[20] Furusyo N, Hayashi J, Ohmiya M, Sawayama Y, Kawakami Y, Ariyama I, et al. Differences between interferon-alpha and -beta treatment for patients with chronic hepatitis C virus infection. Dig Dis Sci 1999;44:608–17.

[21] Barbaro G, Di Lorenzo G, Soldini M, Giancaspro G, Pellicelli A, Grisorio B, et al. Intravenous recombinant interferon-beta versus interferon-alpha-2b and ribavirin in combination for short-term treatment of chronic hepatitis C patients not responding to interferon-alpha. Multicenter Interferon Beta Italian Group Investigators. Scand J Gastroenterol 1999;34:928–33.

[22] Oketani M, Higashi T, Yamasaki N, Shinmyozu K, Osame M, Arima T. Complete response to twice-a-day interferon-beta with standard interferon-alpha therapy in acute hepatitis C after a needle-stick. J Clin Gastroenterol 1999;28:49–51.

[23] Izumi N, Kumada H, Hashimoto N, Harada H, Imawari M, Zeniya M, et al. Rapid decrease of plasma HCV RNA in early phase of twice daily administration of 3(MU doses interferon-beta in patients with genotype 1b hepatitis C infection: a multicenter randomized study. Dig Dis Sci 2001;46:516–23.

[24] Asahina Y, Izumi N, Uchihara M, Noguchi O, Tsuchiya K, Hamano K, et al. A potent antiviral effect on hepatitis C viral dynamics in serum and peripheral blood mononuclear cells during combination therapy with high-dose daily interferon alfa plus ribavirin and intravenous twice-daily treatment with interferon beta. Hepatology 2001;34:377–84.

[25] Watanabe H, Iwata K, Sohda T, Sakisaka S. Interferon beta induction/interferon alpha therapy in patients with interferon-resistant chronic hepatitis C. Hepatol Res 2002;24:355–60.

Short-term Interferon-alfa Therapy for Acute Hepatitis C: A Randomized Controlled Trial

Hideyuki Nomura,[1] Suketo Sou,[1] Hironori Tanimoto,[1] Takashi Nagahama,[1] Yoichi Kimura,[2] Jun Hayashi,[3] Hiromi Ishibashi,[4] and Seizaburo Kashiwagi[5]

Acute hepatitis C often progresses to chronic infection. We undertook a randomized controlled trial to determine whether short-term therapy with interferon (IFN) during acute hepatitis C is effective in preventing the development of chronic hepatitis. Thirty patients with acute hepatitis C were randomized into 1 of 2 treatment groups. IFN therapy was initiated 8 weeks after the onset of acute hepatitis in the early-intervention group and after 1 year of observation in the late-intervention group. Short-term therapy consisted of natural IFN-alfa (6 million units) administered on consecutive days for a period of 4 weeks. Any signs of recrudescence of disease were immediately followed by interval IFN therapy (3 times weekly for 20 weeks). In the early-intervention group, short-term therapy was associated with a sustained virological response in 13 of 15 patients (87%). Follow-up treatment was associated with a sustained virological response in both of the remaining 2 patients (100%). The sustained virological response rate was significantly higher in the early-intervention group (87%, 13 of 15 patients after short-term therapy alone, and 100%, 15 of 15 patients after short-term with or without follow-up therapy) than in the late-intervention group (40%, 6 of 15 patients after short-term therapy alone, and 53%, 8 of 15 patients after short-term therapy with or without follow-up therapy, $P = .021$ and $P = .006$, respectively). In conclusion, short-term (4 weeks) IFN treatment of patients with acute hepatitis C may be associated with satisfactory results, if initiated at an early stage of the disease. (HEPATOLOGY 2004;39:1213–1219.)

