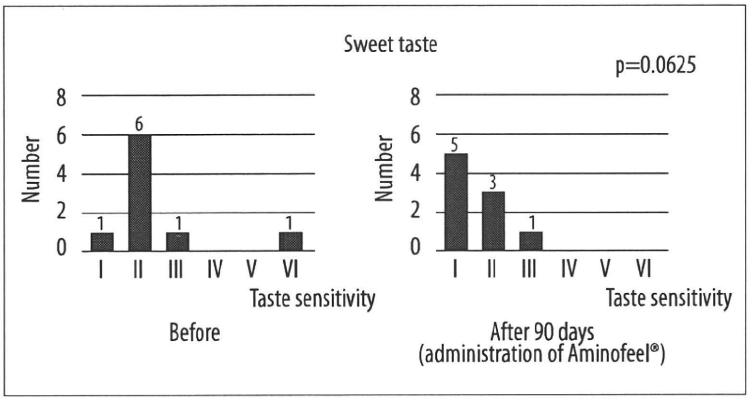


Figure 2. The effects of sweet tastes after administration of Aminofeel®. Sensitivity to sweet tastes was increased 90 days after the administration of Aminofeel® (P=0.06).

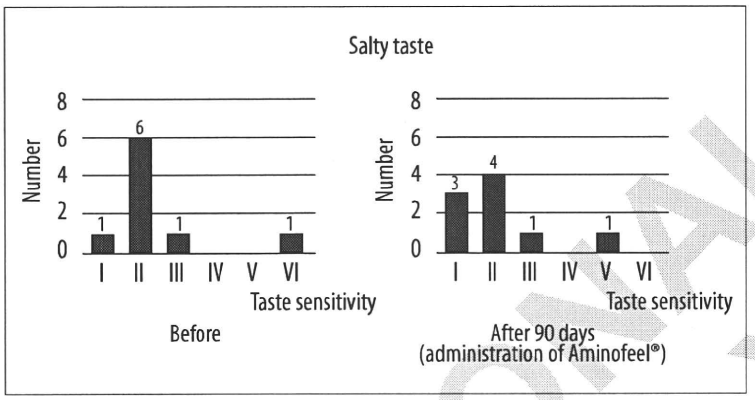


Figure 3. The effects of salty tastes after administration of Aminofeel®.

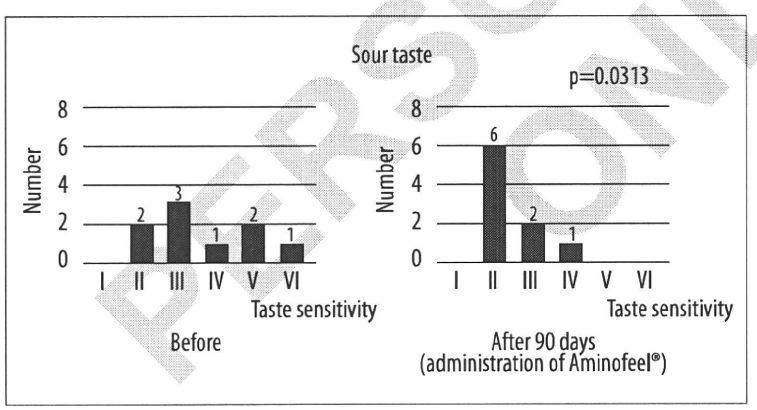


Figure 4. The effects of sour tastes after administration of Aminofeel®. Sensitivity to sour tastes was significantly increased 90 days after the administration of Aminofeel® (P=0.03).

We analyzed for differences before and after the administration of Aminofeel® in AST, ALT, albumin, platelet count and zinc values. These laboratory data are shown in Table 3. The serum zinc value was significantly increased (p=0.02).

Discussion

The number of patients with taste disorders is increasing [1,12]. It is presumed that approximately 240,000/year receive medical treatment for taste disorders from otolaryngologists in Japan [1]. Ikeda et al reported, after administering questionnaires to 1,559 members of the Japan Society of Stomato-pharyngology, that the main treatment used was administration of zinc preparations such as polaprezinc [1]. One reason for the increased number of patients with taste disorders is that the elderly population has increased year after year [13] and it is believed that taste disorders increase with age.

Taste disorders are symptoms of neurological derangement for which there are many reasons such as use of numerous drugs, idiopathic factors, zinc deficiency, psychogenic factors, systemic diseases, etc [5,6,14]. Zinc is essential for many metabolic and enzymatic functions [15]. A zinc deficiency in man has been found to occur not only as a result of nutritional factors, but also in various disease states, including malabsorption syndromes, acrodermatitis enteropathica, Crohn's disease, alcoholism and liver cirrhosis [15].

We found that sensitivity to tastes and zinc levels are decreased in patients with HCV-infected liver disease. Some patients had decreased sensitivity of taste despite the fact that they were

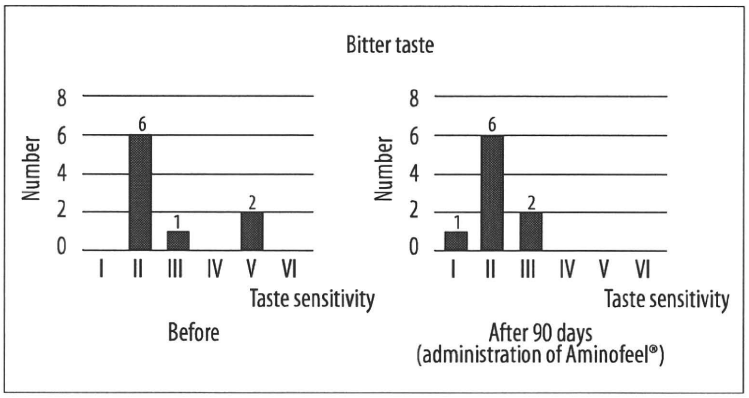


Figure 5. The effects of bitter tastes after administration of Aminofeel®.

Table 3. Laboratory data.

	Before	Administration of Aminofeel®	p value
AST (IU/L) (mean ±SD)	45.1±22.1	44.8±18.3	NS
ALT (IU/L) (mean ±SD)	43.2±28.3	44.0±25.9	NS
Alb (g/dL) (mean ±SD)	3.9±0.2	4.0±0.2	NS
PLT (/mm^3) (mean ±SD)	15.8±5.3	15.8±5.8	NS
Zinc (μg/dL) (mean ±SD)	84.1±18.0	108.4±23.5	0.0209

SD – standard deviation; NS – no significance; AST – serum aspartate aminotransferase; ALT – alanine aminotransferase; Alb – albumin; PLT – platelets.

unaware of their taste disorder. In addition, Aminofeel®, a BCAA-enriched supplement, improved sensitivity to tastes and increased zinc levels. Thus, because Aminofeel® contains zinc, it is a useful therapeutic agent for taste disorders. Hayashi et al reported that combination treatment with BCAA and zinc supplements in cirrhotic liver patients with hypoalbuminemia or hypozincemia showed significantly higher efficacy in correcting amino acid imbalances and significantly greater ability to metabolize ammonia than when BCAA was given alone during the 6 months of the study period [16]. There is a report that zinc only treatment did not improve taste disorder in liver cirrhosis [17]. Combination treatment with BCAA and zinc may be useful for improvement of gustatory sensibility, although it is not clear that whether the combination treatment is more effective for sensitivity to tastes in patients with liver diseases than zinc only or not.

Several studies and our previous reports suggest that HCV infection antedates insulin resistance [18,19], and that insulin resistance is associated with extrahepatic manifestations such as lichen planus [20,21]. We have already reported that Aminofeel® improved insulin resistance and β cell function in male patients with chronic liver disease [10]. A post-marketing surveillance study of Aminofeel® confirmed the usefulness of this supplement (data not shown).

Conclusions

Aminofeel® is a supplement that improves the sensitivity to tastes by increasing zinc levels. It also improves insulin resistance in patients with chronic liver disease. It is hoped that this supplement improves the prognosis of liver disease and the quality of life of these patients.

References:

1. Ikeda M, Aiba T, Ikui A et al: Taste disorders: a survey of the examination methods and treatments used in Japan. Acta Otolaryngol, 2005; 125: 1203–10
2. Marchesini G, Fabbri A, Bianchi G et al: Zinc supplementation and amino acid-nitrogen metabolism in patients with advanced cirrhosis. Hepatology, 1996; 23: 1084–92
3. Rodríguez-Moreno F, González-Reimers E, Santolaria-Fernández F et al: Zinc, copper, manganese, and iron in chronic alcoholic liver disease. Alcohol, 1997; 14: 39–44
4. Hatano R, Ebara M, Fukuda H et al: Accumulation of copper in the liver and hepatic injury in chronic hepatitis C. J Gastroenterol Hepatol, 2000; 15: 786–91
5. Smith FR, Henkin RI, Dell RB: Disordered gustatory acuity in liver disease. Gastroenterology, 1976; 70: 568–71
6. Burch RE, Sackin DA, Ursick JA et al: Decreased taste and smell acuity in cirrhosis. Arch Intern Med, 1978; 138: 743–46
7. McClain CJ, Marsano L, Burk RF, Bacon B: Trace metals in liver disease. Semin Liver Dis, 1991; 11: 321–39
8. Muto Y, Sato S, Watanabe A et al: Effects of oral branchedchain amino acid granules on event-free survival in patients with liver cirrhosis. Clin Gastroenterol Hepatol, 2005; 3: 705–13
9. Marchesini G, Zoli M, Dondi C et al: Anticatabolic effect of branched-chain amino acid-enriched solutions in patients with liver cirrhosis. Hepatology, 1982; 2: 420–25
10. Kawaguchi T, Nagao Y, Matsuoka H et al: Branched-chain amino acid-enriched supplementation improves insulin resistance in patients with chronic liver disease. Int J Mol Med, 2008; 22: 105–12
11. Kawaguchi T, Taniguchi E, Itou M et al: Branched-chain amino acids improve insulin resistance in patients with hepatitis C virus-related liver disease: report of two cases. Liver Int, 2007; 27: 1287–92
12. Hoffman HJ, Ishii EK, MacTurk RH: Age-related changes in the prevalence of smell/taste problems among the United States adult population. Results of the 1994 disability supplement to the National Health Interview Survey (NHIS). Ann NY Acad Sci, 1998; 855: 716–22
13. Ikeda M, Ikui A, Komiyama A et al: Causative factors of taste disorders in the elderly, and therapeutic effects of zinc. J Laryngol Otol, 2008; 122: 155–60
14. Hamada N, Endo S, Tomita H: Characteristics of 2278 patients visiting the Nihon University Hospital Taste Clinic over a 10-year period with special reference to age and sex distributions. Acta Otolaryngol Suppl, 2002; 546: 7–15
15. Prasad AS: The role of zinc in gastrointestinal and liver disease. Clin Gastroenterol, 1983; 12: 713–41

