Baseline characteristics of the patients

The baseline characteristics of the patients at the commencement of ADV therapy were as follows. They were 59 males and 16 females, with a median age of 54 (range 27–79) years. Forty-one (55%) tested positive for HBeAg, and anti-HBe developed in 34 patients. The virus was genotyped for 13 patients, all of whom were infected with HBV of genotype C. The HBV DNA ranged from 3.1 to >7.6 (median 7.1) logcopies/ml, and the median ALT level ranged from 15 to 500 (median 105) IU/L. The median levels of total bilirubin and albumin were 0.8 (range 0.4–3.9) mg/dl and 3.9 (range 2.1–4.8) g/dl, respectively. The median platelet counts were 11.7 (range 3.5–25.5) $\times 10^4/mm^3$. Of the 75 patients, 27 (36%) showed features of cirrhosis by liver biopsy and/or imaging procedures. Five patients (7%) developed HCC as detected by imaging modalities.

HBV testings

HBsAg, HBeAg, and anti-HBe were examined by chemiluminescent immunoassay. HBV DNA was measured by the PCR-based method (Amplicor HBV monitor, Roche Diagnostics, Tokyo, Japan) [13], with a lower detection limit of 2.6 logcopies/ml. The LAM-resistant rtM204V/I mutation was examined by PCR-enzyme-linked minisequence assay [14]. HBV genotype was determined based on PCR-direct sequencing of portions of core and polymerase genes. The primers used for this study were BF1s (5′-TTT TTC ACC TCT GCC TAA TCA-3′, nt 1821–1841), BR3 (5′-TTC CCG AGA TTG AGA TCT TC-3′, nt 2440–2421), BF6 (5′-CCT CCA ATT TGT CCT GGC TA-3′, nt 350–369), and BR8 (5′-TTG CGT CAG CAA ACA CTT GG-3′, nt 1195–1176) [15, 16].

Statistical analysis

Group comparisons were carried out by the chi-square test, Student's *t* test and Mann–Whitney's *U* test. Independent factors contributing to VR during ADV therapy added to ongoing LAM treatment were estimated using multivariate multiple logistic regression analysis in combination with stepwise regression analysis. A *P*-value of less than 0.05 (two-tailed) was considered to indicate a significant difference. All statistical analyses were performed using the SPSS version 15.0J software (SPSS, Chicago, IL).

Results

Virological and biochemical response to ADV therapy added to ongoing LAM in CHB patients showing LAM resistance

Of the 75 CHB patients showing LAM resistance who underwent ADV therapy added to ongoing LAM treatment, HBV DNA clearance was achieved in 29 (39%) of 75 at 6 months, 35 (47%) of 75 at 12 months, and 34 (72%) of 47 at 24 months. Among the HBeAg-positive patients, HBeAg loss was observed in 8 (20%) of 41 at 6 months, 7 (18%) of 39 at 12 months, and 6 (22%) of 27 at 24 months. As for the biochemical response, ALT normalization (≤40 IU/l) was seen in 57 (76%) of 75 at 6 months, 56 (75%) of 75 at 12 months, and 40 (85%) of 47 at 24 months of treatment.

Pretreatment clinical factors associated with therapeutic response to ADV in addition to LAM treatment

We first investigated pretreatment clinical factors associated with the therapeutic efficacy of ADV added to ongoing LAM treatment by univariate analysis. The baseline characteristics of patients at the beginning of ADV therapy in addition to LAM in the presence or absence of VR are shown in Table 1. Patients showing VR had significantly lower HBV DNA at baseline than patients who did not achieve VR [median 6.3 (range 3.1 to >7.6) vs. 7.3

Table 1 Patient clinical characteristics at the beginning of ADV therapy in addition to LAM in LAM-resistant CHB patients in the presence or absence of virological response (VR)

Clinical characteristics	VR ($n = 35$)	Non-VR ($n = 40$)	*P* value
Gender (male/female)	26/9	33/7	0.386
Age (years)	52 (28–67)	55 (27–79)	0.896
Duration of prior LAM therapy (months)	38 (12–83)	37 (13–64)	0.856
Positive HBeAg	12 (34%)	29 (73%)	0.001
HBV DNA (logcopies/ml)	6.3 (3.1 to >7.6)	7.3 (3.9 to >7.6)	0.002
ALT (IU/l)	106 (16–500)	75 (15–455)	0.136
Total bilirubin (mg/dl)	0.9 (0.4–3.9)	0.7 (0.4–3.9)	0.664
Albumin (g/dl)	4.0 (2.4–4.8)	3.8 (2.1–4.6)	0.351
Platelet count ($\times 10^4/mm^3$)	12.2 (4.8–24.1)	11.5 (3.5–25.5)	0.854
Liver disease (chronic hepatitis/cirrhosis)	20/15	28/12	0.247
Presence of HCC (%)	2 (6%)	3 (8%)	0.757

Continuous variables are expressed as median (range)

Table 2 Baseline factors affecting virological response (logistic regression analysis, stepwise method)

Factors	Category	Odds ratio	95% CI	*P*
Gender	Male/female			NS
Age (years)	By 1 year			NS
Duration of prior LAM therapy (months)	By 1 month			NS
HBeAg	Negative/positive	5.766	1.855–36.62	0.009
HBV DNA (logcopies/ml)	By 1 logcopy/ml	2.362	1.335–5.178	0.005
ALT (IU/l)	By 1 IU/l	1.006	1.000–1.011	0.036
Total bilirubin (mg/dl)	By 1 mg/dl			NS
Albumin (g/dl)	By 1 g/dl			NS
Platelet count ($\times 10^4/mm^3$)	By 1 $\times 10^4/mm^3$			NS
Liver disease	Chronic hepatitis/cirrhosis			NS
Presense of HCC (%)	No/yes			NS

CI Confidence interval, *NS* not significant

(range 3.9 to >7.6), $P = 0.002$]. HBeAg was detected in only 12 (34%) of 35 patients with VR, compared with 29 (73%) of 40 patients without VR ($P = 0.001$). Gender ratio, age, duration of preceding LAM therapy, ALT, total bilirubin, albumin, platelet counts, disease severity, and presence of HCC did not differ between VR and non-VR patients.

Factors affecting the therapeutic response to ADV therapy in addition to ongoing LAM were also evaluated by multivariate analysis (Table 2). Eleven pretreatment clinical factors were applied to the analysis as variables. Two factors, lower baseline HBV DNA ($P = 0.005$, odds ratio: 2.362, 95% confidence interval: 1.335–5.178) and negative HBeAg ($P = 0.009$, odds ratio: 5.766, 95% confidence interval: 1.855–36.62), were selected as significant independent factors affecting VR, as was the case for univariate analysis. In addition, higher baseline ALT was also chosen as a significant independent factor ($P = 0.036$, odds ratio 1.006, 95% confidence interval: 1.000–1.011). As for the biochemical response to ADV therapy added to LAM, no pretreatment clinical factors showed a significant relationship with the occurrence of ALT normalization in our 75 LAM-resistant CHB patients.

