis C virus infection? *Clin Transplant* 2005;19:622–5.
14. Sterling RK, Syntal AJ, Luketic VA et al. Chronic hepatitis C infection in patients with end stage disease: characterization of liver histology and viral lord in patients awaiting renal transplantation. *Am J Gastroenterol* 1999;94:3576–82.
15. Trevizoli JE, Menezes RP, Velasco LFR et al. Hepatitis C is less aggressive in hemodialysis patients than in nonuremic patients. *Clin J Am Soc Nephrol* 2008;3:1385–90.
16. Salama G, Rostaing L, Sandres K, Izopet J. Hepatitis C virus infection in French hemodialysis units: a multicenter study. *J Med Virol* 2000;61:44–51.
17. Sabry AA, Sobh MA, Irving WL et al. A comprehensive study of the association between hepatitis C virus and Glomerulopathy. *Nephrol Dial Transplant* 2002;17:239–45.
18. Johnson RJ, Gretch DR, Yamabe H et al. Membranoproliferative glomerulonephritis associated with hepatitis C virus infection. *N Eng J Med* 1993;328:465–70.
19. Ohta S, Yokoyama H, Furuichi K et al. Clinicopathologic feature of glomerular lesion associated with hepatitis C virus infection in Japan. *Clin Exp Nephrol* 1997;1:216–24.
20. Kamar N, Izopet J, Alric L, Guilbeaud-Frugier C, Rostaing L. Hepatitis C virus-related kidney disease: an overview. *Clin Nephrol* 2008;69:149–60.
21. Perico N, Cattaneo D, Bikbov B, Ramuzzi G. Hepatitis C infection and chronic renal diseases. *Clin J Am Soc Nephrol* 2009;4:207–20.
22. Darcia-Valdecases J, Baml C, Garcia F et al. Epidemiology of hepatitis C virus infection in patients with renal disease. *J Am Soc Nephrol* 1994;5:186–92.
23. Lemos LB, Perez RM, Lemos MM et al. Hepatitis C among predialysis patients: prevalence and characteristic in a large Cohort of patients. *Nephron Clin Pract* 2008;108:c135–c140.
24. Ocak S, Duran N, Kaya N, Emir I. Seroprevalence of hepatitis C in patients with type 2 diabetes mellitus and non-diabetic on hemodialysis. *J Clin Pract* 2006;60:670–4.
25. Soma J, Saito T, Taguma Y et al. High prevalence and adverse effect of hepatitis C virus infection in type? Diabetic-related nephropathy. *J Am Soc Nephrol* 2000;11:690–9.
26. Iwasa Y, Otsubo S, Sugi O et al. Patterns in the prevalence of hepatitis C virus infection at the start of hemodialysis in Japan. *Clin Exp Nephrol* 2008;12:53–7.
27. Bergman S, Accortt N, Tumer A, Glaze J. Hepatitis C infection is acquired pre-ESRD. *Am J Kidney Dis* 2005;45:684–9.
28. Fissell RB, Bergg-Gresham JL, Woods JD et al. Patterns of hepatitis C prevalence and seroconversion on hemodialysis units from three continents: the DOPPS. *Kidney Int* 2004;65: 2335–42.
29. Izopet J, Sanders-Sauno K, Kamar N et al. Incidence of HCV infection in French hemodialysis units: a prospective study. *J Med Virol* 2005;77:70–6.
30. Sypsa V, Psichogiou M, Katsoulidou A et al. Incidence and patterns of hepatitis C virus seroconversion in a cohort of hemodialysis patients. *Am J Kidney Dis* 2005;45:334–46.
31. Hoofnagle JH. Course and outcome of hepatitis C. *Hepatology* 2002;36:S21–S29.
32. Kumagai J, Komiya Y, Tanaka J et al. Hepatitis C virus infection in 2744 hemodialysis patients followed regularly at nine centers in Hiroshima during November 1999 through February 2003. *J Med Virol* 2005;76:498–502.
33. Fabrizi F, Lungi G, Guarnori I et al. Incidence of seroconversion for hepatitis C virus in chronic haemodialysis patients: a prospective study. *Nephrol Dial Transplant* 1994;9:1611–5.
34. KDIGO. KDIGO Clinical practice guidelines for the prevention, diagnosis, evaluation and treatment of hepatitis C in chronic kidney disease. *Kidney Int* 2008;73(Suppl 109):S10–S19.
35. Hanuka N, Sikuler D, Tovbin D et al. Hepatitis C virus infection in renal failure patients in the absence of anti-hepatitis C virus antibodies. *J Viral Hepat* 2002;9:141–5.
36. Takeuchi T, Katsume A, Tanaka T et al. Real-time detection system for quantification of hepatitis C virus genome. *Gastroenterology* 1999;116:636–42.