Acute hepatitis that develops after infection with the hepatitis C virus (HCV) is often followed by chronic hepatitis, which may progress eventually to cirrhosis and hepatocellular carcinoma (HCC).[1,2] In the past, the primary causes of infection with HCV were blood transfusion and various medical procedures. Today, blood products in Japan are aggressively screened for HCV and disposable medical devices are in widespread use; there has been a reduction in the incidence of HCV infection. However, patients with acute hepatitis C resulting from treatment-related accidents (needle-stick injury), intravenous drug abuse, sexual contact with HCV-positive partners and unknown causes still occasionally present.[3–5] Interferon (IFN) therapy in patients with chronic hepatitis C has considerable potential for preventing the development of HCC, either by eradicating HCV, or by decreasing the activity of hepatitis.[6–9] However, the therapeutic effects of IFN vary depending on the HCV genotype and viral load.[10,11]

Although much research has already been undertaken on IFN therapy for acute hepatitis C, findings in trials that relate to the effectiveness of this therapy have not been particularly favorable. Possible reasons include differences in types of IFN, differences in study populations, and inclusion of patients with posttransfusion hepatitis.[12–17] However, Jaeckel et al.[3] reported that a 24-week course of IFN therapy was effective, and that the response to IFN treatment was more favorable in acute hepatitis C than in chronic hepatitis C. Although randomized controlled trials have been used to study the effects of IFN therapy on acute hepatitis C, so far there have been no

Abbreviations: HCV, hepatitis C virus; HCC, hepatocellular carcinoma; IFN, interferon; ALT, alanine aminotransferase; ULN, upper limit of the normal range; MU, million units; HLBI, human lymphoblastoid interferon.

From the [1]Department of Internal Medicine, Shin-Kokura Hospital, Fukuoka, Japan; the [2]Department of Medicine and Biosystemic Science, Internal Medicine, Medicine and Surgery, Kyushu University Graduate School of Medical Sciences, Fukuoka, Japan; the [3]Department of Environmental Medicine and Infectious Diseases, Faculty of Medical Sciences, Kyushu University, Fukuoka, Japan; [4]Clinical Research Center, National Nagasaki Medical Center, Omura, Nagasaki, Japan; and [5]Fukuoka Red Cross Blood Center, Fukuoka, Japan.

Received May 19, 2003; accepted February 2, 2004.

Address reprint requests to: Hideyuki Nomura, MD, Dept. of Internal Medicine, Shin-Kokura Hospital, 1-3-1, Kanada, Kokurakita-ku, Kitakyushu, Fukuoka 803-8505, Japan. E-mail: h-nomura@shin-kokura.gr.jp; fax: 81-93-591-0553.

Published online in Wiley InterScience (www.interscience.wiley.com).
DOI 10.1002/hep.20196

reports on the most suitable duration of IFN treatment or timing of its initiation.

Short-term (4 weeks) IFN therapy was administered at an early stage of acute hepatitis in patients who met strict diagnostic criteria for acute hepatitis C. The objective was to corroborate the effectiveness of short-term IFN therapy in the treatment of this condition. A randomized controlled trial was designed to determine the appropriate duration of treatment and the timing of initiation of treatment with IFN therapy for acute hepatitis C. The results indicated that it should not be necessary to treat all patients with acute hepatitis C with the 24-week course of treatment that is most commonly administered for chronic hepatitis C in Japan.

Patients and Methods

Patients. Thirty-nine patients with acute hepatitis C who attended Shin-Kokura Hospital between January 1994, and December 2000, were studied. Criteria for the diagnosis of acute hepatitis C were: (1) At the onset of acute hepatitis, serum alanine aminotransferase (ALT) levels at least 7 × upper limit of the normal range (ULN), HCV-RNA positive and anti-HCV negative; or (2) negative HCV-RNA at the time of a needle-stick accident, but subsequent HCV-RNA positive and ALT levels at least 7 × ULN. All of the patients with acute hepatitis C had no history of blood transfusion. The patients were negative for both immunoglobulin M anti–hepatitis A virus and antinuclear antibody. Patients infected with the human immunodeficiency virus were not included in the study. Two patients were hepatitis B surface antigen positive, and 3 patients had been drinking at least 80 g of alcohol daily; these 5 patients were excluded from the study. At the onset of acute hepatitis, 20 of the remaining 34 patients had symptoms such as general malaise, loss of appetite, and a feeling of abdominal fullness; 14 patients were asymptomatic. The 20 symptomatic patients were diagnosed with acute hepatitis C when they developed symptoms. In 8 of the 14 asymptomatic patients, the diagnosis was made during follow-up after a needle-stick injury. Of the 10 patients followed after needle-stick injury, 8 were asymptomatic and 2 developed symptoms. The remaining 6 asymptomatic patients were diagnosed with acute hepatitis C, as a result of regular tests conducted during clinic visits for other diseases, such as diabetes mellitus.