16. Hayashi M, Ikezawa K, Ono A et al: Evaluation of the effects of combination therapy with branched-chain amino acid and zinc supplements on nitrogen metabolism in liver cirrhosis. Hepatol Res, 2007; 37: 615–19
17. Sturniolo GC, D'Incà R, Parisi G et al: Taste alterations in liver cirrhosis: are they related to zinc deficiency? J Trace Elem Electrolytes Health Dis, 1992; 6: 15–19
18. Hui JM, Sud A, Farrell GC et al: Insulin resistance is associated with chronic hepatitis C and virus infection fibrosis progression. Gastroenterology, 2003; 125: 1695–704
19. Kawaguchi T, Yoshida T, Harada M et al: Hepatitis C virus down-regulates insulin receptor substrates 1 and 2 through up-regulation of suppressor of cytokine signaling 3. Am J Pathol, 2004; 165: 1499–508
20. Nagao Y, Kawaguchi T, Tanaka K et al: Extrahepatic manifestations and insulin resistance in an HCV hyperendemic area. Int J Mol Med, 2005; 16: 291–96
21. Nagao Y, Kawasaki K, Sata M: Insulin resistance and lichen planus in patients with HCV-infectious liver diseases. J Gastroenterol Hepatol, 2008; 23: 580–85

Nagao and Sata *Virology Journal* 2010, **7**:192
http://www.virologyj.com/content/7/1/192

VIROLOGY JOURNAL

RESEARCH Open Access

Dental problems delaying the initiation of interferon therapy for HCV-infected patients

Yumiko Nagao[1*], Michio Sata[1,2†]

Abstract

Background: There has been little discussion about the importance of oral management and interferon (IFN) therapy, although management of the side effects of therapy for chronic hepatitis C has been documented. This study determined whether dental problems delayed the initiation of IFN therapy for hepatitis C virus (HCV)-infected patients.

Results: We analyzed 570 HCV-infected patients who were admitted to our hospital from December 2003 to June 2010 for treatment consisting of pegylated IFN (Peg-IFN) monotherapy or Peg-IFN/ribavirin combination therapy. The group comprised 274 men and 296 women with a mean age 57.2 years. Of the 570 patients, six could not commence Peg-IFN therapy, despite their admission, because of dental problems such as periodontitis, pupitis, and pericoronitis. The ages of six whose dental problems delayed the initiation of Peg-IFN ranged from 25 to 67 years, with a mean age of 47.3 ± 15.2 years. IFN therapy was deferred for 61.3 ± 47.7 days. Among the six subjects for whom IFN treatment was delayed, only one had a salivary flow that was lower than the normal value.

Conclusions: Treatment of dental infections is required before IFN therapy for HCV infection can be started. To increase the depth of understanding of oral health care, it is hoped that dentists and medical specialists in all areas will hold discussions to generate cooperation.

Background

In Japan, hepatocellular carcinoma (HCC) is the fourth leading cause of death in males and the sixth in females according to a recent survey. The incidence of HCC has increased in Japan throughout the past several decades [1]. Hepatitis C virus (HCV) is the major cause of HCC in Japan, with 70% of cases being HCV-related. It is assumed that between one and two million Japanese people are chronically infected with HCV [1].

Interferon (IFN) therapy for chronic hepatitis C is the only treatment for completely eliminating the virus. Combination therapy with pegylated IFN (Peg-IFN) and ribavirin has been recommended widely as the first choice for chronic hepatitis C patients with high viral loads. The sustained virological response (SVR) rate after 48 weeks of treatment at a standard dose is approximately 40 to 50% [2-5]. It has been shown that IFN therapy decreases the rate of development of HCC and improves the long-term prognosis [6-9].

Although IFN therapy has therapeutic benefits, the treatment produces a number of well-described side effects that are dominated by fatigue, influenza-like syndrome and neuropsychiatric symptoms [2-5,10-12] and management of such side effects is required during therapy. Among the side effects in a Japanese Phase III trial of Peg-IFN alfa-2a/alfa-2b and ribavirin, dental problems have been documented in patients with chronic hepatitis C. Meanwhile, it has been reported that hepatitis C infected patients have significant oral health needs [13-16] and that experience of dental caries is significantly worse for HCV-infected patients than patients in general [13].

Therefore, in the present study, we determined whether dental problems delayed the initiation of IFN therapy for HCV-infected patients.

Methods

Patients

A total of 570 HCV-infected patients who admitted to the Kurume University Hospital from December 2003

* Correspondence: nagao@med.kurume-u.ac.jp
† Contributed equally
[1]Department of Digestive Disease Information & Research, Kurume University School of Medicine, Kurume, Fukuoka, 830-0011, Japan
Full list of author information is available at the end of the article

to June 2010 for treatment with Peg-IFN monotherapy or Peg-IFN/ribavirin combination therapy were studied (Table 1). The 570 patients were 274 men and 296 women with a mean age of 57.2 ± 11.6 years. They were consulted by one oral surgeon for each patient about presence of oral infection before commencing IFN treatment. All HCV-infected patients treated with IFN therapy at our hospital were required to undergo hospitalization for two weeks for therapeutic management and education about liver diseases.

We determined whether dental problems delayed the initiation of IFN therapy for these patients. Patients who underwent Peg-IFN therapy during dental treatment were excluded. Informed consent was obtained from all patients after the purpose and methods of the study were explained.

Salivary flow

We used a simple and low-cost test for xerostomia detection, which requires chewing on a piece of gauze for 2 min. The results from 531 of 570 patients were quantified using the Saxon test. A salivary flow rate ≤ 2 g/2 min was judged as decreased salivary secretion.

Serological assays

Serum samples were examined for the presence or absence of markers of HCV and HBV infection. The HCV RNA level before IFN therapy was analyzed by quantitative PCR assay (COBAS AMPLICOR HCV MONITOR v 2.0 Test, COBAS AmpliPrep/COBAS TaqMan HCV Test, Roche Molecular Systems, New Jersey, US) [17,18]. HCV genotype was determined by polymerase chain reaction assay, using a mixture of primers for the subtype, as reported previously [19].

Table 1 Characteristics of 570 patients

Men/Women		274/296	
Age (mean ± SD) years		57.2 ± 11.6	
Liver disease	AH-C	1	(0.2%)
	CH-C	471	(82.6%)
	CH-(B+C)	3	(0.5%)
	CH-C and post HCC treatment	20	(3.5%)
	LC-C	45	(7.9%)
	LC-C and post HCC treatment	30	(5.3%)
Peg-IFN therapy	Peg-IFN alfa-2a monotherapy	104	(18.2%)
	Peg-IFN alfa-2a monotherapy and trial	1	(0.2%)
	Peg-IFN alfa-2a/RBA	14	(2.5%)
	Peg-IFN alfa-2a/RBA and trial	5	(0.9%)
	Peg-IFN alfa-2b/RBA	438	(76.8%)
	Peg-IFN alfa-2b/RBA→Peg-IFN alfa-2a monotherapy	4	(0.7%)
	Peg-IFN alfa-2b/RBA→Peg-IFN alfa-2a monotherapy→Peg-IFN alfa-2a/RBA	1	(0.2%)
	Peg-IFN alfa-2b/RBA→Peg-IFN alfa-2a monotherapy→Peg-IFN alfa-2b/RBA	1	(0.2%)
	Peg-IFN alfa-2b/RBA→Peg-IFN alfa-2a/RBA	2	(0.4%)
HCV genotype	1a	2	(0.4%)
	1a or 1b	1	(0.2%)
	1b	401	(70.4%)
	2a	121	(21.2%)
	2b	24	(4.2%)
	3a	1	(0.2%)
	combination (1a and 1b)	1	(0.2%)
	combination (1b and 2b)	1	(0.2%)
	combination (1b and 3a)	1	(0.2%)
	combination (2a and 2b)	2	(0.4%)
	indeterminable	3	(0.5%)
	untested	12	(2.1%)

CH-C: chronic hepatitis C, CH-(B+C): chronic hepatitis B and C, LC-C: liver cirrhosis, HCC: hepatocelular carcinoma, Peg-IFN: pegylated interferon, RBV: ribavirin

Therapeutic response was judged after IFN therapy as: SVR - normalization of alanine aminotranferase (ALT) levels and HCV RNA negative for six months or more after treatment; transient response (TR) - normalization of ALT levels and undetectable HCV RNA during IFN treatment but HCV RNA-positive after IFN treatment; non-responder (NR) - neither normal nor negative results for six months or more.

As shown in Table 1, chronic hepatitis C with HCV genotype 1b was the most common. Patients with genotypes 2a/2b underwent Peg-IFN monotherapy and those with genotypes 1a/1b, a combination of Peg-IFN and ribavirn.