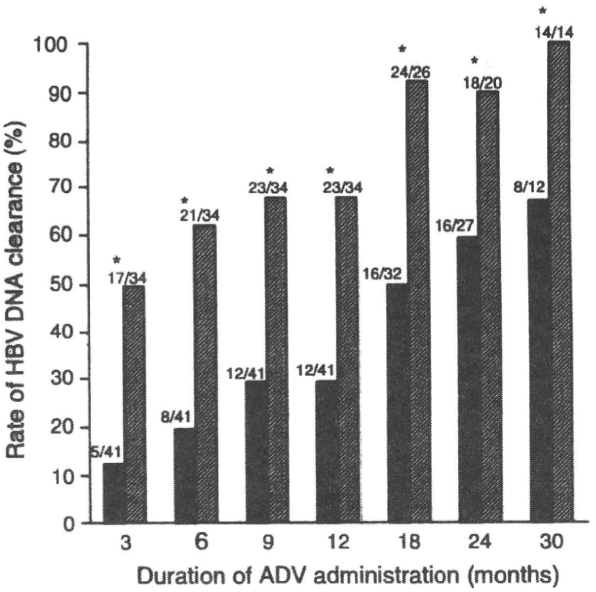

Fig. 1 Rates of HBV DNA clearance in CHB patients positive or negative for HBeAg during ADV therapy in addition to LAM. $*P < 0.05$ between HBeAg-positive and HBeAg-negative patients. *Solid bars* HBeAg-positive patients, *hatched bars* HBeAg-negative patients

HBV DNA clearance during ADV therapy in addition to ongoing LAM treatment according to HBeAg status

Next, we investigated HBV DNA clearance during ADV therapy added to ongoing LAM treatment in LAM-resistant CHB patients positive or negative for HBeAg (Fig. 1). In HBeAg-positive patients, HBV DNA was cleared in 8 (20%) of 41 at 6 months, 12 (29%) of 41 at 12 months, and 16 (59%) of 27 at 24 months. On the other hand, HBV DNA clearance was seen in 21 (62%) of 34 at 6 months, 23 (68%) of 34 at 12 months, and 18 (90%) of 20 at 24 months in HBeAg-negative patients. A significant difference ($P < 0.05$) in the frequency of HBV DNA clearance was observed between HBeAg-positive and HBeAg-negative patients at 3, 6, 9, 12, 18, 24, and 30 months of treatment. Thus, patients negative for HBeAg tended to respond to ADV therapy added to ongoing LAM treatment better than those positive for it in LAM-resistant CHB.

HBV DNA clearance during ADV therapy in addition to ongoing LAM treatment in relation to HBeAg status and baseline HBV DNA

We examined HBV DNA clearance during ADV therapy in addition to ongoing LAM treatment in HBeAg-positive and

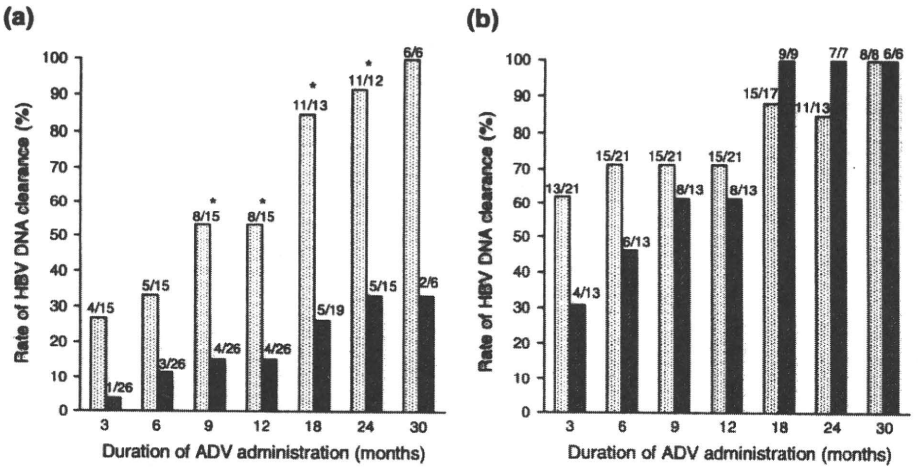

Fig. 2 Rates of HBV DNA clearance during ADV therapy in addition to LAM according to HBV DNA at baseline in **a** HBeAg-positive CHB patients and **b** HBeAg-negative CHB patients. *$P < 0.05$ between patients with low (≤7.0 logcopies/ml) and high (>7.0 logcopies/ml) HBV DNA. *Dotted bars* Patients with HBV DNA ≤7.0 logcopies/ml at baseline, *hatched bars* patients with HBV DNA >7.0 logcopies/ml at baseline

HBeAg-negative CHB patients in relation to baseline HBV DNA. In the case of HBeAg-positive CHB patients (Fig. 2a), the rates of HBV DNA clearance were 33% (5/15) at 6 months, 53% (8/15) at 12 months, and 92% (11/12) at 24 months in patients with low viremia (baseline HBV DNA ≤7.0 logcopies/ml). By contrast, the frequencies of HBV DNA clearance were only in 12% (3/26) at 6 months, 15% (4/26) at 12 months, and 33% (5/15) at 24 months in patients with high viremia (baseline HBV DNA >7.0 logcopies/ml). A significant difference ($P < 0.05$) in the frequency of HBV DNA clearance was observed between patients with low and high viremia at 9, 12, 18, and 24 months of treatment. In the case of HBeAg-negative patients (Fig. 2b), the rates of HBV DNA clearance were 71% (15/21) at 6 months, 71% (15/21) at 12 months, and 85% (11/13) at 24 months in patients with low viremia (baseline HBV DNA ≤7.0 logcopies/ml). The frequencies of HBV DNA clearance were 46% (6/13) at 6 months, 62% (8/13) at 12 months, and 100% (7/7) at 24 months in patients with high viremia (baseline HBV DNA >7.0 logcopies/ml). No significant differences were observed in the frequency of HBV DNA clearance between patients with low and high viremia. According to these findings, the relevance of lower baseline HBV DNA for achieving a better antiviral effect was evident only in HBeAg-positive patients, but not in HBeAg-negative ones in ADV therapy added to LAM treatment for LAM-resistant CHB.

Discussion

This study investigated factors affecting the antiviral efficacy of ADV therapy added to ongoing LAM treatment in LAM-resistant CHB patients. Therapeutic efficacy was assessed as the presence or absence of VR. Both univariate and multivariate analyses revealed that lower baseline HBV DNA and negative HBeAg were strong factors associated with a better therapeutic response. Another significant factor revealed by multivariate analysis was high ALT, although it was weaker than the other two factors. In previous investigations, female gender, lower baseline HBV DNA, negative HBeAg, higher ALT, and genotype D rather than A have been reported to contribute to better VRs to ADV therapy in nucleos(t)ide-naïve and LAM-resistant CHB patients [17–21]. Our results agreed partially with them. The present study, as well as previous studies [18, 19], also revealed that a high baseline ALT may be a determining factor for a better response to ADV therapy in addition to LAM treatment in LAM-resistant CHB. This may be because the host immune response against viral antigens induced by active breakthrough hepatitis has a favorable antiviral effect during ADV therapy. In this study, however, a low baseline viremic level was shown to be a stronger factor than high baseline ALT. The baseline ALT level was the third factor contributing to VR. Therefore, in LAM-resistant CHB, ADV administration should be started before the flare-up of ALT elevation, especially in patients with severe liver disease such as cirrhosis.

In LAM-resistant patients, the HBV DNA level is low during the initial phase, but increases with time, leading to the onset of breakthrough hepatitis. Thus, in ADV therapy added to LAM treatment for LAM-resistant-CHB, the baseline HBV DNA level varies with the observation period after the emergence of LAM resistance. A previous report on Italian HBeAg-negative CHB patients showing LAM resistance revealed that patients with low viremia and normal ALT tended to respond to ADV therapy in addition to LAM treatment better than those with high viremia and abnormal ALT [17]. In the present study conducted in Japan, a genotype C-endemic area, such a close relationship between lower baseline HBV DNA and better therapeutic response was remarkable in

HBeAg-positive patients but not in HBeAg-negative ones. Our finding suggests that, in LAM-resistant CHB, ADV should be added before the HBV DNA begins to increase markedly, especially in HBeAg-positive patients.

In this study, none of the 75 patients showed virological breakthrough after the beginning of ADV administration. All displayed more than 1 log reduction of HBV DNA at 12 months of ADV treatment. This indicates that our patients may not have produced viruses resistant to both LAM and ADV. The emergence of resistant viruses has been reported to be rare in combination therapy using LAM and ADV for LAM-resistant CHB patients, although recent studies have found the existence of a virus resistant to both drugs [22, 23]. The rtA181V/T/S mutation has been reported to confer cross resistance to LAM and ADV [22, 23]. In ADV monotherapy for nucleos(t)ide analog-naïve CHB patients, the absence of HBV DNA reduction to <4 logcopies/ml at 24 weeks of treatment has been reported to be related to the higher emergence of a ADV-resistant virus [24], as is the case in LAM monotherapy [25]. In ADV therapy added to LAM treatment in LAM-resistant CHB patients, the poor response during the initial phase may lead to the development of virus resistance to LAM and ADV as well. From this point of view, the addition of ADV to ongoing LAM treatment before the elevation of HBV DNA may be beneficial in LAM-resistant CHB patients to avoid the development of a multi-drug-resistant virus. Recently, some investigators have reported that tenofovir disoproxil fumarate is effective against a virus resistant to both LAM and ADV [22, 23], but it has not yet been approved for clinical use.