For 8 weeks after developing acute hepatitis C, 34 patients were tested once weekly for serum ALT and once monthly for HCV-RNA. Of these, 4 patients cleared HCV-RNA during the 8 weeks of initial observation. In 3 of 20 patients with symptoms at onset, clearance of HCV-RNA occurred within 8 weeks. Total bilirubin increased to levels greater than 3.0 mg/dL in 3 of 34 patients during the 8-week follow-up period. In 2 of these 3 patients with jaundice, HCV-RNA clearance occurred within 8 weeks. One patient was positive for HCV-RNA after 8 weeks and was treated with IFN. A total of 30 patients, who were HCV-RNA positive and had ALT levels of at least 7 × ULN at 8 weeks, were enrolled in the study. The route of infection was needle-stick accident in 10 patients, intravenous drug use in 3 patients, sexual contact with an infected partner in 4 patients, and unknown in 13 patients. The time from exposure to onset of hepatitis was 7.3 ± 2.1 weeks (mean ± SD) (range, 5-12 weeks) in 10 the patients who had had a needle-stick injury and who were followed from the time of infection until the time symptoms appeared. Of the 5 patients in the early-intervention group, the time from infection to the start of treatment was 15.6 × 2.7 (range, 13-20) weeks.

Thirty patients were randomized at enrollment into 1 of 2 treatment groups using an enrollment sheet method; there were 15 patients per group. IFN therapy was initiated 8 weeks after acute hepatitis was diagnosed in the early-intervention group, and after 1 year of follow-up in the late-intervention group. The initial plan in this study, which was designed in 1994, was to recruit 30 patients. Characteristics of the patients studied are shown in Table 1. The patients included 19 men and 11 women, whose ages ranged from 22 to 59 years; the mean age was 40.4 years in the early-intervention group and 37.6 years in the late-intervention group. There was no significant difference in sex ratio and age between the two groups. Viral

Table 1. Patient Baseline Characteristics

	Early-Intervention Group N = 15	Late-Intervention Group N = 15	Total N = 30
Age (y, mean ± SD)	40 ± 11	38 ± 10	39 ± 10
Gender (male/female)	10/5	9/6	19/11
Baseline test values (before IFN therapy)			
Serum ALT (IU/L, mean ± SD)	491 ± 181	431 ± 143	460 ± 161
HCV-RNA (low/high)*	8/7	9/6	17/13
(10^5 copies/mL, mean ± SD)†	2.91 ± 2.41	2.56 ± 2.78	2.74 ± 2.66
Genotype (1b/others)	12/3	13/2	25/5
Mode of HCV Infection			
Needle-stick injury	5	5	10
Intravenous drug use	1	2	3
Sexual contact with HCV-positive partners	2	2	4
Unclear	7	6	13

Abbreviation: y, years.
*HCV load: low (<1 × 10^5 copies/mL), high (≥ 1 × 10^5 copies/mL)
†Copies/mL refers to HCV-RNA.

load was measured immediately before IFN therapy, using an Amplicor-HCV monitor assay (Roche Molecular Diag., Tokyo, Japan). Patients were designated as having a low viral load (less than 10^5 copies/mL), or a high viral load (10^5 copies/mL or greater). There was no significant difference in viral load between the early-intervention group and the late-intervention group. The genotype of HCV was 1b in about 80% of patients; there was no significant difference in the frequency of this genotype between the two groups. The ULN for serum ALT was set at 40 IU/L.