Results

Dental problems delayed the initiation of IFN therapy

Of 570 patients with HCV-related liver diseases, we documented six whose dental problems delayed the initiation of Peg-IFN therapy. Their ages ranged from 25 to 67 years, with a mean age of 47.3 ± 15.2 years. There were two men and four women (Table 2). These six patients could not commence IFN therapy, despite their admission for this treatment, and their therapy was deferred for 61.3 ± 47.7 days. Patient no. 1 had an acute odontogenic periostitis, resulting from periapical inflammation of endodontic origin. This was treated successfully by nonsurgical endodontics and administration of antibiotics. Patient no. 2 had an acute alveolar abscess, resulting from periodontal disease. His four molars were extracted after local anti-inflammation treatment. Patient no. 3 had a periapical periodontitis of the right mandibular second molar. The molar was extracted. Patient no. 4 had multiple dental problems with pain. After extirpation of dental pulps and extraction of teeth, she received IFN treatment. Patient no. 5 had apical periodontitis with gingival abscess, consequently her teeth were endodontically treated. Patient no. 6 had trismus and painful swallowing caused by pericoronitis of her

Table 2 Characteristics of six patients whose dental problems delayed the initiation of IFN therapy

No.	Age	Sex	Liver Disease	HCV RNA	HCV genotype	Dental problems that delayed the initiation of Peg-IFN therapy	Period to onset of IFN treatment after dental therapy (days)	Underlying disease	IFN therapy	Effect of IFN treatment
1	50	F	CH-C	980 kIU/ml	1b	#1. Acute periostitis of the right maxilla, #2. Periapical periodontitis of the right maxillary first molar	49	Gallbladder polyp	Peg-IFN alfa-2b/ RBA	TR
2	67	M	CH-C	3,940 kIU/ ml	1b	#1. Acute alveolar abscess of bilateral mandibular molars, #2. Periodontal diseases of the right mandibular first and second molars, the left mandibular first molar, and the left maxilla first and second molars	105	Gastric ulcer	Peg-IFN alfa-2b/ RBA	NR
3	36	M	CH-C	over 500 kIU/ml	1b	Periapical periodontitis of the right mandibular second molar	4	None	Peg-IFN alfa-2b/ RBA	SVR
4	47	F	CH-C	43 kIU/ml	2a	#1. Pulpitis of the right maxillary first premolar, the left maxillary second premolar, and the right mandibular second premolar, #2. Tooth stumps of the left maxillary canine and second premolar, and the right mandibular first premolar, #3. Dental caries of the right maxillary lateral incisor	97	Hypertension, Adjustment disorder, Gallstone	Peg-IFN alfa-2a	SVR
5	59	F	LC-C	471 kIU/ml	2a	#1. Periapical periodontitis and gingival abscess of the right mandibular lateral incisor, #2. Dental caries of bilateral mandibular central incisors	105	Depression, Hypertension, Osteoarthritis of the spine, Esophageal varices	Peg-IFN alfa-2b/ RBA	SVR
6	25	F	CH-C	6.2 logIU/ mL	1b	#1. Pericoronitis of the right mandibular wisdom tooth, #2. Horizontal impacted wisdom teeth of bilateral mandibles	8	None	Peg-IFN alfa-2b/ RBA	SVR

CH-C: chronic hepatitis C, LC-C: liver cirrhosis, Peg-IFN: pegylated interferon, RBV: ribavirin,
TR: transient biochemical responders, NR: nonresponder, SVR: sustained virological response

wisdom tooth and she had a high white blood cell count of 10,200/mm3 on the day of admission. All six patients received IFN treatment after their dental treatment was completed. Nobody suffered from diabetes mellitus. The outcome of the patients was classified into three groups: SVR (n = 4), TR (n = 1), and NR (n = 1).

Salivary flow

The level of total saliva production, measured using the Saxon test, was 4.26 ± 1.91 g/2 min. The salivary flow rate was below the normal value in 54 patients (10.2%). Among the six subjects for whom IFN treatment was delayed, only one had a salivary flow that was lower than the normal value.

Discussion

The results indicate that oral health care may be required before HCV-infected patients undergo IFN therapy. In our study, dental problems delayed the initiation of IFN therapy for a maximum of 105 days. HCV-infected patients treated with IFN therapy should be managed by intensive oral care because of lower resistance to infection during the therapy.

Poor of oral health has been reported for HCV-infected patients [13-16]. Coates et al. reported that the dental caries experience of HCV-infected subjects was significantly worse than that of patients in general, that the number of teeth missing from patients with hepatitis C infection also was significantly higher than for patients in general, and that periodontal health tended to be poor [13]. Griffin et al. found that patients with rheumatoid arthritis, diabetes or a liver condition were twice as likely to have an urgent need for dental treatment as patients who did not have these diseases and documented a high burden of unmet dental care needs among patients with chronic diseases [16]. The authors showed that HCV was the strongest predictor of patients reporting poor oral health.

Japanese HCV-infected patients tend to be older than those in other countries and their older age favors the onset of HCC, leading to an increased mortality rate [1]. Peg-IFN-ribavirin combination therapy is the standard treatment for chronic hepatitis C. Meanwhile, the frequency of adverse events in combination therapy is relatively high (20-64%) [2-5,10-12].

In a Japanese Phase III trial of Peg-IFN alfa-2a and ribavirin involving 199 patients with chronic hepatitis C, including 99 patients with IFN treatment-naive genotype 1 and 100 patients with patients whom had not had a SVR after IFN therapy, the oral side effects were: gingival bleeding and gingival swelling (6%), toothache (4.5%), gingivitis and periodontitis (3%), dental caries (1.5%), stomatitis and cheilitis (19.1%), disorder of taste (15.6%), dry mouth (6.5%), glossalgia and glossitis (4.5%), perioral paresthesia (2.5%), oral pain (0.5%), oral mucosal damage (0.5%), oral lichen planus (0.5%), oral hemorrhage (0.5%), dry lip (0.5%), and bulla of lip (0.5%). On the other hand, in a Japanese Phase III trial of Peg-IFN alfa-2b and ribavirin involving 332 chronic hepatitis C patients, including 269 patients for 48 weeks treatment duration with genotype 1b and high virus load, and 63 patients for 24 weeks treatment duration with others, oral side effect were: dental pulpitis, gingivitis, and periodontitis (8.9%), toothache (7.1%), dental abnormity (1.1%), stomatitis and cheilitis (26.8%), disorder of taste (26.8%), dry mouth (15.6%), glossitis (5.9%), oral discomfort feeling (2.6%), oral hemorrhage (0.4%), oral pain (0.4%), dry tongue (0.4%), decreased secretion of saliva (0.4%).

These findings indicate that dental management of HCV-infected patients is required before IFN therapy. However, in Japan the importance of oral health is often overlooked in HCV-infected patients and has not been discussed in detail up to now.

Several studies have shown an association between HCV and sicca symptoms [20,21]. Patients with chronic HCV infection also have been reported to be at a greater risk of developing insulin resistance [22,23]. Severe periodontal disease causes insulin resistance [24]. The reasons that HCV-infected individuals had problems such as dental caries and oral health care may include a decreased salivary flow rate, elicitation of periodontal disease by insulin resistance and difficulties for radical dental treatment of patients with liver disease who may have problems such as prolonged bleeding.

Henderson et al. reported HCV-infected cases and suggested the possibility of occasional discrimination by practitioners. They concluded that more effective oral health education is required for HCV-infected patients and dental practitioners [15]. We distributed a questionnaire to 209 patients who visited our hospital for liver disease treatment to determine whether patients with HCV or hepatitis B virus (HBV) disclosed their disease status to the personnel in dental clinics. We found that 59.8% always did so, 12.0% sometimes did so and 28.2% never did so. The main reason for nondisclosure was failure of dental healthcare workers to ask whether patients had systemic disease. Other reasons included fear of negative reactions from healthcare workers and not wanting dentists or staff to know their specific liver ailment [25]. To increase the depth of understanding of oral health care, it is hoped that dentists and medical specialists in all areas will hold discussions to create cooperation.

Conclusions

In conclusion, the results of this study show that the treatment of dental infection is required before IFN

therapy for HCV infection. On the basis of our results, we introduced systems in our hospital from November 2009 to ensure complete dental treatment before IFN therapy. We should enhance mutual understanding of various issues related to HCV-infected persons between the patient and the physician.

Abbreviations

HCV: hepatitis C virus; HCC: hepatocellular carcinoma; IFN: interferon; Peg-IFN: pegylated IFN; SVR: sustained virological response; TR: transient response; NR: non-responder

Acknowledgements

This study was supported in part by a Grant-in-Aid for Scientific Research (C) (No. 22592354) from the Ministry of Education, Culture, Sports, Science and Technology of Japan, and was supported in part by Health and Labour Sciences Research Grants for Research on Hepatitis from the Ministry of Health, Labour and Welfare of Japan.

Author details

[1]Department of Digestive Disease Information & Research, Kurume University School of Medicine, Kurume, Fukuoka, 830-0011, Japan. [2]Division of Gastroenterology, Department of Medicine, Kurume University School of Medicine, Kurume, Fukuoka, 830-0011, Japan.