Our results conclusively showed that, with ADV therapy added to LAM treatment for LAM-resistant CHB patients, lower baseline HBV DNA and negative HBeAg contributed to a better antiviral effect. After the emergence of LAM resistance, ADV should be added before the marked elevation of HBV DNA in order to attain better antiviral efficacy, especially in HBeAg-positive patients.

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Original Article

Effect of interferon α-2b plus ribavirin therapy on incidence of hepatocellular carcinoma in patients with chronic hepatitis

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Aim: The objective of this study was to elucidate the long-term effects of interferon (IFN)α-2b plus ribavirin combination therapy and to clarify whether this therapy can reduce the incidence of hepatocellular carcinoma (HCC) in patients with chronic hepatitis C.

Methods: A total of 403 patients infected with hepatitis C virus (HCV) were enrolled in a multicenter trial. All patients were treated with a combination of IFN-α-2b plus ribavirin therapy. We examined the incidence of HCC after combination therapy and analyzed the risk factors for liver carcinogenesis.

Results: A sustained virological response (SVR) was achieved by 139 (34%) of the patients. The cumulative rate of incidence of HCC was significantly lower in SVR patients than in non-SVR patients ($P = 0.03$), while there was no difference in the cumulative incidence of HCC between the transient response (TR) group and the no response (NR) group. Cox's regression analysis indicated the following risk factors as independently significant in relation to the development of HCC: age being > 60 years ($P = 0.006$), advanced histological staging ($P = 0.033$), non-SVR to IFN therapy ($P = 0.044$). The cumulative incidence rate of HCC was significantly lower in patients who had average serum alanine aminotransferase (ALT) levels of < 40 IU/L than in those who showed average serum ALT levels of ≧ 40 IU/L after the combination therapy ($P = 0.021$).

Conclusions: These results suggest that the attainment of SVR or continuous normalization of ALT levels after IFN therapy can affect patients apart from HCC development.

Key words: chronic hepatitis C, continuous normalization of ALT, hepatocellular carcinoma, interferon plus ribavirin combination therapy, sustained virological response

INTRODUCTION

HEPATOCELLULAR CARCINOMA (HCC) is one of the most common malignancies in Japan and its incidence has been increasing over the last 30 years. Recently, various treatments such as transcatheter arterial embolization/chemoembolization, radio frequency ablation and hepatic resection have been reported to yield significant improvements in overall patient survival,[1–3] but HCC relapse has thus far been observed in a majority of treated patients due to the highly malignant potential of the liver. In general, approximately 70–80% of Japanese HCC patients are also diagnosed with type C chronic hepatitis or cirrhosis.[4] It has also been shown that the chronic hepatitis C (CHC) liver slowly but steadily progresses to cirrhosis[5,6] and the risk of HCC increases according to the degree of liver fibrosis.[7,8] In this regard, the success of treatment

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for chronic hepatitis C virus (HCV) infection is expected to prevent the patient's liver from progressing to cirrhosis and to reduce the risk of development of HCC. Interferon (IFN) has been proven to be effective in reducing and in eliminating HCV from the circulation; in decreasing serum alanine aminotransferase (ALT) levels; and in improving the histological appearance of the liver in patients with CHC.[9–11] Moreover, it has been demonstrated that IFN monotherapy in CHC patients is associated with reducing the incidence of HCC, especially in those patients who achieved a sustained virological response (SVR).[12–14] Recently, many investigators have reported that combination therapy using IFN-α-2b or pegylated IFN (Peg-IFN) N plus ribavirin is more effective for eradicating HCV than IFN monotherapy.[15–17] However, it has not been accurately evaluated whether or not the combination therapy using Peg-IFN plus ribavirin could reduce HCC development in patients infected with HCV.

In this study, we evaluated the long-term effect of IFN-α-2b plus ribavirin therapy on the incidence of HCC in HCV-infected patients treated with the combination therapy by retrospective examination of the clinical outcomes.

METHODS

Patients

THIS STUDY WAS a multicenter trial conducted by Osaka University Hospital and other institutions participating in the Osaka Liver Forum in Japan. A total of 459 patients with HCV infection were treated with a combination of IFN-α-2b (Intron; Schering-Plough Corporation, Kenilworth, NJ, USA) plus ribavirin (Rebetol; Schering-Plough, Auxerre, France) between June 2002 and March 2005. All patients were treated with 6 MU of IFN-α-2b subcutaneously thrice a week and with oral ribavirin daily. Ribavirin was given at a total daily dose of 600 mg for patients who weighed < 60 kg and 800 mg for patients who weighed ≧ 60 kg. Patients who were positive for hepatitis B surface antigen, anti-human immunodeficiency virus antibody or those with other liver diseases (alcoholic liver disease, autoimmune liver disease, etc) were excluded from this study. Also excluded were patients with a history of HCC and those who developed HCC within the first 6 months of the follow-up period after the end of IFN therapy, because of the possibility that microscopic HCC had been present before initiation of the treatment. The remaining 403 patients infected with HCV were enrolled and followed in this study. The observation term was terminated upon the start of the next IFN therapy, such as Peg-IFN plus ribavirin after a combination of IFN-α-2b plus ribavirin therapy. Responses to IFN therapy were divided into the following three groups based on the viral load: sustained virological response (SVR) was defined as the absence of detectable serum HCV-RNA at 24 weeks after completion of IFN therapy. Transient response (TR) was defined as the absence of HCV-RNA from the serum at the end of treatment but detectable at 24 weeks after completion of therapy. Those categorized as having no response (NR) did not meet these criteria.

This study protocol followed the ethical guidelines of the 1975 Declaration of Helsinki, and informed consent was obtained from each patient.

Blood tests

Serum samples were stored frozen at −80°C. HCV-RNA levels were analyzed by quantitative reverse transcription (RT)–PCR assay (Amplicor-HCV version 2.0; Roche Diagnostic Systems, Tokyo, Japan). The lowest detection limit of this assay was 50 IU/mL. All patients were examined for serum HCV-RNA level and underwent hematological and biochemical tests just before therapy, every 4 weeks during treatment and every 12 weeks thereafter until the end of treatment.

Normal serum ALT is defined as < 40 IU/L. In addition, the biological response to IFN therapy was defined based on "the average serum ALT level", which was calculated from all data of ALT levels after completion of IFN therapy.

Histological evaluation

The patients underwent liver biopsies within 6 months before the start of therapy. Histopathological interpretation of specimens was done by experienced liver pathologists who had no clinical information. The histological appearance of the liver sample sections was evaluated according to METAVIR's histological score.[18] Fibrosis stage was evaluated on a scale from 0 to 4.

Diagnosis and follow up of HCC

Ultrasonography was carried out before IFN therapy and every 3 to 6 months during the follow-up period. New space-occupying lesions detected or suspected at the time of ultrasonography were further examined by computed tomography (CT) or hepatic angiography. HCC was diagnosed by the presence of typical hypervascular characteristics on angiography, in addition to the findings from CT. If no typical image of HCC was observed, fine-needle aspiration biopsy was carried out with the

patient's consent, or the patient was carefully followed until a diagnosis was possible with a definite observation by CT or angiography.

Statistical analysis

Quantitative variables were expressed as mean ± SD. The Kaplan–Meier method was used to calculate the cumulative incidence of HCC. The prognostic relevance of clinical variables and HCC incidence was evaluated by univariate analysis with log-rank test and by multivariate Cox's regression analysis. A value of $P < 0.05$ (two-tailed) was considered to indicate significance. All calculations were performed with SPSS version 15.0J (SPSS, Chicago, IL, USA).