37. Chevaliedz S, Pawlotsky JM. Hepatitis C virus serologic and virologic tests and clinical diagnosis of HCV-related liver disease. *Int J Med Sci* 2006;3:35–40.
38. Courouce AM, LeMarrec N, Bouchardeau F et al. Efficacy of HCV core antigen detection during the preseroconversion period. *Transfusion* 2000;40:1193–220.
39. Bouzgarrou N, Fodha I, Orthman SB et al. Evaluation of a total core antigen assay for the diagnosis of hepatitis C virus infection in hemodialysis patients. *J Med Virol* 2005;77:502–8.

MANAGEMENT OF HEPATITIS C IN DIALYSIS PATIENTS (METHODS, FREQUENCY OF BLOOD TESTS AND IMAGING STUDIES)

[Statements]

1 Similar to patients with normal renal function, liver biopsy is the most reliable method to evaluate the liver disease of HCV-infected dialysis patients. It is mostly recommended, when transplantation is considered. (Evidence level: Low, Recommendation level: Weak)
2 The prognosis is significantly worse in HCV-infected dialysis patients than in uninfected dialysis patients. (Evidence level: High, Recommendation level: None)
3 It is recommended to periodically follow-up HCV-infected dialysis patients to screen for liver cirrhosis and early detection of hepatocellular carcinoma. (Evidence level: High, Recommendation level: Strong)
4 Iron has hepatocyte toxicity, and excessive hepatic iron deposition is an exacerbating factor of chronic hepatitis C and promotes hepatocarcinogenesis. In consideration of these facts, it is desirable to avoid iron overload in HCV-infected dialysis patients. (Evidence level: Low, Recommendation level: Weak)

[Comments]

1. Evaluation of the liver disease in HCV-infected dialysis patients

Similar to HCV-infected patients with normal renal function, liver biopsy is the most reliable method to evaluate the liver disease in HCV-infected dialysis patients. It is mostly recommended when kidney transplantation is considered. (Evidence level: Low, Recommendation level: Weak)

In dialysis patients, the aminotransferase levels are often low even when they are infected with HCV, and liver biopsy is the most reliable method to evaluate the liver disease of HCV-infected dialysis patients as well as HCV-infected patients with normal renal function.

Concerning histological changes of the liver, there have been many reports that inflammation and fibrosis are observed less frequently in HCV-infected dialysis patients than in HCV-infected patients with normal renal function (1–5). Cotler et al. (3) showed that HCV-infected dialysis patients had less inflammatory activity and a lower proportion of bridging fibrosis or cirrhosis than in hepatitis C patients with normal renal function. In addition, as a histological finding by liver biopsy, Shiavon et al. (4) and Hu et al. (6) reported that HCV-infected dialysis patients showed stage III and IV severe fibrosis significantly less frequently than those with normal renal function. Also, Sterling et al. (7) noted that the severity of liver fibrosis and liver cirrhosis was similar to that in hepatitis C patients with normal renal function showing a normal ALT level but was milder than in those showing a high ALT level. There is also a report that the progression rate of liver fibrosis corrected for the infected period was relatively slow (8). However, de Paula Farah et al. (9) have reported that histological findings of both fibrosis and inflammation are comparable between HCV-infected dialysis patients and HCV-infected patients with normal renal function.