Authors' contributions

YN carried out most of the data collection and drafted the manuscript. MS contributed to data analysis. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Received: 22 July 2010 Accepted: 17 August 2010
Published: 17 August 2010

References

1. Yoshizawa H: **Hepatocellular carcinoma associated with hepatitis C virus infection in Japan: projection to other countries in the foreseeable future.** *Oncology* 2002, **62(Suppl 1)**:8-17.
2. Hadziyannis SJ, Settee H Jr, Morgan TR, Balan V, Diago M, Marcellin P, Ramadori G, Bodenheimer H Jr, Bernstein D, Rizzetto M, Zeuzem S, Pockros PJ, Lin A, Ackrill AM, PEGASYS International Study Group: **Peginterferonalpha 2a and ribavirin combination therapy in chronic hepatitis C: A randomized study of treatment duration and ribavirin dose.** *Ann Intern Med* 2004, **140**:346-355.
3. Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, Goodman ZD, Koury K, Ling M, Albrecht JK: **Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomized trial.** *Lancet* 2001, **358**:958-965.
4. Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Gonçales FL Jr, Häussinger D, Diago M, Carosi G, Dhumeaux D, Craxi A, Lin A, Hoffman J, Yu J: **Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection.** *N Engl J Med* 2002, **347**:975-982.
5. Mangia A, Minerva N, Bacca D, Cozzolongo R, Ricci GL, Carretta V, Vinelli F, Scotto G, Montalto G, Romano M, Cristofaro G, Mottola L, Spirito F, Andriulli A: **Individualized treatment duration for hepatitis C genotype 1 patients: a randomized controlled trial.** *Hepatology* 2008, **47**:43-50.
6. Yoshida H, Shiratori Y, Moriyama M, Arakawa Y, Ide T, Sata M, Inoue O, Yano M, Tanaka M, Fujiyama S, Nishiguchi S, Kuroki T, Imazeki F, Yokosuka O, Kinoyama S, Yamada G, Omata M: **Interferon therapy reduces the risk for hepatocellular carcinoma: national surveillance program of cirrhotic and noncirrhotic patients with chronic hepatitis C in Japan. IHIT Study Group. Inhibition of Hepatocarcinogenesis by Interferon Therapy.** *Ann Intern Med* 1999, **131**:174-181.
7. Yoshida H, Arakawa Y, Sata M, Nishiguchi S, Yano M, Fujiyama S, Yamada G, Yokosuka O, Shiratori Y, Omata M: **Interferon therapy prolonged life expectancy among chronic hepatitis C patients.** *Gastroenterology* 2002, **123**:483-491.
8. Okanoue T, Itoh Y, Minami M, Sakamoto S, Yasui K, Sakamoto M, Nishioji K, Murakami Y, Kashima K: **Interferon therapy lowers the rate of progression to hepatocellular carcinoma in chronic hepatitis C but not significantly in an advanced stage: a retrospective study in 1148 patients. Viral Hepatitis Therapy Study Group.** *J Hepatol* 1999, **30**:653-659.
9. Mazzaferro V, Romito R, Schiavo M, Mariani L, Camerini T, Bhoori S, Capussotti L, Calise F, Pellicci R, Belli G, Tagger A, Colombo M, Bonino F, Majno P, Llovet JM, HCC Italian Task Force: **Prevention of hepatocellular carcinoma recurrence with alpha-interferon after liver resection in HCV cirrhosis.** *Hepatology* 2006, **44**:1543-1554.
10. Fried MW: **Side effects of therapy of hepatitis C and their management.** *Hepatology* 2002, **36(5 Suppl 1)**:237-244.
11. Russo MW, Fried MW: **Side effects of therapy for chronic hepatitis C.** *Gastroenterology* 2003, **124**:1711-1719.
12. Hoofnagle JH, Seeff LB: **Peginterferon and ribavirin for chronic hepatitis C.** *N Engl J Med* 2006, **355**:2444-2451.
13. Coates EA, Brennan D, Logan RM, Goss AN, Scopacasa B, Spencer AJ, Gorkic E: **Hepatitis C infection and associated oral health problems.** *Aust Dent J* 2000, **45**:108-114.
14. Coates EA, Walsh L, Logan R: **The increasing problem of hepatitis C virus infection.** *Aust Dent J* 2001, **46**:13-17.
15. Henderson L, Muir M, Mills PR, Spence E, Fox R, McCruden EA, Bagg J: **Oral health of patients with hepatitis C virus infection: a pilot study.** *Oral Dis* 2001, **7**:271-275.
16. Griffin SO, Barker LK, Griffin PM, Cleveland JL, Kohn W: **Oral health needs among adults in the United States with chronic diseases.** *J Am Dent Assoc* 2009, **140**:1266-1274.
17. Lee SC, Antony A, Lee N, Leibow J, Yang JQ, Soviero S, Gutekunst K, Rosenstraus M: **Improved version 2.0 qualitative and quantitative AMPLICOR reverse transcription-PCR tests for hepatitis C virus RNA: calibration to international units, enhanced genotype reactivity, and performance characteristics.** *J Clin Microbiol* 2000, **38**:4171-4179.
18. Sizmann D, Boeck C, Boelter J, Fischer D, Miethke M, Nicolaus S, Zadak M, Babiel R: **Fully automated quantification of hepatitis C virus (HCV) RNA in human plasma and human serum by the COBAS AmpliPrep/COBAS TaqMan system.** *J Clin Virol* 2007, **38**:326-333.
19. Dusheiko G, Schmilovitz-Weiss H, Brown D, McOmish F, Yap PL, Sherlock S, McIntyre N, Simmonds P: **Hepatitis C virus genotypes: an investigation of type-specific differences in geographic origin and disease.** *Hepatology* 1994, **19**:13-18.
20. Carrozzo M: **Oral diseases associated with hepatitis C virus infection. Part 1. sialadenitis and salivary glands lymphoma.** *Oral Dis* 2008, **14**:123-130.
21. Nagao Y, Hanada S, Shishido S, Ide T, Kumashiro R, Ueno T, Sata M: **Incidence of Sjögren's syndrome in Japanese patients with hepatitis C virus infection.** *J Gastroenterol Hepatol* 2003, **18**:258-266.
22. Serfaty L, Capeau J: **Hepatitis C, insulin resistance and diabetes: clinical and pathogenic data.** *Liver Int* 2009, **29(Suppl 2)**:13-25.
23. Nagao Y, Kawasaki K, Sata M: **Insulin resistance and lichen planus in patients with HCV-infectious liver diseases.** *J Gastroenterol Hepatol* 2008, **23**:580-585.
24. Nishimura F, Murayama Y: **Periodontal inflammation and insulin resistance - lessons from obesity.** *J Dent Res* 2001, **80**:1690-1694.
25. Nagao Y, Kawaguchi T, Ide T, Sata M: **HCV or HBV infection self-disclosure to dentist.** *Kansenshogaku Zasshi* 2008, **82**:213-219.

doi:10.1186/1743-422X-7-192
Cite this article as: Nagao and Sata: **Dental problems delaying the initiation of interferon therapy for HCV-infected patients.** *Virology Journal* 2010 **7**:192.

Nagao and Sata *Virology Journal* 2010, **7**:375
http://www.virologyj.com/content/7/1/375

VIROLOGY JOURNAL

RESEARCH Open Access

Serum albumin and mortality risk in a hyperendemic area of HCV infection in Japan

Yumiko Nagao[1*], Michio Sata[1,2†]

Abstract

Background: Hypoalbuminemia has been shown to be associated with increased mortality. We reported a mass screening in 1990 of X town in Japan, which demonstrated a high prevalence of hepatitis C virus (HCV) infection. This follow-up study determined, through a period of 12 years, whether serum albumin levels impact on the life prognosis of the residents of X town.

Results: Of the 509 subjects, 69 had died and 55 had moved to other regions by 2002. Therefore, we analyzed 454 people for whom we could confirm life and death between 1990 and 2002. Albumin levels were assigned to two groups, low (<4.0 g/L, group A) and normal (≥4.0 g/L, group B). Of the 454 subjects analyzed, 25 were in group A and 429 in group B and the mortality was 68.0% (17/25 cases, $P < 0.00001$ vs. group B) and 12.1% (52/429), respectively. Mortality from hepatocellular carcinoma (HCC) was 66.7% in group A (6/9 cases, $P = 0.01$ vs. group B) and 15.8% (3/19) in group B. According to multivariate analysis, five factors - 50 years or older, low albumin level (<4.0 g/L), abnormal AST level, history of smoking, and absence of alcohol consumption - were associated with death. The adjusted odds ratios for these five factors were 20.65, 10.79, 2.58, 2.24 and 2.08, respectively, and each was statistically significant.

Conclusions: We show that the serum albumin level is an independent risk factor for mortality from all causes in the residents of X town and an important prognostic indicator. Improvement of hypoalbuminaemia should be considered for improvement of prognosis.

Background

Hypoalbuminemia can be caused by various conditions, including nephrotic syndrome [1,2], heart failure [3], liver disease [4,5] and malnutrition [6]. Most cases of hypoalbuminemia among hospitalized patients are caused by acute and chronic inflammatory responses [7]. Moreover, a strong association has been reported between the serum albumin level and mortality [8]. The serum albumin level is an independent risk factor for all-cause mortality in older persons and an important prognostic indicator [9].

From 1990, we have continued carrying out health screenings of the residents of X town (adult population: 7,389) in northern Kyushu, Japan, where the prevalence of hepatitis C virus (HCV) infection is the highest in the country and the mortality from liver cancer is about three times the national average [10-23]. The positive rates of antibodies to HCV (anti-HCV), HCV RNA and hepatitis B surface antigen (HBsAg) were, respectively, 23.6%, 17.9%, and 2.6% in 1990 [15]. We demonstrated extrahepatic manifestations as well as the natural course and carcinogenesis of HCV-infected persons in X town.

There has been little discussion about hypoalbuminemia and mortality over the long term in residents of the area. In this study, we determined whether serum albumin levels impact on the life prognosis of the residents of X town after a follow-up period of 12 years.

Methods

Subjects

In 1990, 10% (739 people) of the 7,389 inhabitants were selected randomly and, as a result, 509 subjects participated in the study for examination of liver diseases accompanying HCV or hepatitis B virus (HBV) infections [15]. We studied 509 consecutive residents

* Correspondence: nagao@med.kurume-u.ac.jp
† Contributed equally
[1]Department of Digestive Disease Information & Research, Kurume University School of Medicine, Kurume, Fukuoka, 830-0011, Japan
Full list of author information is available at the end of the article

prospectively for 12 years. Of these 509 subjects, 69 had died and 55 had moved to other regions by May 31, 2002. Therefore, 385 of the original inhabitants investigated in 1990 continued to reside in X town in May 2002. Consequently, 454 residents, whose life and death could be confirmed between 1990 and 2002, were studied. The albumin levels were categorized into two groups, low (<4.0 g/L, group A) and normal (≥4.0 g/L, group B) and there were 25 subjects in group A and 429 in group B.