RESULTS

Baseline characteristics in patients treated with interferon therapy

THE BASELINE CLINICAL features of the enrolled patients are shown in Table 1. The mean age of the patients was 55.8 ± 10.9 years, and 64% of the total cases were male. Two hundred and sixty-one patients (73%) were infected with HCV genotype 1 and had a viral load of more than 10^5 IU/ml. Liver biopsy was done for 320 cases and the ratio of patients with severe fibrosis (F3–4) diagnosed by the HAI score was more than 31%. The mean platelet count was 14.8 ± 5.1 × 10^4/μl, and the ALT level was 96.0 ± 62.6 IU/L. A sustained virological response (SVR) was achieved by 139 patients (34%) by combination therapy of IFN-α-2b plus ribavirin. According to an intent-to-treat analysis, 20% (51/261) of patients with HCV genotype 1 and a high viral load (≧ 100KIU/mL) achieved SVR by the combination therapy, whereas 75% (73/97) of the patients with HCV genotype 2 or a low load showed SVR. The median observation period for all patients was 36.5 ± 14.8 months with a range of 6 to 62 months from the end-point of IFN treatment.

Table 1 Baseline characteristics in patients treated with interferon therapy

	All cases
Number of patients	403
Age	55.8 ± 10.9
Gender (male/female)	257/145
Genotype and viral load (1H/non-1H)	261/97
Fibrosis (F0/1/2/3/4)	15/149/56/92/8
WBC (/μl)	5113 ± 1487
Platelet (× 10^4/μl)	14.8 ± 5.1
ALT (IU/l)	96.0 ± 62.6
IFN effect (SVR/TR/NR/cessation)	139/109/110/45

Data are number of patients, mean ± standard deviation. Fibrosis stage is evaluated on a scale from 0 to 4 according to METAVIR's histological score. 1H, Genotype 1 and high viral load; non-1H, all except for 1H; ALT, alanine aminotransferase; IFN, interferon; NR, no response; SVR, sustained virological response; TR, transient response; WBC, white blood cells.

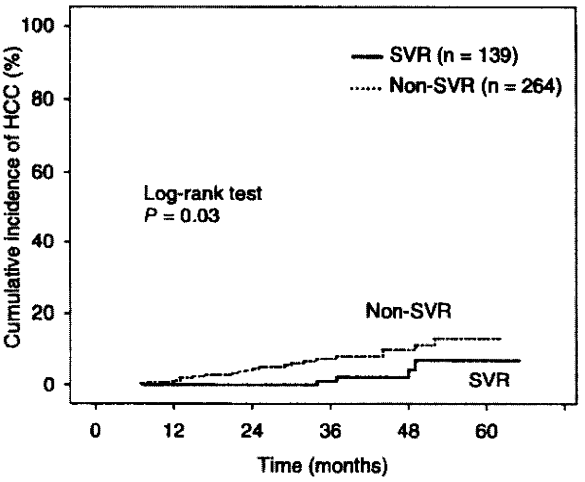

Figure 1 Cumulative incidence of development of hepatocellular carcinoma (HCC) according to treatment effect: (—) sustained virological response; (.....) non-sustained virological response.

Cumulative incidence of development of HCC according to the treatment effect (SVR vs. non-SVR)

Figure 1 shows the Kaplan–Meier estimates of the cumulative HCC incidence according to the treatment effect (SVR vs. non-SVR). Twenty-five (6%) of the 403 enrolled patients developed HCC; four (2.9%) of the SVR group and 21 (8.0%) of the non-SVR group. The cumulative incidence rate of HCC was significantly lower in patients of the SVR group than in those of the non-SVR group ($P = 0.03$).

Cumulative incidence of HCC development according to the treatment effect (SVR vs. TR vs. NR vs. cessation)

Figure 2 shows the Kaplan–Meier estimates of the cumulative HCC incidence according to the treatment effect (SVR vs. TR vs. NR vs. cessation). Five patients (4.6%) of the TR group, nine (8.2%) of the NR group and seven (15.6 %) of the cessation group developed

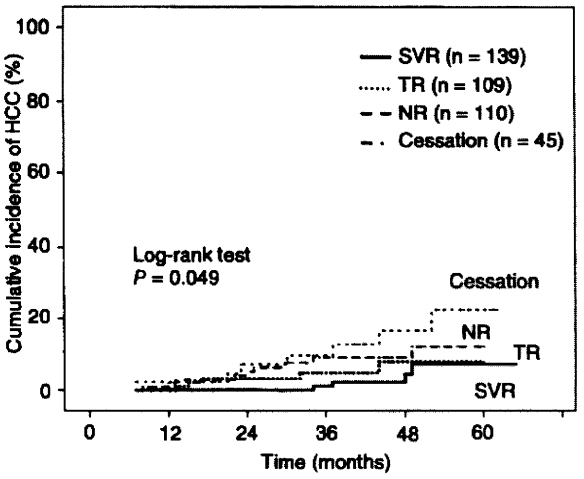

Figure 2 Cumulative incidence of hepatocellular carcinoma (HCC) development according to treatment effect: (—) sustained virological response; (.....) transient response group; (– –) no response; (– ·) cessation.

HCC. There was no significant difference in the cumulative incidence of HCC between the TR and NR groups ($P = 0.394$). In contrast, the cumulative incidence rate of HCC was significantly lower in patients of the SVR group than in those of the NR group ($P = 0.05$). These results indicate that treatment of the TR group with IFN-α-2b plus ribavirin therapy did not reduce HCC development when compared to the NR group.

Risk factors for cumulative incidence of HCC development

Univariate analysis with the log-rank test showed that the following were significant risk factors for the development of HCC; older age (> 65 years) ($P = 0.01$), severe fibrosis ($P = 0.006$), high platelet count ($> 14 \times 10^4/\mu l$) ($P = 0.017$) and non-SVR ($P = 0.03$). Stepwise multivariate analyses of these four variables were performed for all patients treated with combination therapy of IFN-α-2b plus ribavirin by Cox's regression analysis, as shown in Table 2. The analysis indicated the following factors as independent significant risk factors related to the development of HCC: older age (risk ratio, 3.23; 95% CI, 1.37–8.56; $P = 0.006$), fibrosis staging (risk ratio, 1.69; 95% CI, 1.04–2.67; $P = 0.033$) and non-SVR to IFN therapy (risk ratio, 3.57; 95% CI, 1.04–12.36; $P = 0.044$).

Cumulative incidence of HCC development according to average serum ALT levels after combination therapy

The average serum ALT levels in 134 patients (96.4%) of the SVR group were < 40 IU/L after completion of the combination therapy, while 63 patients (24.4%) of the non-SVR group showed serum ALT levels of ≧ 40 IU/L. Figure 3 shows Kaplan–Meier estimates of the cumulative HCC incidence according to the average serum ALT levels after combination therapy. The cumulative incidence rate of HCC was significantly lower in patients with average serum ALT levels of < 40 IU/L than with average serum ALT levels of ≧ 40 IU/L ($P = 0.021$).

Cumulative incidence of HCC development according to the treatment effect (SVR vs. non-SVR) in patients showing less than 40 IU/L average ALT levels after the combination therapy

Figure 4 shows Kaplan–Meier estimates of the cumulative HCC incidence according to the treatment effect (SVR vs. non-SVR) in patients who showed less than 40 IU/L average ALT levels after the combination therapy. There was no significant difference in the cumulative incidence rate of HCC between the SVR and non-SVR groups ($P = 0.37$).

Table 2 Risk factors for cumulative incidence of HCC development

Variable	Category	Risk ratio	*P* value	95% CI
Gender	male	1		
	female	0.34	0.053	0.11–1.01
Age (years)	65 <	1		
	65 ≥	3.23	0.006	1.37–8.56
Fibrosis	F0/1/2/3/4	1.69	0.033	1.04–2.67
IFN therapy	Non-SVR	1		
	SVR	0.28	0.044	1.04–12.36

CI, confidence interval; IFN, interferon; SVR, sustained virological response.

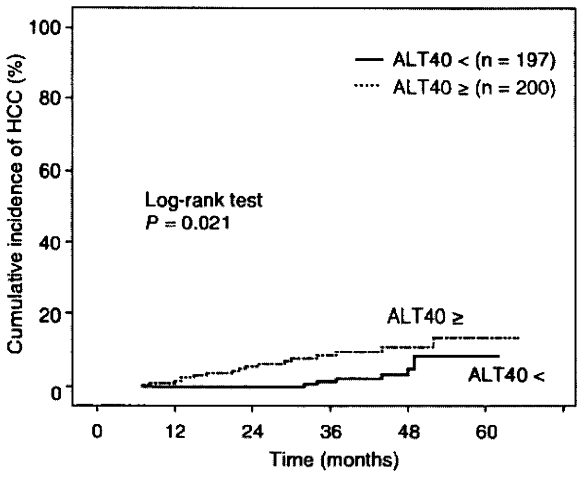

Figure 3 Cumulative incidence of HCC development according to average alanine aminotransferase (ALT) levels after the combination therapy. (—) ALT < 40 IU/ml; (.....) ALT > 40 IU/ml.