On histological examination of the liver in HCV-infected dialysis patients before kidney transplantation, severe liver fibrosis or cirrhosis was noted in 5.5–32%, and liver cirrhosis was noted in 0–24% (2,3,5–8,10,11). The survival rate of dialysis patients with biopsy-proven cirrhosis during 10 years after transplantation was low at 26%, indicating that liver cirrhosis is an independent risk factor of poor prognosis, and liver cirrhosis is a contraindication for kidney transplantation (12). It has also been clarified that the prevalence of liver disorders after transplantation increases markedly (five times) if there is HCV infection before transplantation (13), and that the progression of hepatic lesions is faster in HCV-infected kidney transplantation patients than in HCV-infected patients with normal kidney function (14). Since the results of blood tests are not correlated with these histological changes of the liver, it is necessary to evaluate histological changes by liver biopsy before kidney transplantation (5,7,10,11,15,16).

In dialysis patients, it has been reported that percutaneous liver biopsy can be performed safely (17), but it generally increases the risk of hemorrhage. Transjugular liver biopsy is safer but is not performed widely.

2. Prognosis of HCV-infected patients

The prognosis is significantly worse in HCV-infected dialysis patients than in uninfected dialysis patients. (Evidence level: High, Recommendation level: None)

In 90% or more of dialysis patients, HCV infection leads to chronic hepatitis (18). The effects of HCV infection on the prognosis of dialysis patients have become an important issue due to the increase in patients with longer dialysis duration.

Many studies have indicated that the prognosis of HCV-infected dialysis patients is significantly worse than that of uninfected dialysis patients (19–25). According to meta-analysis by Fabrizi et al. (26), adjusted relative risk of all-cause mortality in HCV-infected dialysis patients was 1.34 on the basis of seven clinical studies involving 11 589 patients. Causes of death related to liver diseases such as hepatocellular carcinoma and liver cirrhosis were 5.89 times more frequent in the former group.

The incidence of liver cirrhosis in HCV-infected dialysis patients varies among reports from 1.3–12.5% (10,11,16,27). According to the investigation by Akiba et al. (28), the incidence of liver cirrhosis in HCV-antibody-positive dialysis patients was 8.57/1000/year.

There have been a few reports that the prognosis of liver disease is better in HCV-infected dialysis patients than in patients with normal renal function. Okuda et al. (29) reported that none of the 189 patients with HCV-infected dialysis patients showed progression to liver cirrhosis. Also, Ishida et al. (30) showed by a questionnaire survey of 6366 dialysis patients that hepatocellular carcinoma and liver cirrhosis were observed in 1.8% and 8.6%, respectively, which were lower than the percentages in patients with normal renal function. However, reports regarding the progression of liver diseases have been inconsistent, with an 8-year prospective cohort study by Espinosa et al. (31) showing the rapid progression to liver cirrhosis in dialysis patients, being observed after a median of 7 years from the initial elevation in ALT, which is in contrast to the general population.

Generally, the incidence of hepatocellular carcinoma in HCV-infected patients is proportionate to the severity of liver fibrosis, and its incidence in patients with liver cirrhosis showing severest fibrosis is reported to be about 8%/year (32). However, there is no detailed report on the incidence of hepatocellular carcinoma in HCV-infected dialysis patients. Nakayama et al. (20) followed up 276 HCV-antibody-positive dialysis patients over 6 years and reported liver cirrhosis in 30 and hepatocellular carcinoma in eight at the end of the follow-up period. If most hepatocellular carcinomas are assumed to have occurred in liver cirrhosis, the annual rate of progression from liver cirrhosis to hepatocellular carcinoma is considered to be at least 4%. The finding that liver cirrhosis was noted in 30 (13.2%) of the 276 patients suggests that the progression rate to liver cirrhosis is nearly the same as that in non-dialysis patients.

In dialysis patients, the incidence of, and mortality due to, cancers have often been reported to be higher than in the general population. According to a report from Italy, the incidence of hepatocellular carcinoma is 2.41 times higher in dialysis patients than in those with normal renal function (33). According to a study in Okinawa, Japan, the incidence of cancer in dialysis patients was 2.48 times higher in males and 3.99 times higher in females than that in the general population, but the incidence of hepatocellular carcinoma was similar in males and lower in females compared with that in the general population (34). In a prospective study of a cohort of 233 HCV-infected dialysis patients, hepatocellular carcinoma was observed in three patients during 10 years (0.53%/year) (35). According to a questionnaire survey of 67 970 patients, the incidence of hepatocellular carcinoma was reported to be 3.87/1000 HCV-infected dialysis patients/year during a 3-year period (28).