Protocol for Interferon Treatment

Initial Interferon Therapy (Short-term Interferon Therapy). Patients in the early-intervention group were treated with 6 million units (MU) of natural IFN-alfa (human lymphoblastoid interferon [HLBI], Sumitomo Pharmaceutical, Osaka, Japan) by intramuscular injection, once daily for 4 consecutive weeks during the early stage of acute hepatitis. The clinical course of patients in the late-intervention group was monitored for 1 year; patients continuing to be HCV-RNA positive after 1 year were treated with 6 MU of HLBI by intramuscular injection once daily for a period of 4 consecutive weeks.

Follow-up Interferon Therapy. Following completion of 4 the initial weeks of IFN therapy, all patients were followed-up, and HCV-RNA and serum ALT were monitored. Additional IFN therapy was administered to patients who were HCV-RNA positive after completion of the initial course of IFN therapy or who relapsed and became HCV-RNA positive again after completion of the initial course of IFN therapy. IFN therapy was 6 MU of HLBI injected intramuscularly, 3 times weekly, for 20 weeks. For all patients, IFN therapy was administered at Shin-Kokura Hospital.

Serological and Virological Assays. Serum ALT levels were measured once weekly during the initial 4-week period of treatment, and once every 4 weeks during follow-up IFN therapy and monitoring after treatment. During initial treatment, HCV-RNA was measured at Week 1, Week 2, and upon completion of treatment. In addition, these measurements were also undertaken at 4, 8, 12, 16, 20, and 24 weeks after completion of the initial course of treatment or follow-up IFN therapy. Anti-HCV antibodies were determined at the onset of hepatitis and 24 weeks after completion of IFN therapy, using a second-generation enzyme immunoassay. Effective IFN therapy was considered to be the induction of a sustained virological response—that is, HCV-RNA remaining negative for 24 weeks after completion of the initial course or the follow-up course of IFN therapy. HCV-RNA was measured using 2 methods, nested polymerase chain reaction and Amplicor-HCV assay, version 2.0 (Roche Molecular Diag., Tokyo, Japan), 24 weeks after completion of the initial or follow-up course of IFN therapy. Negative results of both tests were required to infer a sustained virological response. Those patients who were not classified as having undergone a sustained virological response were considered to be nonresponsive. Patients who underwent a sustained virological response were followed for at least 2 years after treatment, and HCV-RNA was measured again at the end of the 2-year period of follow-up, using the Amplicor-HCV assay, version 2.0. HCV genotyping was undertaken as previously described.[18]

Informed Consent. The study protocol was approved by institutional ethics committees. All patients gave written informed consent to participate in this study. The study was conducted in accordance with ethical guidelines of the Declaration of Helsinki and the International Conference on Harmonization guidelines for good clinical practice. No patient withdrew informed consent to participate in the study.

Statistical Analysis. The early-intervention and late-intervention groups, and the sustained virological response and nonresponsive groups were compared using the unpaired Student *t* test or Fisher exact test. All *P* values reported in this study were 2-tailed. *P* values less than .05 were considered to be statistically significant.

Results

Effect of Early- vs. Late-Intervention IFN Therapy. Results of IFN therapy are shown in Table 2. A sustained virological response occurred in 13 out of 15 (87%) patients in the early-intervention group following initial therapy. A recrudescence of disease developed in 2 patients in the early-intervention group 4 weeks after completion of the initial therapy. In these 2 patients a sustained virological response occurred after a 20-week course of follow-up IFN therapy. Thus, sustained virological responses occurred in all 15 patients in this group. In the late-intervention group, serum ALT levels fell below 2 × ULN in 6 patients during the 1-year monitoring period, but all patients were HCV-RNA positive immediately before IFN therapy. A sustained virological response occurred after initial IFN therapy in 6 (40%) patients in this group; a recrudescence of disease occurred in 9 patients. These 9 patients received follow-up IFN therapy, and a sustained virological response subsequently occurred in 2 of them. Thus, 8 of 15 (53%) patients in the late-intervention group had a sustained virological response. The sustained virological response rate was significantly higher in the early-intervention group than in the