DISCUSSION

COMBINATION THERAPIES USING IFN-α-2b or Peg-IFN plus ribavirin have been proven to be more effective in treating for HCV infection than IFN monotherapy.[15–17] However, it has not been accurately evaluated whether the combination therapies using IFN-α-2b or Peg-IFN plus ribavirin could reduce the development of HCC, and what the risk factors of HCC incidence were in patients infected with HCV. In this study, we retrospectively examined the incidence of HCC with IFN-α-2b plus ribavirin therapy to clarify the indicators of combination therapy for reducing HCC in patients infected with HCV. We also evaluated whether or not SVR or continuous normalization of ALT levels could reduce the risk of development of HCC.

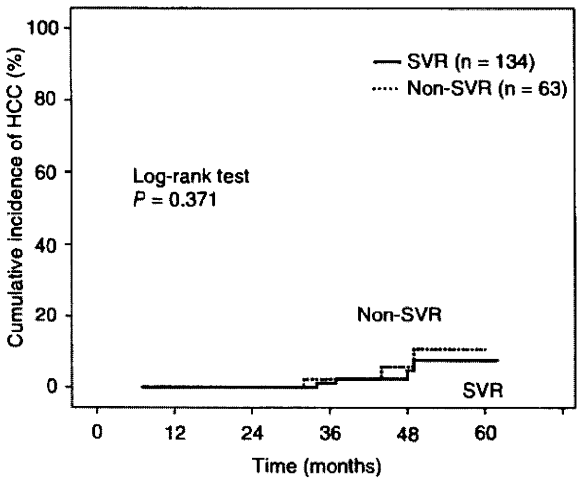

Figure 4 Cumulative incidence of hepatocellular carcinoma (HCC) development according to the treatment effect in patients who showed less than 40 IU/L average alanine aminotransferase (ALT) levels after the combination therapy. (—) Sustained virological response; (.....) non-sustained virological response.

Previous studies have demonstrated that IFN monotherapy has a preventive effect on the development of HCC, especially in patients with SVR.[12–14] In this study, using the combination of IFN-α-2b plus ribavirin, we obtained almost the same result for the SVR group treated with IFN-α-2b plus ribavirin therapy, which showed a significantly lower possibility of HCC development over a long-term period when compared with the non-SVR group. In contrast, we found no difference in the cumulative incidence of HCC between the TR and NR groups, while Kasahara *et al.* reported that the cumulative incidence of HCC in patients who achieved TR by IFN monotherapy was significantly lower than those with NR.[13] Recent reports have demonstrated that the combination therapy of IFN-α-2b plus ribavirin is able to induce a SVR in a significant proportion of patients with IFN monotherapy-resistant chronic hepatitis C,[19,20] suggesting that a viral relapse after IFN therapy is efficiently suppressed by combination with ribavirin. Since the combination therapy was a more effective treatment for HCV infection than IFN monotherapy[15–17] and there are fewer TR patients with combination therapy than with monotherapy, we speculate that not all, but quite a few patients of the TR group given IFN monotherapy corresponded to the SVR group given the combination therapy, and that the TR group given the combination therapy might have been included in the NR group of IFN monotherapy. This would mean that the "TR group given combination therapy" should be distinguished from the "TR group given IFN monotherapy", and might explain why the results of this study were inconsistent with previous reports of the cumulative incidence of HCC in the TR group given IFN monotherapy being significantly lower than those with NR.[13]

The Kaplan–Meier method showed that older age (> 65 years), severe fibrosis (F2–4), high platelet count ($> 14 \times 10^4$) and non-SVR were significantly associated with the development of HCC. The Cox's regression analysis indicated that older age, fibrosis staging and non-SVR to IFN therapy were significant risk factors related to the development of HCC. These results were

almost comparable with those of previous reports using IFN monotherapy[12–14,21] and IFN plus ribavirin combination therapy,[22–24] suggesting that the factors associated with the development of HCC are common among these treatments and that patients of older age, with advanced fibrosis and showing non-SVR to IFN therapy should be followed up carefully for longer periods, even if IFN therapy could be performed completely. In addition, four of the SVR group patients developed HCC at more than 6 months after the treatment, which means these patients need careful follow-up even if SVR has been achieved.[25]

The incidence of HCC has been reported to be lower in patients with normal ALT levels, even if serum HCV-RNA was positive 6 or 12 months after IFN monotherapy, when compared to those without a biochemical response,[13,26,27] suggesting that the aim of IFN therapy for patients infected with HCV should be not only HCV eradication, but also the achievement of a biochemical response in order to reduce the incidence of HCC. In this study, we divided the patients into two groups, one with persistently normal serum ALT levels and the other with elevated serum ALT levels based on "the average serum ALT levels" after completion of IFN therapy. We then evaluated the cumulative HCC incidence of each group using the Kaplan–Meier estimation. Our data showed that patients with continuous normalization of ALT levels have a lower possibility of HCC development than those showing elevated ALT after the combination therapy, suggesting that continuous normalization of ALT levels after the combination therapy is an important factor for reducing HCC development. Interestingly, based on the Kaplan–Meier estimates of the cumulative HCC incidence according to the treatment effect in patients who showed less than 40 IU/L average ALT levels after the combination therapy, we found no difference in HCC incidence rates between the SVR group and non-SVR group. Figure 1 shows that the combination therapy is strongly associated with a reduced incidence of HCC in the patients who attain SVR, which seems to be a means for achieving normalization of serum ALT levels in HCV patients. However, it was also shown that, even in the non-SVR group, patients with persistently normal serum ALT levels achieved a reduced risk of HCC development. Taken together, our aim of treatment for patients infected with HCV is to primarily completely eradicate HCV. Next, for the non-SVR group patients, we would speculate that maintaining normalization of ALT levels by some other treatments may prevent HCC development in HCV-infected patients with abnormal serum ALT levels even if SVR is not achieved. Other treatments should be used to decrease serum ALT levels to below the upper limit of the normal range. Hopefully, the new treatments such as those with protease inhibitors can be helpful for these patients.[28]

Although IFN monotherapy in CHC patients has been demonstrated to be associated with reducing the incidence of HCC, especially in patients who attain SVR,[12–14] what actually occurs in IFN plus ribavirin combination therapy has not been clarified and the indicator for reducing HCC in patients infected with HCV has not been defined. We showed that this combination therapy could reduce the incidence of HCC and that older age, severe fibrosis and non-SVR were risk factors for HCC development. This therapy can increase the SVR patient ratio, and SVR or continuous normalization of ALT levels after combination therapy using IFN-α-2b plus ribavirin reduce the incidence of HCC in patients with HCV infection. Therefore, this therapy can not only avert the advance of the disease toward liver cirrhosis, but also decrease the risk of HCC. IFN plus ribavirin combination therapy is beneficial for HCV patients from both aspects. In conclusion, the present study shows that the attainment of SVR or continuous normalization of serum ALT levels induced by the combination therapy has a significantly beneficial effect on the clinical course of HCV patients by decreasing the incidence of HCC.