At the end of 1999, the prevalence of liver cirrhosis was 8.25% and 11.84% in HCV-antibody-positive patients and HCV-RNA-positive dialysis patients, respectively, and that of hepatocellular carcinoma was 2.16% and 2.59%, respectively. In those coinfected with HBV and HCV, the prevalences of liver cirrhosis and hepatocellular carcinoma were 12.2% and 2.7%, respectively (36). In patients coinfected with HBV and HCV, liver damage is notable even in those with normal renal function. However, as the same is observed also in HCV-infected dialysis patients (8), particularly close follow-up is needed.

To date, there has been no control study comparing the prognosis between HCV-infected dialysis patients and HCV-infected patients with normal renal function. This comparison may be difficult because of the reduced life expectancy in dialysis patients.

There has been no report on the prognosis-improving effect of therapeutic intervention in HCV-infected dialysis patients.

Reports on the viral load level in dialysis patients have been inconsistent: It has been reported to be low by some (37,38), not to differ by others (2,39), and to be high in still others (6). The HCV RNA levels were reported to decrease in dialysis patients but not to change in the control group during a 3-year follow-up by Furusyo et al. (38) and during a 10-year follow-up by Okuda et al. (29), respectively.

In a comparison concerning comobidities, hypertension, hepatitis B, liver cirrhosis, wasting, anemia, and HIV infection were more prevalent, but coronary artery disease and stroke were less prevalent in 5737 HCV-infected dialysis patients than in 11 228

uninfected dialysis patients matched for the time at which dialysis was initiated. On the other hand, there is also a report that coronary artery disease was more prevalent in HCV-infected dialysis patients (40).

3. Follow-up

It is recommended to periodically follow-up HCV-infected dialysis patients for the diagnosis of liver cirrhosis and early detection of hepatocellular carcinoma. (Evidence level: High, Recommendation level: Strong)

HCV-infected dialysis patients develop liver cirrhosis or hepatocellular carcinoma more frequently than uninfected dialysis patients, and periodic follow-up for the diagnosis of liver cirrhosis and early detection of hepatocellular carcinoma is necessary.

Follow up testing to evaluate the progression of liver disease (liver fibrosis, liver cirrhosis, hepatocellular carcinoma) include blood tests of AST, ALT, γ-GTP, total bilirubin, albumin, platelet count, and AST/platelet ratio and imaging techniques such as abdominal ultrasonography and contrast-enhanced CT.

Since the AST and ALT levels are low in dialysis patients regardless of the presence or absence of liver disease, blood tests of liver fibrosis are necessary as well as those of AST and ALT for the follow-up of dialysis patients. In patients with chronic hepatitis C, in general, the platelet count has been reported to reflect liver fibrosis (41). The platelet count is also useful as a marker of liver fibrosis in dialysis patients (4). In HCV-infected dialysis patients, it has been reported that platelets decrease with time compared with uninfected dialysis patients and that the increases in ALT and decreases in the platelet count are related (42).

Generally, a high AST level as well as a low platelet count is related to liver fibrosis, and the AST (IU/L)/platelet count ($\times 10^4/\mu L$) ratio is useful as a marker of liver fibrosis. This marker is also useful in dialysis patients, indicating no fibrosis when it is less than 0.40 but fibrosis when it is 0.95 or higher (4,7).

In dialysis patients with liver cirrhosis, a high ALT level and low albumin, total cholesterol, and white blood cell count have been reported in addition to a low platelet count (36).

Ultrasonography is also considered useful for the dialysis of liver disorders in dialysis patients, and ultrasound findings are correlated with the hyaluronic acid level and platelet count (35).