Serological assays

In 1990, sera were provided by the 454 subjects for the following serological assays: albumin, serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Sera were also examined for the presence or absence of markers of HCV and HBV infection. Anti-HCV was measured by a chemiluminescent enzyme immunoassay (CLEIA) kit (Lumipulse II HCV, Fujirebio Inc., Tokyo, Japan). HCV RNA was detected in the sera using the Amplicor HCV test (Nippon Roche, Tokyo, Japan). HBsAg was assayed by a chemiluminescent immunoassay (CLIA) kit (Architect™, HBsAg QT, Dainabot Co. Ltd., Tokyo, Japan). Ultrasonographic examination of subjects with abnormalities in their liver function tests and who were positive for anti-HCV or HBsAg was performed in order to investigate the shape of the liver and lesions occupying the hepatic space.

Physical examination

Obesity was defined as a body mass index (BMI) ≥ 25 kg/m^2 or greater. We also took a history of liver diseases, smoking, and alcohol consumption. We compared these factors between group A and group B. The total intake of alcohol was estimated on the basis of information about the consumption of beer, wine, whisky, Japanese sake, and shochu. In addition, the cumulative ethanol consumption up to 1990, expressed in kilograms, was calculated approximately by converting the alcohol intake in a serving of each type of alcoholic beverage into grams.

Analysis of cause of death of the 69 individuals who had died by 2002

Of the 509 inhabitants examined in 1990, 69 (34 men and 35 women; mean age at death, 76.6 years) had died by 2002. We compared the causes of death in group A and group B.

Statistical analysis

All data are expressed as mean ± standard error. Differences between the two groups were analyzed using the Mann-Whitney U test, Wilcoxon's test, and the Fisher's exact test. Differences were judged significant for $p < 0.05$ (two-tailed). Adjusted odds ratios were calculated using logistic regression analysis. All statistical analyses were conducted using JMP Version 6 (SAS Institute, Cary, NC, USA). The level of statistical significance was defined as 0.05. Survival analysis was carried out using the Kaplan-Meier method.

Results

Risk factors by univariate analysis

The details of the 454 subjects studied are shown in Table 1. We compared the characteristics of 25 subjects whose serum albumin was <4.0 g/L (group A) and 429 subjects whose serum albumin was ≥4.0 g/L (group B). The mean age in group A was 68.8 ± 14.5 years and there were 16 men and nine women. The mean age in group B was 51.9 ± 15.9 years and there were 180 men and 249 women. Being male ($P < 0.05$), elderly ($P < 0.0001$), having a history of liver diseases ($P < 0.01$), history of smoking ($P < 0.05$), abnormal AST level ($P < 0.01$), being positive for anti-HCV ($P = 0.0001$), positive for HCV RNA ($P < 0.001$), and occurrence of death ($P < 0.00001$) were significantly more common in group A than in group B (Table 1). Mortality was 68.0% in group A (17/25 cases, $P < 0.00001$ vs. group B) and 12.1% (52/429) in group B, as shown in Table 1 and Figure 1. No significant differences were observed between the two groups regarding BMI, alcohol consumption, ALT level, and positive rate of HBsAg.

Individuals were stratified according to cumulative ethanol consumption by 1990: non-drinkers (227, 50.0%), <10 kilogram (62, 13.7%), 10-50 kilogram (37, 8.1%), 50-100 kilogram (21, 4.6%), and ≥100 kilogram (107, 23.6%).

Table 1 Characteristics of subjects with low and normal albumin levels

	Group A Alb < 4.0 g/L n = 25		Group B Alb ≥ 4.0 g/L n = 429		P value
Age (mean ± SD), years	68.8 ± 14.5		51.9 ± 15.9		<0.0001
Sex (male/female)	16/9		180/249		<0.05
BMI ≥ 25	4	(16.0%)	54	(12.6%)	NS
History of liver diseases (yes)	15	(60.0%)	143	(33.3%)	<0.01
Alcohol consumption (yes)	13	(52.0%)	214	(49.9%)	NS
History of smoking (yes)	13	(52.0%)	139	(32.4%)	<0.05
AST (IU/L) (mean ± SD)	47.0 ± 45.8		23.6 ± 14.7		<0.01
ALT (IU/L) (mean ± SD)	44.0 ± 71.2		22.8 ± 21.4		NS
Anti-HCV, positive	14	(56.0%)	96	(22.4%)	0.0001
HCV RNA, positive	11	(44.0%)	67	(15.6%)	<0.001
HBsAg, positive	1	(4.0%)	9	(2.1%)	NS
Death by 2002	17	(68.0%)	52	(12.1%)	<0.00001

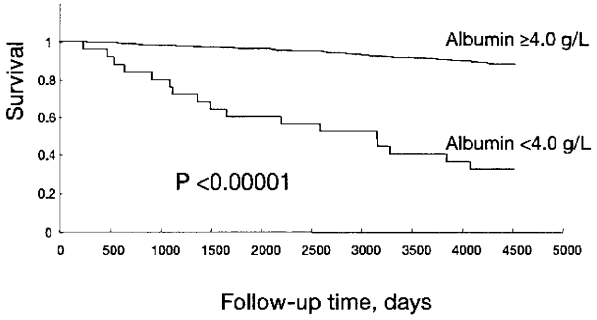


Figure 1 12-year cumulative survival from 1990 to 2002 according to serum albumin concentration. Mortality of group A (albumin < 4.0 g/L) and group B (albumin ≥ 4.0 g/L) was 68.0% (17/25 cases, P < 0.00001 vs. group B) and 12.1% (52/429), respectively.

Table 2 shows causes of death for groups A and B. The numbers of deaths from malignant tumor were 9 (52.9%) in group A and 19 (36.5%) in group B. These fatal malignant tumors were hepatocellular carcinoma (HCC, six), gastric cancer (two) and prostate cancer (one) in group A and lung cancer (six), colon cancer (four), HCC (three), gastric cancer (two), esophageal cancer (one), leukemia (one), malignant lymphoma (one) and unknown (one) in group B. Mortality from HCC was 66.7% (6/9 cases, P = 0.01 vs. group B) in group A and 15.8% (3/19) in group B. No significant differences were observed between these two groups in terms of the numbers of death from malignant tumors other than HCC.

No significant differences were observed between the two groups for mortality from cerebrovascular disease, cardiac disease, pneumonia, liver disease, diabetes mellitus, suicide, tuberculosis, a freak accident, feebleness of age, and others.

Table 2 Causes of death of subjects with low and normal albumin levels

		Group A Alb < 4.0 g/L n = 17		Group B Alb ≥ 4.0 g/L n = 52		P value
Malignant tumor	HCC	6	66.7%	3	15.8%	0.01
	gastric cancer	2	22.2%	2	10.5%	NS
	prostate cancer	1	11.1%	0	0.0%	NS
	lung cancer	0	0.0%	6	31.6%	NS
	colon cancer	0	0.0%	4	21.1%	NS
	esophageal cancer	0	0.0%	1	5.3%	NS
	leukemia	0	0.0%	1	5.3%	NS
	malignant lymphoma	0	0.0%	1	5.3%	NS
	unknown	0	0.0%	1	5.3%	NS
	total	9	52.9%	19	36.5%	NS
Cerebrovascular disease		0	0.0%	10	19.2%	NS
Cardiac disease		3	17.6%	6	11.5%	NS
Pneumonia		3	17.6%	6	11.5%	NS
Liver disease		1	5.9%	3	5.8%	NS
Diabetes mellitus		0	0.0%	2	3.8%	NS
Suicide		0	0.0%	2	3.8%	NS
Tuberculosis		0	0.0%	1	1.9%	NS
Freak accident		1	5.9%	1	1.9%	NS
Feebleness of age		0	0.0%	1	1.9%	NS
Other		0	0.0%	1	1.9%	NS

HCC, hepatocellular carcinoma

Multivariate analysis

According to multivariate analysis, five factors - 50 years or older, low albumin level (<4.0 g/L), abnormal AST level, history of smoking, and absence of alcohol consumption - were associated with death. The adjusted odds ratios for these five factors were 20.65, 10.79, 2.58, 2.24 and 2.08, respectively, and each was statistically significant (Table 3).

Cumulative ethanol consumption of <10 kilogram or 10-50 kilogram played an important role in survival. The adjusted odds ratios compared to absence of alcohol consumption were 6.44 (95% confidence interval: 1.93-39.92), and 7.72 (95% confidence interval: 1.62-138.46), respectively.

Discussion

Low serum albumin levels are an important predictor of morbidity and mortality [8,9] and correlate with an increased risk of morbidity and mortality in hospitalized patients. However, there has been little discussion about hypoalbuminemia and mortality of the residents of an area with an exceptionally high prevalence of HCV infection. In this study, we determined whether serum albumin levels affect the life prognosis of the residents of X town.

Our results indicate a strong association between hypoalbuminemia and mortality in this hyperendemic area of HCV infection in Japan. Residents with hypoalbuminemia had a mortality of 68.0%; dramatically higher than the rate of 12.1% among residents who had normal

Table 3 Results of multivariate analysis

	Adjusted odds ratio (95% confidence interval)				P value
50 years or older	20.65	7.08	-	88.71	<0.0001
Albumin < 4.0 g/L	10.79	4.02	-	32.75	<0.0001
Abnormal AST level (≥40 IU/L)	2.58	1.14	-	5.79	<0.05
History of smoking (yes)	2.24	1.08	-	4.65	<0.05
Non-alcohol consumption	2.08	1.03	-	4.36	<0.05

albumin levels. We previously reported that HCV infection and ALT value were associated with deaths due to HCC or liver cirrhosis in this X town [17]. We also showed that hypoalbuminemia was prognostic factor about all-cause mortality.

It is estimated that ~170 million people worldwide are infected with HCV [24], some two million (1%) of whom reside in Japan [25]. HCV leads to serious consequences such as liver cirrhosis and HCC. Of the HCC cases in Japan, around 16% are caused by hepatitis B virus (HBV) infection and around 80% by HCV infection. The increase in the number of HCC patients due to HCV contributes to the increase in total deaths in Japan from HCC. This trend is expected to continue until 2015 [25].