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＜特別寄稿＞

ユニバーサルHBワクチネーション：是か非か？

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索引用語：　B型肝炎ウイルス　　ワクチン　　性行為

はじめに

平成21年6月4日　第45回日本肝臓学会総会　工藤正俊会長のご提案により「ユニバーサルHBワクチン：是か非か？」というタイトルでワークショップが企画された．

本邦において1986年に導入された母子感染予防対策によりB型肝炎ウイルス(HBV)キャリアは激減した．一方，性交感染(STD)を中心としたB型急性肝炎は，いまだ減少傾向になく，また国際交流が盛んになったため成人感染で慢性化したHBV genotype A(HBV/A)や海外からのHBVキャリアの移住など母子感染予防だけでは，HBV感染を完全に制圧できない状況である．

B型急性肝炎は，感染症発生動向調査における全数把握の5類感染症に分類されているが，その実態は正確には把握されていない．WHOから推奨されている全出生児を対象としたHBワクチン接種(universal vaccination，以下UV)の是非を問うためには，献血者や一般住民における年齢別HBs抗原陽性率，さらには近年増加が予測されている欧米型genotype Aの頻度やescape mutantの感染状況を調査する必要がある．すでに，若年男性を中心にSTDとしてのB型急性肝炎の慢性化例や父子感染を主体とする家族内感染が注目されており，新たなHBV感染が拡大しつつあることから，B型慢性肝疾患におけるHBV genotypeの実態も再評価する必要がある．こうした近年の状況を踏まえて，内科医のみならず，小児科医からの先進的な意見が重要であり，今回のワークショップではUVの是非，さらにはUVの接種時期に関する議論が活発に交わされた．なお，本ワークショップに先立って日本肝臓学会の役員・評議員の先生方のご協力を得て，ユニバーサルHBワクチネーションに関するアンケート調査を実施した．

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1. B型急性肝炎の実態

1）HBV genotype Aの増加

B型急性肝炎（AH-B）は現在，改正感染症予防法5類に指定され，全数把握の対象であるが，経年的変遷は不明な部分が多い．矢野らの報告によると，国立病院急性肝炎共同研究班の集計の結果，1990年代に減少傾向にあったAH-Bは90年代後半に増加傾向に転じている．1990年代前半に6.4%であったHBV genotype A(HBV/A)の頻度は漸増し，2000年代後半には38.5%，2008年に至っては53%を占めた．首都圏においては，HBV/Aの増加は1990年代後半より始まり，2000年代に入ると着実に増加傾向を示し，近年では7割強をHBV/Aが占めた．その他の地域では，2000年頃からHBV/Aの漸増が認められている．これらの報告は，四柳らの首都圏での報告でも同様で，若年男性を中心にHBV/Aが増加している[1)2)]．HBV/Aの感染ルートに関しては，これまでは同性間性交渉，不特定異性との性交渉であっ

たが，現在は特定の異性との性交渉による感染例が見られるようになった．即ちHBV/Aのキャリアが既に本邦において広く潜在していることがわかる．実際に，多くが無症候である献血者においても若年男性を中心にHBV/Aは約5%と報告されている[3]．内田らの報告では，HBV/Aは若い男性を中心として2002年以降新規感染者の20%以上を占めている．

ワークショップの中で，AII-Bの全数把握の重要性が議論され，今後の検討課題となったが，現時点での国立機構のデータから推測すると，AH-Bによる新規の推定入院患者数は年間1800人程度で，軽症や潜伏感染例も含めると5000人以上の新規感染者が想定された．

2) HIV/HBV重感染の増加

小池らの全国調査では，HIV患者におけるHBs抗原陽性率は6.4%(377/5998)で，同性愛者が70%以上を占めていた[4]．HIV/HCV重感染が主に血液製剤を介して感染しているのとは対照的であった．

酒匂らは，2002年から2008年に国立国際医療センターを受診したB型急性肝炎患者56人についてレトロスペクティブに検討し，HIV/HBV重感染について触れた．若年男性が圧倒的に多く，推定感染経路は同性間性交渉及び異性間性交渉がみられ，梅毒やHIVとの重感染例も多い(梅毒のRPR陽性4人/TPHA陽性14人．HIV診断時が肝炎に先行12人/肝炎と同時3人/肝炎軽快後3人であった)．HBV/Aが26人と最も多く(46%)，特に，同性間性交渉の内17人(71%)がHBV/Aであった．長期にフォローできた49人中3人(6%)に慢性化を認めた．また，三田らは大阪医療センターにおけるHIV carrierのHBV感染率を約10%と報告している．HIV+HBV重複感染者の大半がHBV/Aで，2006-2008年HIV carrierのB型急性肝炎13例(2008年10例)では，11例がgenotype A，残り2例がgenotype Cであった．

以上をまとめると，都市圏の若年男性を中心としたHIV感染者におけるB型急性肝炎の急増は，本邦におけるHIV感染者の増加と強い相関があり，今後も増加するものと考えられる．これらHIV/HBV重感染における90%以上がgenotype A感染であり，こうした従来は稀と考えられていたgenotypeの増加で，今後慢性化が増える懸念がある．

3) B型急性肝炎は治療すべきか？

HBV/Aの大きな問題点は，肝炎の遷延化・慢性化する症例が10%程度存在する点であり，慢性化を阻止する必要がある．治療のタイミングに関するコンセンサスは得られていないが，発症後2-4週間の経過でHBV DNAの低下が見られずALTが遷延化する症例はエンテカビルなどの抗ウイルス療法を行っている施設が多かった．エンテカビルは平均半年程度の投与で慢性化は予防され，薬剤の中止も可能であったとする意見が大半であった．一方で，エンテカビルを最初から導入した方が遷延化しやすいとの意見もあり，今後多数例での検証が必要と思われた．

近年，HIV/HBV重感染例は増加傾向で，HBVキャリア化の報告も多い．ここで注意しないといけないのは，エンテカビル単独投与によるHIV耐性株の誘導であり，B型急性肝炎例，特にHBV/A感染例においてはHIV抗体の検査は必須である．

2. B型慢性肝炎の実態

2001年，わが国のB型慢性肝疾患患者におけるHBV genotypeの分布はgenotype B (HBV/B)，HBV/Cが大部分を占め，HBV/Aは1.7%であった．近年，B型急性肝炎患者においては，都市部を中心にHBV/Aが増加していることが報告されている[1)2)5)6)]．松浦らは2005-2006年に，全国16施設へ通院中であったB型慢性肝疾患患者1272例のgenotype分布について再調査した．HBV/Aは44例(3.5%)，Bは179例(14.1%)，Cは1046例(82.2%)であり，2001年の報告と比べ有意にHBV/Aの割合が約2倍に増えていた($P<.05$)．地域別にみると，関東，沖縄でHBV/Aの割合が高かった．遺伝子系統解析からは海外各国よりHBV/Aは流入し，わが国ですでに複数の株が存在していること，それらの一部は水平感染により国内で蔓延していることが証明された[7]．臨床的には，肝硬変，肝細胞癌に至る速度はHBV/Cほどではないが，HBV/Aの肝炎もこうした進展した肝疾患に至るリスクがある．

3. 乳幼児期のHBV感染の実態

最近，問題になっている父子感染を中心とした家族内感染は重要である．藤澤らは母子感染以外のHBV感染を検討した結果，父子感染が無視できないことを確認した．国際的なUVは生後7日以内，1カ月，3-6カ月にHBワクチンを接種しており，たとえ2回の接種だけでも基礎免疫が獲得される．わが国の母子感染予防法ではHBワクチン接種は生後2，3，6カ月であり免疫獲得まで長期間を要し，脱落例が少なくない．HBV母子感染予防により母子感染によるキャリア化例は1/10に減少したが，予防不成功例の多くは脱落例を含む人

為的な失敗例である．先の父子感染によるキャリア化例と母子感染予防不成功を合わせると毎年500人近いキャリアが発生すると推定される．諸外国で行われている新生児を対象としたUVで小児期の新規感染のみならず，成人のB型急性肝炎も予防できる可能性があり，UVを導入する際には国際方式に切り替えるべきと考えられる．

4. ワクチンエスケープ変異の実態

WHOの推奨により，2007年までに世界171カ国でHBVに対するUVが導入されている．その一方で，中国や台湾などからHBワクチンで感染防御できないワクチンエスケープ変異（VEM）が報告されている．林らは，B型肝炎関連疾患におけるVEMと報告されているS領域の変異（T/I126S/N，G145R）の頻度を解析した．その結果，急性肝炎2例（1.6%），慢性肝炎・肝硬変12例（6.5%），肝癌5例（17.9%）に存在しており，特に肝癌に多い傾向があった．これらのようなワクチンにより誘導されたのではないが，自然に発生したS領域の変異（T/I126S/N，G145R）がVEMと同様にワクチン抵抗性の機能を有するのであれば，費用対効果を含めUV導入時に考慮すべき問題であると結論付けた．