Table 2. Results of Interferon Treatment

	Early-Intervention Group SR/N (%)*	Late-Intervention Group SR/N (%)*	Total SR/N (%)*	P Value†
After short-term IFN therapy				
$< 1 \times 10^5$ copies/mL‡				
1b	6/6 (100)	4/7 (57)	10/13 (77)	>.1
others	2/2 (100)	2/2 (100)	4/4 (100)	
total	8/8 (100)	6/9 (67)	14/17 (82)	>.1
$\geq 1 \times 10^5$ copies/mL‡				
1b	4/6 (67)	0/6 (0)	4/12 (33)	.061
others	1/1 (100)	0/0 (0)	1/1 (100)	
total	5/7 (71)	0/6 (0)	5/13 (38)	.021
Total	13/15 (87)	6/15 (40)	19/30 (63)	.021
After follow-up IFN therapy				
$< 1 \times 10^5$ copies/mL‡				
1b	6/6 (100)	5/7 (71)	11/13 (85)	>.1
others	2/2 (100)	2/2 (100)	4/4 (100)	
total	8/8 (100)	7/9 (78)	15/17 (88)	>.1
$\geq 1 \times 10^5$ copies/mL‡				
1b	6/6 (100)	1/6 (17)	7/12 (58)	.015
others	1/1 (100)	0/0 (0)	1/1 (100)	
total	7/7 (100)	1/6 (17)	8/13 (62)	.005
Total	15/15 (100)	8/15 (53)	23/30 (77)	.006

Abbreviation: SR: sustained virological response.

*(%): Rate of sustained virological response.

†P value for the comparison of early-intervention group to late-intervention group by Fisher exact test (2-tailed).

‡Copies/mL refers to HCV-RNA.

late-intervention group, after both initial and follow-up therapy ($P = .021$ and $P = .006$, respectively). All patients who were considered to have a sustained virological response were monitored for at least 2 years after treatment; during this period, serum ALT levels did not exceed the ULN in any of these patients. In addition, in these patients HCV-RNA remained negative at the end of the 2-year period. All patients seroconverted and became anti-HCV antibody–positive.

Results of short-term IFN administration, stratified by viral load and genotype, were as follows. A low viral load in the early-intervention group was associated with a sustained virological response in all patients, regardless of genotype. In the late-intervention group, the sustained virological response rate was 57% (4/7) for patients with genotype 1b. In the early-intervention group, among patients with a high viral load, a sustained virological response occurred in 5 of 7 (71%) patients and in 4 of 6 (67%) of those with genotype 1b. In the late-intervention group, sustained virological responses did not occur in any patient with a high viral load. Thus, the sustained virological response rate was significantly higher in the early-intervention group than in the late-intervention group ($P = .021$).

After follow-up IFN therapy, sustained virological responses occurred in the 2 patients with a high viral load in the early-intervention group, so that sustained virological responses eventually occurred in all patients in this group. In the late-intervention group, a sustained virological response occurred after follow-up therapy in 1 patient with a low viral load and 1 patient with a high viral load. Results after follow-up indicated that the sustained virological response rate for patients with a high viral load in the early-intervention group was significantly higher than that in the late-intervention group ($P = .005$).

The presence or absence of symptoms at the onset of hepatitis and the efficacy of IFN therapy were investigated. In the early-intervention group, 8 patients were symptomatic and 7 patients were asymptomatic. There was no difference in the sustained virological response rate between symptomatic patients (88%, 7 out of 8 patients) and asymptomatic patients (86%, 6 out of 7 patients) after short-term therapy. In the late-intervention group, 9 patients were symptomatic and 6 patients were asymptomatic. After short-term therapy, the sustained virological response rate was higher in the symptomatic patients (56 %, 5 out of 9 patients) than in the asymptomatic patients (17%, 1 out of 6 patients), but the difference was not significant. After additional therapy, the sustained virological response rate was higher in the symptomatic patients (67%, 6 out of 9 patients) than in the asymptomatic patients (33%, 2 out of 6 patients), but the difference was not significant. There was, therefore, no relationship between the presence or absence of symptoms at the onset of hepatitis and the efficacy of IFN therapy.