The concentrations of α-fetoprotein and PIVKA-II, which are markers of hepatocellular carcinoma, can be interpreted in dialysis patients similar to patients with normal renal function (43,44).

Since some dialysis patients as well as patients with normal renal function are positive for HCV antibody but negative for HCV-RNA, the HCV-RNA test is necessary if HCV antibody is positive.

There is no evidence concerning the frequency of follow-up tests.

In Japan, there was a nationwide survey of the state of execution of tests for viral hepatitis in dialysis patients, particularly those for the detection of hepatocellular carcinoma, in 2009 (45). According to this survey, periodic follow-up using imaging techniques including ultrasonography and CT are performed in patients positive for hepatitis virus at 80% of the facilities, and the frequency of the follow-up was less than once a year in 5.4%, once a year in 56.5%, two times a year in 28.8%, and three or more times a year in 9.3%. Tumor markers were measured periodically at only 48.9% of the facilities, and the establishment of follow-up plans and systems according to the guidelines is anticipated.

The KDIGO guidelines recommend that follow up testing for HCV-related comobidities (such as liver cirrhosis and hepatocellular carcinoma) should be performed every 6 months in patients with liver cirrhosis and every year in those without liver cirrhosis (46).

However, the working group proposes the more close follow-up plan for the detection of hepatocellular carcinoma on the basis of the follow-up plan for patients with chronic hepatitis C recommended by the Japan Society of Hepatology (47).

Patients with chronic hepatitis, patients with a platelet count of $10^5/\mu L$ or higher
Tests: AFP, PIVKA-II, abdominal ultrasonography (about once every 6 months-1 year)
Liver cirrhosis patients, patients with a platelet count of less than $10^5/\mu L$
Tests: AFP, PIVKA-II, abdominal US (about once every 3 months), contrast-enhanced CT (about once every 6 months)

If contrast-enhanced CT cannot be performed, or if the diagnosis is difficult, MRI using EOB containing a small amount of gadolinium, which, in principle, should be substituted for another test in dialysis patients, should be considered.

A test of the AFP-L3 fraction must be considered when the AFP level is high.

4. Administration of iron preparations

Iron has hepatocyte toxicity, and excessive hepatic iron deposition is an exacerbating factor of chronic hepatitis C and promotes hepatocarcinogenesis. In consideration of these facts, it is desirable to avoid

iron overload in HCV-infected dialysis patients. (Evidence level: Low, Recommendation level: Weak)

Iron is a trace element indispensable for hemoglobin synthesis. Iron stored in the liver is released into blood when necessary. It has been shown that iron has hepatocyte toxicity and that excessive hepatic iron deposition is an exacerbating factor of chronic hepatitis C and promotes hepatocarcinogenesis. Patients with chronic hepatitis C show excessive iron deposition in liver tissue, and iron-dependent oxidative stress has been suggested to be involved in various stages including hepatocyte damage, fatty degeneration, fibrosis, and carcinogenesis. Iron deposition in the liver has also been reported to be related to hyporesponsiveness to interferon therapy in patients with normal renal function (48). Moreover, iron depletion therapy has been reported to significantly lower the risk of hepatocellular carcinoma in hepatitis C patients (49).

In hemodialysis patients, also, the serum ferritin level shows significant positive correlations with the AST and ALT levels in those positive for HCV antibody (50). There has been no large-scale clinical study evaluating the effects of iron administration on the liver in HCV-infected dialysis patients. Kurihara et al. (51) administered an intravenous iron preparation to HCV-antibody-positive dialysis patients for one year with a target serum ferritin level of 200–300 ng/mL, though the number of patients was small, observed changes in the liver function, and compared them with those in HCV-antibody-negative dialysis patients. According to this study, the AST and ALT levels increased in two of the seven HCV-antibody-positive patients but could be controlled by the administration of stronger neo-minophagen C, no change was observed in other markers such as the viral level, cholinesterase level, and platelet count, and the administration of an iron preparation to HCV-antibody-positive patients was safe. In their study, however, no histological evaluation was made, and long-term consequences are unknown. Kato et al. (52) showed that the oxidative stress marker levels were high in HCV-infected dialysis patients and were increased further by the administration of an iron preparation.