柘植らは，HBV関連肝疾患に伴い肝移植を行った33症例について，HBワクチンの有効性とHBs抗体に対するVEM出現について検討を行った．移植後のHBワクチン長期投与により，HBs抗体獲得率の改善が認められた一方，移植後1年以上経過観察が可能であった29症例のうち，2例にHBs抗体に対するVEMを認めた．いずれの症例もS蛋白145番のアミノ酸変異が確認された．UVは若年者の感染・発癌予防として有用であると考えられるが，HBs抗体に対するVEMの出現も考慮すべき問題の一つと考えられた．一方，吉岡らは，過去に南アフリカで導入された国家規模のユニバーサルHBワクチネーションに関連してVEMの出現を前向きに検討した結果を報告した．南アフリカはHBV高浸淫地区であること，乳幼児の感染は水平感染であることなど本邦と異なる点も多いが，UVによりHBc抗体陽性率からみたHBV感染率は明らかに減少し，しかもVEMの出現を助長しないと結論付けた．

田尻らは，本邦で広く使用されているHBワクチン（ビームゲン®，genotype C，adr）接種により得られたモノクローナル抗体（Mab）の認識する部位とHBV中和活性につき検討した．臨床分離株のa determinantは多様性があるものの，MabでもHBV中和効果が認められることから，抗体価が十分上昇すればgenotypeが異なるHBVに対しても現行のワクチンが有効であることが示唆された．

5. ユニバーサルHBワクチネーションの是非

2009年2～5月にかけて日本肝臓学会役員・評議員を対象に，ユニバーサルHBワクチネーションの是非に関するアンケート調査を実施した．アンケート項目をTable 1に示す．回収率は全体で約65%（139/213）であった．

質問1：内科系の回答が88%，外科系　9%，小児科2%，放射線科　1%であった（Fig. 1）．

質問2：UV賛成　83%：反対　16%：その他　1%であった（Fig. 2）．

質問3：賛成の理由（複数回答可）（Fig. 3）

a）B型急性肝炎が減少しないから　29%

b）HBV genotype Aが増加し，キャリア化が危惧されるから　38%

c）父子感染の割合が高いから　7%

d）将来のHBV再活性化の予防　20%

e）その他

（性感染予防，肝発癌予防，輸血後肝炎の予防）6%

質問4：UV接種時期（Fig. 4）

乳幼児期まで　49%，中学生まで　43%，大学生まで　8%

質問5：ユニバーサルHBワクチネーション反対の理由

・費用対効果を考えると不要

・本邦の医療で財政投融資の優先順位として高くない

・副作用の面から勧められない

・母子感染の予防だけで十分

・B型肝炎の浸淫度が必ずしも高くない

・HIV/AIDS対策の方が優先

・新規AH-Bの全数調査及び新規の母子・父子感染の実態の把握が必要

・医療費の高騰化が社会問題としてあるので，UVを導入することによる経済効果をシミュレーションすべきである．

UV導入に対する賛成意見が多かったが，上記のような解決すべき点もあり，今後の検討課題と思われた．

6. 今後の展望

これまでの問題点として，各医師（主治医）の5類感染症の届出義務に関する認識不足が挙げられる．全出生児を対象としたユニバーサルHBワクチネーション

Table 1　アンケート内容

第45回日本肝臓学会総会

ワークショップ：ユニバーサルHBワクチン：是か非か？

WHOから推奨されている全出生児を対象としたHBワクチン接種(universal vaccination、以下UV)の是非についてのアンケートのご協力をお願い致します。結果を集計致しまして、肝臓学会総会ワークショップの際に結果をまとめて報告させて頂きます。ご協力のほどよろしくお願い申し上げます。

1．　先生の専門分野を教えて下さい。

　　内科系　　外科系　　小児科系　　その他

2．　UVに賛成ですか？　　はい　　いいえ

3．　はいの場合：理由（複数回答可）

a）B型急性肝炎が減少しないから

b）HBV genotype Aが増加し、キャリア化が危惧されるから

c）父子感染の割合が高いから

d）将来のHBV再活性化の予防

e）その他（具体的にお願いします）

4．　はいの場合：接種時期についてご意見をお願いします。

　　乳幼児期　　～中学生まで　　～大学生まで

5．　いいえの場合：理由をお願いします。

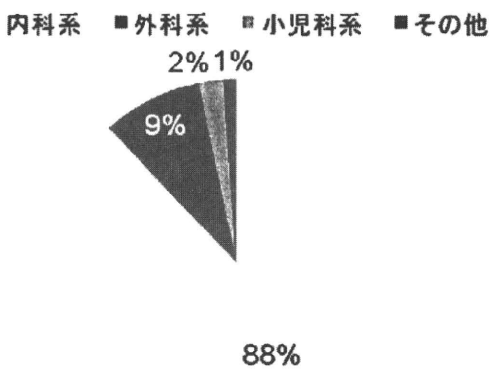

Fig. 1

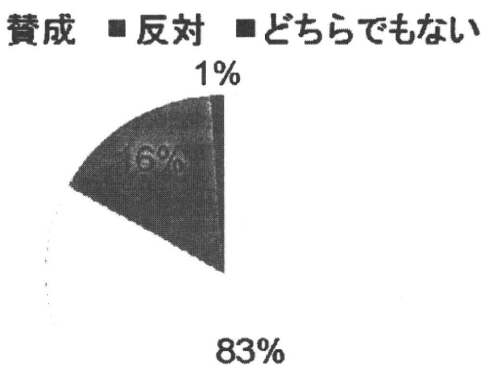

Fig. 2

の是非を検討するためには，5類感染症の届出を適正化するなどの保健行政対策を講じた上で，医師一人一人が5類感染症の届出義務を認識し遂行する必要がある．加えて，現行の母子感染予防成績，年齢階級別HBV

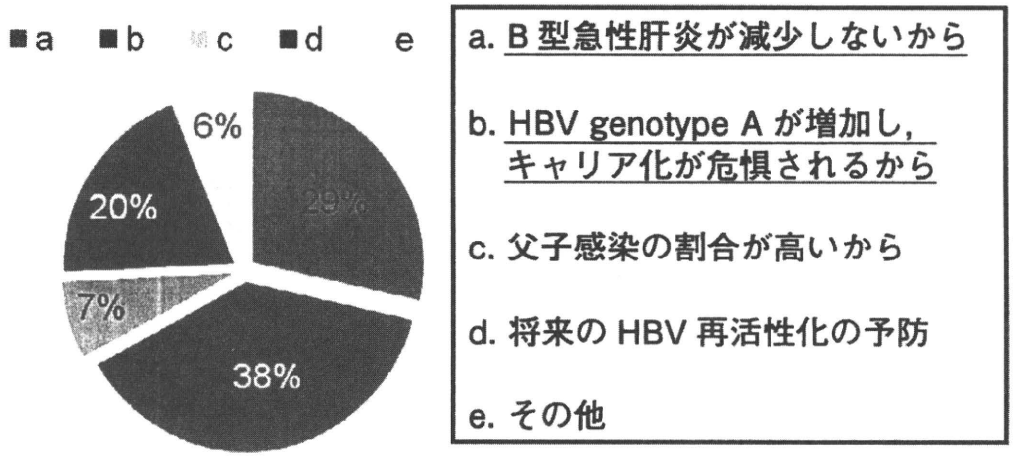

Fig. 3

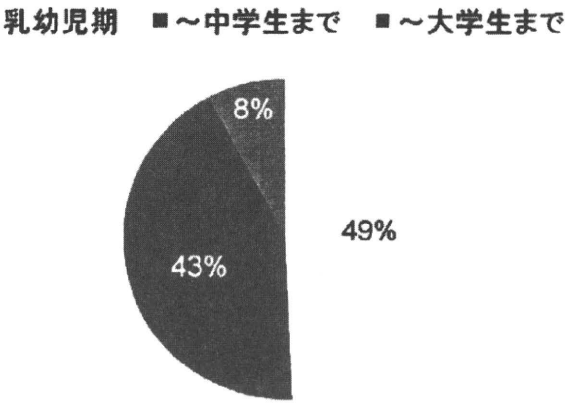

Fig. 4

感染のコホート調査，HBV/A 感染の趨勢などを知る必要がある．また，従来既往感染と考えられていた HBc 抗体陽性例からの HBV 再活性の報告が相次ぎ[8]，一過性あるいは不顕性 HBV 感染予防の必要性も問われるようになった．こうした5類感染症届出の適正化による国内発症数の把握やそれを基にした急性肝炎，劇症化や慢性化，そして将来の肝硬変・肝癌及び HBV 再活性化を防ぐための費用対効果を明らかにしていくことが重要である．