Sustained Virological Response and Eradication of HCV-RNA During Initial Therapy. Table 3 shows the virological state of patients who became negative for HCV-RNA during initial IFN therapy. HCV-RNA became negative at Week 1 after the start of treatment in 13

Table 3. Patients Becoming HCV-RNA Negative During Short-Term Therapy and Sustained Virological Response

	Early-Intervention Group N = 15	Late-Intervention Group N = 15	Total N = 30
HCV-RNA negative at Week 1 after starting treatment	13*	5*	18
HCV-RNA negative at Week 2 after starting treatment	15**	8**	23
HCV-RNA negative at the completion of 4-week treatment	15**	8**	23
SR (%)† after short-term therapy	13 (87%)	6 (40%)	19 (63%)
SR (%)† after follow-up therapy	15 (100%)	8 (53%)	23 (77%)

Abbreviation: SR, sustained virological response.

*P = .008 for the comparison of early-intervention group to late-intervention group by the Fisher exact test (2-tailed)

**P = .006 for the comparison of early-intervention group to late-intervention group by the Fisher exact test (2-tailed).

†(%): Rate of sustained virological response.

Table 4. Efficacy of Initial Interferon Treatment Classified According to Factor

	Sustained Virological Response N = 19	No Response N = 11	P Value*
Age (y, mean ± SD)	40 ± 12	37 ± 8	.467
Gender (male/female)	14/5	5/6	.238
Baseline test values (before IFN therapy)			
Serum ALT (IU/L, mean ± SD)	493 ± 201	406 ± 143	.218
HCV load (low/high)†	14/5	3/8	.023
(10^5 copies/mL, mean ± SD)‡	1.78 ± 2.24	4.40 ± 2.81	.009
Genotype (1b/others)	14/5	11/0	.129
Time of treatment initiation (early-intervention group/ late-intervention group)	13/6	2/9	.021
HCV-RNA at Week 1 (negative/positive)	18/1	0/11	<.001

Abbreviation: y, years.

*P value for comparison with sustained virological response to nonresponse by the Fisher exact test (2-tailed) or the unpaired Student t test.

†HCV load: low (< 1×10^5 copies/mL), high (≥ 1×10^5 copies/mL).

‡Copies/mL refers to HCV-RNA.

patients in the early-intervention group and in 5 patients in the late-intervention group; the higher conversion rate for the early-intervention group was significant (P = .008). A sustained virological response occurred after initial treatment in all 18 patients who tested negative for HCV-RNA at Week 1. An additional 5 patients were negative for HCV-RNA at Week 2. Of these, 1 patient from the late-intervention group underwent a sustained virological response at the completion of the initial therapy; a recrudescence of disease occurred in the other 4 patients. After follow-up therapy, all 4 of these patients also underwent a sustained virological response. All 7 patients who continued to be positive for HCV-RNA at Week 2 were in the late-intervention group. These 7 patients continued to be HCV-RNA positive after completion of the initial treatment and continued to be virological nonresponders after follow-up therapy.

Factors Influencing the Efficacy of Initial IFN Treatment. Table 4 shows the results of initial IFN treatment classified according to various factors. Univariable analysis of sustained virological response after initial therapy yielded the following results: age (P = .467), gender (P = .238), pretreatment serum ALT levels (P = .218), HCV load (P = .009), genotype (P = .129), timing of initial treatment (P = .021), and loss of HCV-RNA by Week 1 (P < .001). Significant factors were viral load (low viral load group), the timing of initial treatment (early-intervention group), and loss of HCV-RNA by Week 1.

Discussion

Our randomized controlled trial in patients with acute hepatitis C demonstrates that short-term (4 weeks) IFN therapy is effective when the treatment is initiated 8 weeks after the onset of acute hepatitis. In this study, to demonstrate the efficacy of short-term IFN therapy for acute hepatitis C, we applied strict criteria for the diagnosis; patients with posttransfusion hepatitis were excluded. As substantiated by our study, acute hepatitis C is associated with a few subjective symptoms that are easily overlooked by many patients. Diagnosis requires finding elevated serum ALT levels, and conversion from HCV-RNA negative to HCV-RNA positive.