On the other hand, HCV-infected dialysis patients have been shown to have a high endogenous erythropoietin concentration and need a lower dose of erythropoietin (53). This is considered to be due to an increase in the erythropoietin production by hepatocytes in the process of hepatocyte regeneration. The same report showed that they also require a lower dose of iron. This is considered to be due to the release of iron stored in hepatocytes induced by inflammation, causing an increase in ferritin.

From these observations, caution to avoid iron overload is necessary in administering iron preparations to HCV-infected dialysis patients. Therefore, in HCV-infected dialysis patients, iron supplementations should be restricted to anemia not responding even to the maximum dose of an ESA preparation (54).

Package inserts mention severe liver disorder as a contraindication of intravenous iron preparations.

REFERENCES

1. Espinosa M, Martin-Malo A, Alvarez de Lara MA, Soriano S, Aljama P. High ALT levels predict viremia in anti-HCV-positive HD patients if a modified normal range of ALT is applied. *Clin Nephrol* 2000;54:151–6.
2. Alric L, Di-Martino V, Selves J et al. Long-term impact of renal transplantation on liver fibrosis during hepatitis C virus infection. *Gastroenterology* 2002;123:1494–9.
3. Cotler SJ, Diaz G, Gundlapalli S et al. Characteristics of hepatitis C in renal transplant candidates. *J Clin Gastroenterol* 2002;35:191–5.
4. Schiavon LL, Schiavon JL, Filho RJ et al. Simple blood tests as noninvasive markers of liver fibrosis in hemodialysis patients with chronic hepatitis C virus infection. *Hepatology* 2007;46:307–14.
5. Trevizoli JE, de Paula Menezes R, Ribeiro Velasco LF et al. Hepatitis C is less aggressive in hemodialysis patients than in nonuremic patients. *Clin J Am Soc Nephrol* 2008;3:1385–90.
6. Hu KQ, Lee SM, Hu SX, Xia VW, Hillebrand DJ, Kyulo NL. Clinical presentation of chronic hepatitis C in patients with end-stage renal disease and on hemodialysis versus those with normal renal function. *Am J Gastroenterol* 2005;100:2010–8.
7. Sterling RK, Sanyal AJ, Luketic VA et al. Chronic hepatitis C infection in patients with end stage renal disease: characterization of liver histology and viral load in patients awaiting renal transplantation. *Am J Gastroenterol* 1999;94:3576–82.
8. Becker VR, Badiani RG, Lemos LB et al. Factors associated with the progression of hepatic fibrosis in end-stage kidney disease patients with hepatitis C virus infection. *Eur J Gastroenterol Hepatol* 2009;21:1395–9.
9. de Paula Farah K, Carmo RA, de Figueiredo Antunes CM et al. Hepatitis C, HCV genotypes and hepatic siderosis in patients with chronic renal failure on haemodialysis in Brazil. *Nephrol Dial Transplant* 2007;22:2027–31.
10. Martin P, Carter D, Fabrizi F et al. Histopathological features of hepatitis C in renal transplant candidates. *Transplantation* 2000;69:1479–84.
11. Pol S, Romeo R, Zins B et al. Hepatitis C virus RNA in anti-HCV positive hemodialyzed patients: significance and therapeutic implications. *Kidney Int* 1993;44:1097–100.
12. Mathurin P, Mouquet C, Poynard T et al. Impact of hepatitis B and C virus on kidney transplantation outcome. *Hepatology* 1999;29:257–63.
13. Gentil MA, Rocha JL, Rodríguez-Algarra G et al. Impaired kidney transplant survival in patients with antibodies to hepatitis C virus. *Nephrol Dial Transplant* 1999;14:2455–60.
14. Zylberberg H, Nalpas B, Carnot F et al. Severe evolution of chronic hepatitis C in renal transplantation: a case control study. *Nephrol Dial Transplant* 2002;17:129–33.
15. Caramelo C, Ortiz A, Aguilera B et al. Liver disease patterns in hemodialysis patients with antibodies to hepatitis C virus. *Am J Kidney Dis* 1993;22:822–8.