1991年に universal policy を導入した米国で B 型急性肝炎が減少しているのとは対照的に，本邦では20年前とは比較できないほど国際交流が盛んになっている現状の中，外来種の水平感染が増加し，免疫を持たない世代への脅威が広がっている．この HBV/A の感染拡大を「ある特定の集団内での感染」と現状のまま放置すると，キャリア化した例からの二次感染等によって感染が広がる可能性がある．基本的には AH-B 拡散予防として①教育を含むキャンペーンの実施　② infant universal vaccination を基軸に，catch up を目的とした adolescent vaccination が必要であると考える．今回のワークショップでも，日本肝臓学会役員・評議員アンケート調査でも，概ね UV 導入を是とする意見が多数を占めている．その一方で，医療費の高騰化が社会問題としてあるのも事実で，UV に関する費用対効果は重要であり，UV を導入することによる経済効果をシミュレーションすべきである．今後も継続して議論していきたい．

今回のワークショップの総合討論の際に，矢野右人先生から貴重なご意見を頂き，以下，御自身の筆で文章にして頂きました．

＜追加発言＞

長崎県病院企業団　矢野右人

1975年ころ我が国における HBV 母子感染が集中的に検討され HBV キャリアのうち e 抗原陽性の母より出産した場合95％の確率で児は3カ月以内にキャリアに移行することが解明された．一方国立病院共同研究などの報告よりこれまで常識とされていた HBV 急性肝炎の一部がキャリアへ移行する説が否定的になり，日本では特殊例を除き HBV キャリアは“母子感染より成立する”とのコンセンサスが確立した．しかし WHO 西太平洋事務局の頻回にわたるタスクフォース会議で東南アジア諸国，韓国などより完全な同意は得られなかった．

この背景の中でHBIGによるHBV母子感染予防が施行され症例が集積された．1985年HB Vaccineが認可され待ちかねたようにHBIGとHBワクチンを併用する受動—能動免疫法が国の対策としてスタートした．当時は世界のリーダー役であった．WHOタスクフォース会議で日本の方法，出産後ただちにHBIGを投与しHBVを中和，排除しその後のHB Vaccineで永続的に免疫を獲得する方法は理論的で効果的と理解はされた．しかし我が国の方法は妊婦に対する頻回のHBs抗原，e抗原の測定，出産児に対するHBIGの投与はあまりにも高額かつ手間暇かかる予防法として近隣諸国にはとうてい受け入れられない方法であった．当時WHOでは1ドルHB Vaccineの開発を推奨してきた事もあり，開発途上国では検査もHBIGも必要ない全出産児にHB Vaccineのみを接種するいわゆるHB Universal Vaccinationがスタートした．

この展開過程で一部の学者より出産直後のHBIGあるいはHB Vaccine接種に強い反論がありその後のHB Vaccineの展開が頓挫したことは誠に残念であった．

時を経てHBV genotypeの感染性が議論され原則的に外来種であったHBV genotype Aによる急性感染でキャリアが容易に成立することが報じられ日本のキャリア成立に関するこれまでのコンセンサスと外国のそれの間に格差があることが判明した．一方，母子感染以外に水平感染による劇症肝炎は当時より問題視されていたが，外国よりHBV genotype Aの浸淫，STDの激増によりHBV感染対策は母子感染対策のみでは抑制できないとの議論が再燃し，今回も肝臓学会総会で議論されるまでになった．

1796年Edward Jennerが天然痘予防に初めて牛痘接種を行った．その後50年を経て日本で接種が行われ，約200年を経過した1979年WHOより地球上の天然痘が撲滅された終息宣言がなされた．200年の日時が費やされている．同様な撲滅成功は小児麻痺（ポリオ）にも言える．現在ほぼ地球上より小児麻痺の原因となるポリオウイルスは撲滅に成功したといえる状況である．

天然痘，ポリオ，麻疹に次ぐのは発がんリスクが明確なそして劇症肝炎による死亡が予測されるB型肝炎であることは明白である．それはHB Vaccineにより予防法が完成しているからでもある．その次は疾病の性格，社会的にみても，HIV感染対策であることも明白である．

ウイルスは新しく姿を変えて次々に人類に襲い掛かる．予防法が確立している重大疾病の撲滅に取り組まないのは肝臓病に携わる研究者にとっては怠慢である．HBV感染は最高裁でも判決されごとく後世に責任を追及される事例ともなりうる．世界中の国がHBV Universal Vaccinationで地球上よりHBV感染を撲滅しようとしている今，日本はこれを無視して良いであろうか．注目を喚起したい．

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Universal hepatitis B vaccination: pros and cons

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Key words: hepatitis B virus　vaccination　sexual transmission

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＜症例報告＞

骨転移巣で発見された異所性肝細胞癌の1例

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要旨：症例は70歳男性．右臀部痛にて受診し，右恥骨に骨融解像を認めたため，転移性骨腫瘍を疑い精査を行った．しかし明らかな原発を認めなかったため，腫瘍生検を行い中分化型肝細胞癌の骨転移と診断した．脾臓頭側，左横隔膜下に肝臓，脾臓と連続しない4 cmの腫瘍が認められたが，肝臓内には腫瘍性病変を認めず．脾臓頭側の腫瘍に対して腹腔鏡下に生検を行い，骨腫瘍と同様の結果を得た．これらより脾臓頭側の腫瘍を原発とする異所性肝細胞癌および骨転移と診断した．異所性肝細胞癌は，非常にまれな疾患であり文献的に検索しえた本邦での報告例は自験例を含め39例であった．

索引用語：　異所性肝細胞癌　　異所性肝　　骨転移

はじめに

発生の過程で異常が生じ，肝臓と実質的な連絡がない部位に肝組織が存在することがある．これを異所肝と呼ぶ．発生における肝臓の異常はまれであるが，異所性肝から発生した癌（異所性肝細胞癌）はさらにまれであり，その発生機序は明らかでない．

今回我々は，転移性骨腫瘍から発見された異所性肝細胞癌を経験したので，文献的考察を加えて報告する．

症　例

患者：70歳，男性．

主訴：右臀部痛．

家族歴：特記すべきことなし．

既往歴：特記すべきことなし．

現病歴：2007年4月15日，転倒を機に右臀部の疼痛が出現し近医を受診した．右恥骨の骨融解像を認め，4月24日に精査加療のため当院を紹介受診した．転移性骨腫瘍を疑い，外来にて原発巣の検索を行った．

初診時現症：身長172 cm，体重60 kg，体温36.2℃，脈拍72/分・整，血圧126/82 mmHg．結膜に貧血や黄疸なし．胸部：異常所見なし．腹部：平坦軟，肝脾触知せず．四肢：浮腫なし．神経学的所見：異常なし．右臀部に自発痛・圧痛を認める．

初診時血液検査（Table 1）：腫瘍マーカーでは，AFP 258 ng/ml（L3分画33.2%），PIVKA-II 47,600 mAU/mlが高値であった．

上部消化管内視鏡：胃体上部大弯に胃潰瘍瘢痕を認めるのみであった．

下部消化管内視鏡：回腸末端まで挿入し観察するが，異常を認めず．

腹部骨盤造影CT：右恥骨に約8 cmの腫瘍を認め（**Fig. 1a**），脾臓と横隔膜の間に約4 cmの腫瘤を認めた（**Fig. 1b**）．肝臓との連続性は認めなかった．

腹部エコー：脾臓頭側に4×2.5 cmの腫瘤を認めた．

胸部単純CT：両肺野，縦隔に明らかな異常を認めず．リンパ節腫大もなし．

骨シンチ：右恥骨上枝に強い集積あり．同下枝，右坐骨にも軽度の集積あり．

PET-CT：恥骨に溶骨性変化を伴う径12 cmの腫瘤を認めた．FDGの集積増強あり．肝内に明らかなSOL，FDGの集積を認めず．

骨変化は転移性骨腫瘍を示唆するものの，原発巣の

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