Albumin, produced only by the liver, is the major protein that circulates in the blood. Albumin consists of 585 amino acids, has a molecular weight of approximately 69 kDa and is the most abundant plasma protein, although 60% of the total albumin pool is in the interstitial space [26]. Albumin is essential for maintaining the oncotic pressure in the vascular system. A decrease in oncotic pressure due to a low albumin level allows fluid to leak from the interstitial spaces into the peritoneal cavity, producing ascites. Albumin is also very important in the transportation of various molecules, including bilirubin, free fatty acids, drugs, and hormones. Serum albumin is an abundant multifunctional non-glycosylated, negatively charged plasma protein, with ascribed ligand-binding and transport properties, antioxidant functions, and enzymatic activities [27].

A low serum albumin concentration indicates poor liver function. Decreased serum albumin levels are not seen in acute liver failure because it takes several weeks of impaired albumin production until the serum albumin level drops. The most common reason for a low albumin is chronic liver failure caused by cirrhosis. The serum albumin concentration is usually normal in chronic liver disease, until cirrhosis and significant liver damage develops. In advanced liver disease, the serum albumin level may be less than 3.5 g/dl. The albumin level is clinically important as a predictive factor for patients with liver cirrhosis, because decreased serum albumin levels cause ascites and edema.

Recent studies have demonstrated the efficacy of branched-chain amino acid (BCAA) supplementation in improving hypoalbuminemia in cirrhotic patients [28]. Kotho et al. investigated the correlation between albumin levels and the fat-free mass in cirrhotic patients [29]. They showed that exercise and protein-rich nutrition at the early stage of liver cirrhosis may be advisable for maintaining or increasing muscular volume. Nishiguchi et al reported that if cirrhotic patients were in the compensated stage at the entry but with lower BCAA tyrosine ratio (BTR), oral BCAA supplementation might be effective in maintaining serum albumin [30]. Stating appropriate nutritional interventions, such as supplementation of BCAA, in the early stage of cirrhosis may improve prognosis and maintain QOL. We also reported that the administration of BCAA supplement (Aminofeel®) increases serum albumin levels and serum zinc levels, and improves sensitivity to different tastes [31-33].

Conclusions

In conclusion, we demonstrated that the serum albumin level is an independent risk factor for mortality from all causes and an important prognostic indicator in the residents of X town. In particular, improvement of hypoalbuminaemia as well as the eradication of HCV, such as by interferon therapy, should be considered for improvement of prognosis in this hyperendemic area of HCV infection in Japan.

Abbreviations

HBV: hepatitis B virus; HBsAg: hepatitis B surface antigen; HCV: hepatitis C virus; anti-HCV: anti-bodies to HCV; HCC: hepatocellular carcinoma; CLEIA: chemiluminescent enzyme immunoassay; BCAA: branched-chain amino acids

Acknowledgements

This study was supported in part by a Grant-in-Aid for Scientific Research (C) (No. 22592354) from the Ministry of Education, Culture, Sports, Science and Technology of Japan, and was supported in part by Health and Labour Sciences Research Grants for Research on Hepatitis from the Ministry of Health, Labour and Welfare of Japan.

Author details

[1]Department of Digestive Disease Information & Research, Kurume University School of Medicine, Kurume, Fukuoka, 830-0011, Japan. [2]Division of Gastroenterology, Department of Medicine, Kurume University School of Medicine, Kurume, Fukuoka, 830-0011, Japan.

Authors' contributions

YN carried out most of the data collection and drafted the manuscript. MS contributed to data analysis. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Received: 5 November 2010 Accepted: 31 December 2010
Published: 31 December 2010

References

1. Fliser D, Zurbruggen I, Mutschler E, Bischoff I, Nussberger J, Franek E, Ritz E: **Coadministration of albumin and furosemide in patients with the nephrotic syndrome.** *Kidney Int* 1999, **55**:629-634.
2. de Seigneux S, Martin PY: **Management of patients with nephrotic syndrome.** *Swiss Med Wkly* 2009, **139**:416-422.
3. Djoussé L, Rothman KJ, Cupples LA, Levy D, Ellison RC: **Serum albumin and risk of myocardial infarction and all-cause mortality in the Framingham Offspring Study.** *Circulation* 2002, **106**:2919-2924.
4. Faloon WW, Eckhardt RD, Murphy TL, Cooper AM, Davidson CS: **An Evaluation of human serum albumin in the treatment of cirrhosis of the liver.** *J Clin Invest* 1949, **28**:583-594.
5. Rothschild MA, Oratz M, Schreiber SS: **Effects of nutrition and alcohol on albumin synthesis.** *Alcohol Clin Exp Res* 1983, **7**:28-30.

6. Kuzuya M, Izawa S, Enoki H, Okada K, Iguchi A: **Is serum albumin a good marker for malnutrition in the physically impaired elderly?** *Clin Nutr* 2007, **26**:84-90.
7. Herrmann FR, Safran C, Levkoff SE, Minaker KL: **Serum albumin level on admission as a predictor of death, length of stay, and readmission.** *Arch Intern Med* 1992, **152**:125-130.
8. Goldwasser P, Feldman J: **Association of serum albumin and mortality risk.** *J Clin Epidemiol* 1997, **50**:693-703.
9. Corti MC, Salive ME, Guralnik JM: **Serum albumin and physical function as predictors of coronary heart disease mortality and incidence in older persons.** *J Clin Epidemiol* 1996, **49**:519-526.
10. Yamakawa Y, Sata M, Suzuki H, Noguchi S, Tanikawa K: **Higher elimination rate of hepatitis C virus among women.** *J Viral Hepat* 1996, **3**:317-321.
11. Noguchi S, Sata M, Suzuki H, Mizokami M, Tanikawa K: **Routes of transmission of hepatitis C virus in an endemic rural area of Japan.** *Scand J Infect Dis* 1997, **29**:23-28.
12. Fukuizumi K, Sata M, Suzuki H, Nakano H, Tanikawa K: **Hepatitis C virus seroconversion rate in a hyperendemic area of HCV in Japan: a prospective study.** *Scand J Infect Dis* 1997, **29**:345-347.
13. Fukuizumi K, Sata M, Suzuki H, Kumashiro R, Tanikawa K: **Natural disappearance of serum HCV RNA: prospective study in a hyperendemic area.** *Hepatol Res* 1997, **9**:144-151.
14. Nagao Y, Sata M, Fukuizumi K, Tanikawa K, Kameyama T: **High incidence of oral precancerous lesions in a hyperendemic area of hepatitis C virus infection.** *Hepatol Res* 1997, **8**:173-177.
15. Sata M, Nakano H, Suzuki H, Noguchi S, Yamakawa Y, Tanaka E, Fukuizumi K, Tanaka K, Yoshida H, Tanikawa K: **Sero-epidemiologic study of hepatitis C virus infection in Fukuoka, Japan.** *J Gastroenterol* 1998, **33**:218-222.
16. Nagao Y, Sata M, Fukuizumi K, Ryu F, Ueno T: **High incidence of oral lichen planus in HCV hyperendemic area.** *Gastroenterology* 2000, **119**:882-883.
17. Nagao Y, Fukuizumi K, Kumashiro R, Tanaka K, Sata M: **The prognosis for life in an HCV hyperendemic area.** *Gastroenterology* 2003, **125**:628-629.
18. Nagao Y, Tanaka K, Kobayashi K, Kumashiro R, Sata M: **A cohort study of chronic liver disease in an HCV hyperendemic area of Japan: a prospective analysis for 12 years.** *Int J Mol Med* 2004, **13**:257-265.
19. Nagao Y, Tanaka K, Kobayashi K, Kumashiro R, Sata M: **Analysis of approach to therapy for chronic liver disease in an HCV hyperendemic area of Japan.** *Hepatol Res* 2004, **28**:30-35.
20. Kawaguchi T, Nagao Y, Tanaka K, Harada M, Kumashiro R, Sata M: **Causal relationship between hepatitis C virus core and the development of type 2 diabetes mellitus in a hepatitis C virus hyperendemic area: a pilot study.** *Int J Mol Med* 2005, **16**:109-114.
21. Nagao Y, Kawaguchi T, Tanaka K, Kumashiro R, Sata M: **Extrahepatic manifestations and insulin resistance in an HCV hyperendemic area.** *Int J Mol Med* 2005, **16**:291-296.
22. Tanaka K, Nagao Y, Ide T, Kumashiro R, Sata M: **Antibody to hepatitis B core antigen is associated with the development of hepatocellular carcinoma in hepatitis C virus-infected persons: a 12-year prospective study.** *Int J Mol Med* 2006, **17**:827-832.
23. Nagao Y, Kawakami Y, Yoshiyama T, Sata M: **Analysis of factors interfering with the acceptance of interferon therapy by HCV-infected patients.** *Med Sci Monit* 2008, **14**:PI45-52[http://www.medscimonit.com/fulltxt.php?ICID=869425].
24. **Global surveillance and control of hepatitis C. Report of a WHO Consultation organized in collaboration with the Viral Hepatitis Prevention Board, Antwerp, Belgium.** *J Viral Hepat* 1999, 6:35-47.
25. Yoshizawa H: **Hepatocellular carcinoma associated with hepatitis C virus infection in Japan: projection to other countries in the foreseeable future.** *Oncology* 2002, **62(Suppl 1)**:8-17.
26. Don BR, Kaysen G: **Serum albumin: relationship to inflammation and nutrition.** *Semin Dial* 2004, 17:432-437.
27. Quinlan GJ, Martin GS, Evans TW: **Albumin: biochemical properties and therapeutic potential.** *Hepatology* 2005, **41**:1211-1219.
28. Marchesini G, Bianchi G, Merli M, Amodio P, Panella C, Loguercio C, Rossi Fanelli F, Abbiati R, Italian BCAA Study Group: **Nutritional supplementation with branched-chain amino acids in advanced cirrhosis: A double blind, randomized trial.** *Gastroenterology* 2003, **124**:1792-1801.
29. Kotoh K, Nakamuta M, Fukushima M, Matsuzaki C, Enjoji M, Sakai H, Nawata H: **High relative fat-free mass is important for maintaining serum albumin levels in patients with compensated liver cirrhosis.** *World J Gastroenterol* 2005, **11**:1356-1360.
30. Nishiguchi S, Habu D: **Effect of oral supplementation with branched-chain amino acid granules in the early stage of cirrhosis.** *Hepatol Res* 2004, **30S**:36-41.
31. Kawaguchi T, Taniguchi E, Itou M, Sumie S, Oriishi T, Matsuoka H, Nagao Y, Sata M: **Branched-chain amino acids improve insulin resistance in patients with hepatitis C virus-related liver disease: report of two cases.** *Liver Int* 2007, **27**:1287-1292.
32. Kawaguchi T, Nagao Y, Matsuoka H, Ide T, Sata M: **Branched-chain amino acidenriched supplementation improves insulin resistance in patients with chronic liver disease.** *Int J Mol Med* 2008, **22**:105-112.
33. Nagao Y, Matsuoka H, Kawaguchi T, Sata M: **Aminofeel® improves the sensitivity to taste in patients with HCV-infected liver disease.** *Med Sci Monit* 2010, **16**:PI7-12 [http://www.medscimonit.com/fulltxt.php?ICID=878481].

doi:10.1186/1743-422X-7-375
Cite this article as: Nagao and Sata: **Serum albumin and mortality risk in a hyperendemic area of HCV infection in Japan.** *Virology Journal* 2010 7:375.