There are no standard methods for treatment of acute hepatitis C. Both IFN-alfa[3–5,13,15–17] and IFN-beta[12,14] have been used. Previous studies have involved predominantly asymptomatic patients with posttransfusion hepatitis.[13–15] Recent studies by European researchers[4,5] have shown that 75% or 68% of patients have jaundice at the onset of acute hepatitis C, but Japanese studies have found that few patients have jaundice at the onset.[12,19] The latter finding is consistent with the results of this study, in which only 3 of 34 patients had jaundice. The reason for this difference in the incidence of jaundice at the onset of acute hepatitis C between Europeans and Japanese is unclear. A recent study of the natural history of acute hepatitis C found spontaneous viral clearance within 5 weeks of the onset of symptoms in a high proportion of patients with symptomatic hepatitis.[4] As a 24-week course of IFN therapy starting immediately after the onset of acute hepatitis C was very effective (sustained response of 95%),[3] deciding when to start IFN therapy is important; spontaneous clearance of HCV may occur within 5 weeks of the onset of acute hepatitis C. In addition, asymptomatic acute hepatitis C is common in Japan. Therefore, in this study we monitored serum ALT levels and HCV-RNA for 8 weeks before initiating of IFN therapy. Clearance of HCV occurred within this 8-week period in 4 of 34 patients. All patients in the late-intervention group underwent some changes in serum ALT levels during the 1-year period of observation, but none of these patients became HCV-RNA negative after 1 year.

Recent reports of European studies[4,5] indicated a high rate (67%-68%) of spontaneous HCV clearance within 12 weeks of the onset of acute hepatitis C, but the corresponding rate was low in our study (12%). The reason for this difference is unclear, but the fact that we observed our patients for only an 8-week period may have been a contributing factor. In Japan, patients are often referred to a specialist hospital by the doctor who made the initial di-

agnosis of acute hepatitis, if treatment is considered to be necessary. Since most patients referred do require treatment, it is possible that patients in whom hepatitis resolves spontaneously would have been excluded. Spontaneous clearance of HCV should be investigated in a large group of patients who have been followed from the time of infection to the onset of acute hepatitis C. In our study, spontaneous clearance of HCV was not observed in any patients who had a needle-stick injury and who had been followed from the time of the infection to the onset of acute hepatitis C. The natural history of acute hepatitis C in the Japanese seems to be different from that in Europeans, but there are no data available to indicate whether this is the case.

We found no relationship between the presence or absence of symptoms at the onset of hepatitis and the efficacy of IFN therapy, although spontaneous clearance of HCV occurred in many patients with symptoms at the onset.[4,5] In this study, short-term daily IFN therapy was associated with a high (87%) sustained virological response rate. When a recrudescence of disease occurred in the early-intervention group, patients received an additional 20-week course of follow-up therapy; sustained virological responses occurred in all patients. In this respect our results are similar to those reported by Jaeckel et al.[3] It appears that IFN therapy is more effective in acute hepatitis C than in chronic hepatitis C. Due to IFN treatment's high cost and frequency of adverse events, it is desirable to shorten the duration of treatment with IFN as much as is practicable.

When we studied the efficacy of IFN therapy in patients in whom HCV-RNA became negative during short-term (4 weeks) treatment, we found that it was necessary for patients to become HCV-RNA negative within the first week of treatment for a sustained virological response to occur. A sustained virological response occurred in all 18 patients, in whom this early event occurred; monitoring for at least the following 2 years indicated that no recurrence of HCV-RNA positivity and no relapse of elevated serum ALT levels occurred in any of these patients. In IFN therapy for chronic hepatitis C, the sustained virological response rate is low if the HCV load does not decrease early after the start of therapy.[20] These findings suggest that short-term IFN therapy may be associated with satisfactory results in acute hepatitis C, if patients become HCV-RNA negative within the first week of treatment. Conversion from HCV-RNA positive to HCV-RNA negative within 2 weeks of the start of IFN therapy is one indicator that treatment of chronic hepatitis C may be efficacious.[21,22] We also found that a 20-week course of follow-up IFN therapy may be associated with a sustained virological response in patients who are HCV-RNA negative within 2 weeks of starting treatment.