Session 3 肝外病変

〈演題2〉HCV感染とB cell clonality, 口腔癌, インスリン抵抗性についての検討

佐田 通夫*, **・長尾 由実子**・大坪 維範***
岡村 孝***

はじめに

C型肝炎ウイルス(HCV)は、肝疾患だけでなく肝疾患以外の重篤な疾患の発症にも関与している。悪性新生物としては、悪性リンパ腫と口腔扁平上皮癌が、肝外病変の代表疾患である。一方、発癌のメカニズムについては不明のままである。本研究では、HCVと発癌との関連や病態を明らかにするために、HCV陽性者における末梢血Bリンパ球のclonality解析並びに口腔扁平上皮癌患者におけるHCVと重複癌との関連について検討した[1) 2)]。

研究1：HCV陽性者における末梢血Bリンパ球のclonality解析

A. 目的

フローサイトメトリーを用いて、HCV陽性者における末梢血Bリンパ球のclonality解析を行ない、その発生頻度を検討する。さらに、clonalな増殖を示すB細胞の性状について精査することにより、HCVとリンパ増殖性疾患との関連を検討する。

B. 対象と方法

HCV感染者240例(インターフェロン治療、化学療法、免疫療法施行中、リンパ腫瘍・血液疾患を有する患者は除く)と、HCV非感染者150例(コントロール)の末梢血リンパ球をCD19、κ, λの3種の抗体を用いて染色し、B細胞のκ, λの発現比率を解析し、clonalityの有無を検討した。Clonality陽性例では、CD5, CD20染色を追加し、免疫グロブリン重鎖遺伝子の再構成(IgH rearrangement)とBcl-2/IgH(t(14 ; 18)転座の有無に関してPCR法を用いて検討した。

C. 結果

HCV感染者と非感染者の間では、年齢、性別、白血球数、T. Bil値に有意な差は認められなかった。血清ALT値は、HCV感染者56.0±36.9IU、非感染者 38.3±70.0 IUと有意差があった(p<0.001)。

一方、HCV感染者240例中では、7例(2.9%)にclonalなBリンパ球増殖が認められたのに対し、コントロールでは認めなかった(p<0.05)。7例全てにIgH rearrangementが確認され、Bcl-2/IgH(t(14 ; 18)転座は7例中1例で陽性であった(表1, 図1)。

Clonalに増殖したBリンパ球のCD5発現強度は均一ではなく、正常のBリンパ球と比較して有意差は認めなかった。7例中2例がインターフェロン治療を受けたが、2例ともにclonalなBリンパ球の消失がみられた。

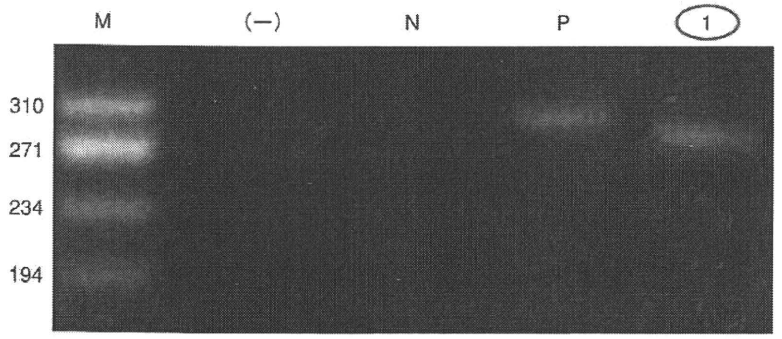
*久留米大学医学部 内科学講座消化器内科部門〔〒830-0011 福岡県久留米市旭町67〕
**久留米大学医学部 消化器疾患情報講座
***久留米大学医学部 内科学講座血液・腫瘍内科学部門

表1　The clinical data of the 7 cases with monoclonal B cells

Case No	Age	Sex	Cryoglobulin	HCV genotype	WBC count./uL	Lymphocyte count./uL	CD19+ cells in lymphocytes, %	Light chain	κ/λ raio	CD5+ B cell, %
1	78	M	+	2a	2,800	710	26.46	κ	33.59	17.45
2	65	M	−	2a	3,400	720	5.41	λ	0.23	15.93
3	84	M	+	1b	5,700	3,520	46.68	κ	11.31	6.8
4	74	F	−	1b	3,300	1,750	15.01	λ	0.037	46.31
5	65	F	+	1b	2,500	580	34.46	κ	8.07	40.17
6	72	F	−	1b	2,000	940	25.4	λ	0.198	38.77
7	66	M	+	1b	4,200	1,380	9.73	λ	0.41	3.53

Ohtsubo K, Sata M et al : *Int J Haematol* 89 : 452-459, 2009.

図1　Analysis of the presence of t(14 ; 18) fusion gene in the 7 cases



The amplified products generated by using primers for the minor cluster region (mcr) of the *bcl-2* gene were analyzed by 8% polyacrylamide gel electrophoresis.
M, molecular-weigt marker ; N, negative control ; P, positive control ; lane 1, case 1

Ohtsubo K, Sata M et al : *Int J Haematol* 89 : 452-459, 2009.

D. 考察

本研究では、clonalなBリンパ球の増殖がコントロール患者と比較して、HCV感染者の末梢血に有意に多く認められた[1]。この事実は、HCVがリンパ球をclonalに増殖させる作用があることを示唆する。さらに、HCVの消失と出現がclonalなBリンパ球の消失と再燃に並行する事実は、HCVとリンパ増殖性疾患との関係を強く示唆するものである。

海外の論文では、PCR法を用いてHCV感染者の末梢血にclonalなBリンパ球が存在することは示されているが、その集団がBリンパ球集団全体の中で、どの程度を占めるかは検討されていない。筆者らは、フローサイトメトリーを用いて同内容を検討した。その結果、Bリンパ球数は正常範囲を維持しつつ、その中でclonalな腫瘍性Bリンパ球が大多数を占めていることが示された。

また、HCV感染に伴うCD5陽性Bリンパ球の増殖に関しては以前よりいくつかの報告はあるが、見解は一致していない。そこで本研究では、HCV陽性者においてclonalに増殖することが確認されたBリンパ球のCD5発現に関して、正常リンパ球と比較して検討した。

その結果、HCV関連のclonalなBリンパ球は正常Bリンパ球と同様、個々の細胞によりそのCD5発現強度が異なり、またCD5陽性細胞の占める割合も正常Bリンパ球と比較して有意差はないという事実が示された。これは、末梢血で増殖するHCV関連clonal Bリンパ球細胞は、「慢

性リンパ性白血病細胞」とは異なるphenotype細胞であることを示している。

HCV関連clonal Bリンパ球細胞が、将来悪性リンパ腫、クリオグロブリン血症などのリンパ増殖性疾患へと進展していくか否かに関して、今後の経時的観察が必要である。

研究2：口腔扁平上皮癌患者におけるHCVと重複癌とインスリン抵抗性

A. 目的

口腔扁平上皮癌(SCC)患者は、消化器癌(食道癌、胃癌、大腸癌)の中でHCV感染率が高く(24%)、コントロール患者より有意にHCV感染率が高率である[3]。このことは、国内多施設共同研究(北海道大・神奈川がんセンター・日本大・熊本大・久留米大)においても、頭頸部SCC患者は、コントロール患者よりも有意にHCV感染率が高率であることがわかっている[4]。

一方、1974年～1995年までの口腔SCC患者327例における多重複癌例は57例(17.4%)であり、その重複臓器は胃に続き、肝臓が第2位である。重複癌患者のHCV感染率(36.7%)は有意に高率である[5]。

さらに、HCV感染者の口腔SCC組織において、(＋)鎖及び(－)鎖のHCV RNAの存在を確認した[6][7]。

頭頸部SCCは、全身の癌を母集団とした場合に比較して、有意に多重複癌の発症率が高い。また、頭頸部における多重複癌症例は、年々増加している。一方、口腔SCCは、HCV感染が引き起こす肝外病変である。

本調査では、1992年～1994年に口腔SCCを発症し、初めて久留米大学病院を受診し入院加療した患者60例について、HCV感染者と非感染者における重複癌について検討した。

B. 研究方法

全対象患者は、初診時もしくは入院時に上部消化管検査、腹部エコー検査、生化学検査、肝炎ウイルスマーカーが検査された。

重複癌発生の観察期間は、久留米大学初診から最終再来日まで(2008年10月17日直近日)とした。レトロスペクティブにカルテを調査すると共に、全診療科から提出された病理組織学的診断を確認した。

重複癌の定義は、(i) 個々の腫瘍は、明らかに悪性像を呈する、(ii) 個々の腫瘍は、別個に存在する、(iii) 一方の腫瘍は、他方からの転移ではないとした。第1癌と第2癌の診断間隔が6ヵ月未満を同時性、6ヵ月以上を異時性とした。口腔内に複数の腫瘍が多発した場合は、同じ組織型は口腔多発癌、異なる組織型は重複癌とし、今回の検討では口腔多発癌は除外した。

C. 結果

口腔SCC患者60例において、多重複癌の発生率は35%(21/60)、HCV抗体陽性率は26.7%(16/60)であった。

HCV抗体陽性者における多重複癌発生率(62.5%)は、HCV抗体陰性者(25%)よりも有意に高率であった。HCV抗体陽性者における多重複癌として最も多く認められた臓器は肝臓であり、HCV抗体陰性者では胃であった(表2)。

重複癌21例と口腔単発癌39例における有意な因子は、肝疾患の既往歴、輸血歴、HCV抗体陽性率であった。多変量解析により重複癌発生に関わる因子は、StageⅣ、HCV抗体陽性、70歳以上の年齢層であった(表3)。

HCV感染のある重複癌患者(SCC)は、HCV感染も重複癌も認めないSCC患者よりも、初診時のインスリン値が有意に高かった(図2)。

表2　HCV感染有無による重複癌の発生

		HCV抗体陰性 n=44(%)	HCV抗体陽性 n=16(%)	p value
年　齢		64.3±14.5	66.1±11.0	NS
男性・女性		30・14	9・7	NS
重複癌	発生数	11(25.0)	10(62.5)	p<0.01
	発生臓器	胃 6 食道 2 皮膚 2 甲状腺 1 咽頭 1 腎臓 1 肝臓 1	肝臓 5 大腸 2 肺 1 甲状腺 1 AML 1	
	発生時期	同時性6・異時性6※	同時性5・異時性5	

※歯肉ー食道ー皮膚の同時性癌発症後、異時性に下咽頭癌発症症例あり

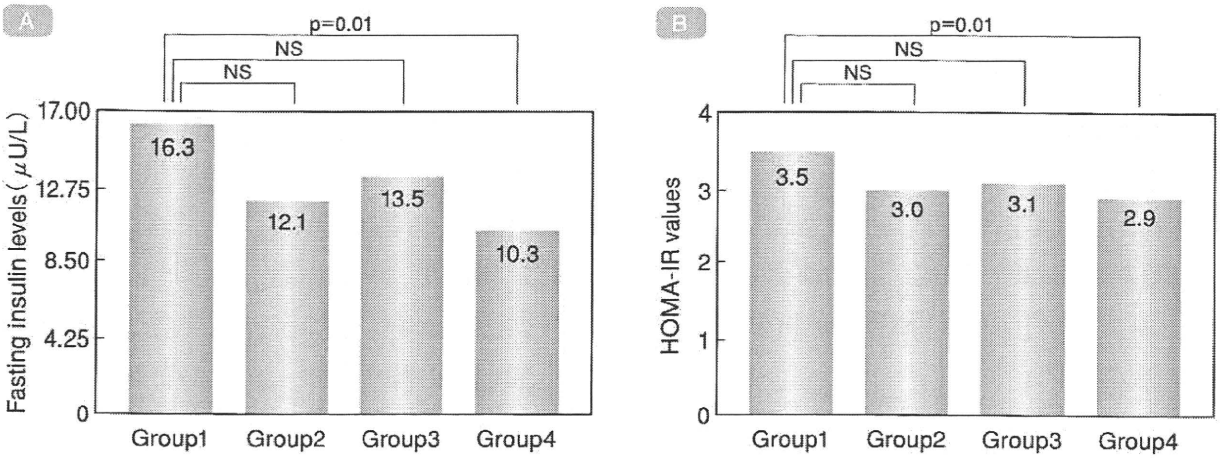
Nagao Y, Sata M：*Med Sci Monit* **15**：453-459, 2009.

表3　多変量解析による重複癌発生因子

	Adjusted odds ratio (95% confidence interval)		p value
StageⅣ	15.50	(0.39-2.58)	p=0.0124
HCV抗体陽性	13.45	(0.50-2.30)	p=0.0039
70歳以上	4.46	(0.04-1.56)	p=0.0480

Nagao Y, Sata M：*Med Sci Monit* **15**：453-459, 2009.

図2　重複癌とインスリン抵抗性



	Group1	Group2	Group3	Group4
重複癌	あり	あり	なし	なし
HCV感染	あり	なし	あり	なし
n	10	11	6	33
平均年齢	67.9	66.8	63.2	63.4

Nagao Y, Sata M：*Med Sci Monit* **15**：453-459, 2009.

D. 考察

わが国で1997年～2001年までに全国で病理解剖された症例総数は34,997例であり、このうち舌癌剖検症例は321例である。321例中、多重複癌発生率は35.2%(113/321)で、発生臓器は、肺、肝臓、食道、甲状腺等と報告されている。国内における舌癌剖検症例の重複臓器の第2位が肝臓であることから、HCVと口腔SCCは強い関連があることが推測された。

今回の結果により、HCV感染のある口腔SCC患者では、とくに多重複癌について注意深く経過観察する必要がある。一方、HCV感染者においても肝疾患以外の疾患について診査するべきである。またHCV感染者に多重複癌が多い理由や、発癌のメカニズムを明らかにする必要がある。

〈文 献〉

1) Ohtsubo K, Sata M, Kawaguchi T et al : Characterization of the light chain-restricted clonal B cells in peripheral blood of HCV-positive patients. *Int J Hematol* **89** : 452-459, 2009.
2) Nagao Y and Sata M : High incidence of multiple primary carcinomas in HCV-infected patients with oral squamous cell carcinoma. *Med Sci Monit* **15** : 453-459, 2009.
3) Nagao Y, Sata M, Tanikawa K et al : High prevalence of hepatitis C virus antibody and RNA in patients with oral cancer. *J Oral Pathol Med* **24** : 354-360, 1995.
4) Nagao Y, Sata M, Itoh K et al : High prevalence of hepatitis C virus antibody and RNA in patients with head and neck squamous cell carcinoma. *Hepatol Res* **7** : 206-212, 1997.
5) Yoshida M, Nagao Y, Sata M et al : Multiple primary neoplasms and hepatitis C virus infection in oral cancer patients. *Heparol Res* **9** : 75-81, 1997.
6) Nagao Y, Kameyama T, Sata M : Hepatitis C virus RNA detection in oral lichen planus tissue. *Am J Gastroenterol* **93** : 850, 1998.
7) Nagao Y, Sata M, Noguchi S et al : Detection of hepatitis C virus RNA in oral lichen planus and oral cancer tissues. *J Oral Pathol Med* **29** : 259-266, 2000.

*　　*　　*

討　論

【小池】ありがとうございました。前半はB cell clonality、後半は口腔内の扁平上皮癌とHCV感染の関係についてお話いただきました。佐田先生のご施設では、B cell clonalityが2.9％ですね。井廻先生のご報告では10.7％でしたので、それに比べると少し低いですね。

それでは、ご質問はございませんか。

【石橋】以前から口腔癌との関係については聞かせていただいておりますが、どのような原因が考えられますか。

【佐田】HCVが関与する口腔癌は、白板症や扁平苔癬などの前癌病変を経て発症することがあります。HCV感染のある口腔癌がなぜ重複癌を発症するかは明らかではありません。われわれの検討からは、HCV感染によって引き起こされるインスリン抵抗性の病態が重複癌の発症に何らかの影響を及ぼしている可能性はあると思われます。

【石橋】CD-81などのレセプターは証明されているのですか。

【佐田】レセプターとの関係は、まだ検討しておりません。ただ言えることは、口腔癌の患者さんの組織中に見られるHCVのアミノ酸配列と、血中で見られる配列は異なります。HCV側の因子と生体側の因子の両方があると思いますが、現時点ではよくわかっていません。

【小池】以前、扁平苔癬にHCVが存在するとお聞きしたことがありますが、前癌病変と考えられるところでも同じですか。

【佐田】ええ、同じです。

＊　　＊　　＊

C型肝炎の臨床最前線
肝胆膵増刊号

IFN治療普及のための戦略

長尾　由実子[*1]　佐田　通夫[*1,*2]

索引用語：医療連携，インターフェロン治療，肝臓専門医，消化器病教室

1 はじめに

ペグインターフェロン(Peg-IFN)・リバビリン併用療法は，わが国におけるC型慢性肝炎に対する標準治療である．現在，治療の副作用に関する軽減と治癒率の向上を目指した種々の解析や工夫が検討されている．

しかし，どんなに優れた薬物療法であっても，IFN療法の適応患者に治療が導入されなければ価値はない．IFN治療を適切に普及するためには，どのような戦略が必要なのだろうか？　ここでは，IFN治療の導入が妨げられている要因について解析した内容を報告する．

2 患者中心の医療

インターネットの普及により病気に関する知識や情報の共有化が進む一方で，医療現場を取り巻く環境も変化している．このようなわが国の医療環境の変化に伴い，「患者の視点に立って考える医療」が医療の在り方を見直すものとして注目されている．従来の医師にすべてを委ねる医師中心の医療ではなく，患者の意思と判断を尊重した，いわゆる患者中心の医療である．

患者中心の医療を実現するためには，患者自身も医療に参加する必要がある．その医療を選択する根拠として，EBM(Evidenced Based Medicine)すなわち科学的根拠に基づいた医療の実践が求められる時代を迎えている．

医薬品が発売後も長く消費できるかどうかは，主要疾患や医療習慣の要因に加え，保険制度・薬価制度や医薬品に関する法規なども密接に影響する[1]．一方で，優れた薬物療法を普及させるためには，患者の視点に立って考える医療，すなわち医師による患者教育が受療率の向上につながるポイントの一つではないかと考える．

3 日本の現状

日本における急速な高齢化は，死亡原因の変化をもたらしている．1981年以降，悪性新生物による死亡が死因の第1位となり，今

Yumiko NAGAO et al: Strategy to use IFN therapy widely for HCV carriers in Japan
*1 久留米大学医学部消化器疾患情報講座［〒830-0011 福岡県久留米市旭町67］
*2 同 内科学講座消化器内科部門