In this study, significant predictive factors were viral load (low viral load), timing of initial treatment (early-intervention group), and conversion to HCV-RNA negative at Week 1. Although viral load is the best predictor of the efficacy of IFN therapy for chronic hepatitis C,[10,11] it was also found to be a significant predictor of a sustained virological response in patients with acute hepatitis C. Our results suggest that a short course (4 weeks) of IFN therapy for acute hepatitis C may be associated with satisfactory results in patients who have low viral loads, by whom IFN therapy is started early, or who become HCV-RNA negative within one week of the initiation of treatment.

In chronic cases that had been monitored for 1 year, the viral elimination rate was also high for those with a low viral load. As fulminant hepatic failure is rare in acute hepatitis C, it was previously believed that spontaneous clearance of HCV would occur after the hepatitis had spontaneously subsided. Accordingly, patients were followed for 1 year, rather than having costly IFN treatment at an early stage of the disease. However, in this study we found that IFN therapy was more effective when the treatment was initiated at an early stage after the onset of acute hepatitis. We studied 2 groups; treatment was initiated after 8 weeks of monitoring in the early-intervention group and after observation for a year or more in the late-intervention group. However, we were unable to investigate the timing of initiation of IFN therapy after the onset of acute hepatitis C. Hofer et al.[4] reported that patients with acute hepatitis C had a high rate of spontaneous viral clearance within one month of onset of symptoms, and that IFN therapy was indicated in patients who failed to clear the virus within 35 days of the onset of symptoms. Gerlach et al.[5] observed that spontaneous clearance of HCV usually occurs within 12 weeks of the onset of symptoms; no spontaneous clearance of HCV occurred after 16 weeks. The timing of IFN therapy for acute hepatitis C should, therefore, be investigated in a larger study.

In conclusion, short-term (4 weeks) IFN therapy at an early stage of acute hepatitis C may be associated with satisfactory results, especially when HCV-RNA becomes negative within the first week of treatment. If the patient remains HCV-RNA positive after Week 1 of IFN treatment, a 24-week course of IFN therapy is recommended to try to achieve a satisfactory result.

References

1. Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. Lancet 1997;22:825–832.

2. Takano S, Yokosuka O, Imazeki F, Tagawa M, Omata M. Incidence of hepatocellular carcinoma in chronic hepatitis B and C: a prospective study of 251 patients. HEPATOLOGY 1995;21:650–655.
3. Jaeckel E, Cornberg M, Wedemeyer H, Santantonio T, Mayer J, Zankel M, et al. German Acute Hepatitis C Therapy Group. Treatment of acute hepatitis C with interferon alfa-2b. N Engl J Med 2001;15:1452–1457.
4. Hofer H, Watkins-Riedel T, Janata O, Penner E, Holzmann H, Steindl-Munda P, et al. Spontaneous viral clearance in patients with acute hepatitis C can be predicted by repeated measurements of serum viral load. HEPATOLOGY 2003;37:60–64.
5. Gerlach JT, Diepolder HM, Zachoval R, Gruener NH, Jung MC, Ulsenheimer A, et al. Acute hepatitis C: high rate of both spontaneous and treatment-induced viral clearance. Gastroenterology 2003;125:80–88.
6. Ikeda K, Saitoh S, Arase Y, Chayama K, Suzuki Y, Kobayashi M, et al. Effect of interferon therapy on hepatocellular carcinogenesis in patients with chronic hepatitis type C: a long-term observation study of 1,643 patients using statistical bias correction with proportional hazard analysis. HEPATOLOGY 1999;29:1124–1130.
7. Kasahara A, Hayashi N, Mochizuki K, Takayanagi M, Yoshioka K, Kakumu S, et al. Risk factors for hepatocellular carcinoma and its incidence after interferon treatment in patients with chronic hepatitis C. Osaka Liver Disease Study Group. HEPATOLOGY 1998;27:1394–1402.
8. Imazeki F, Yokosuka O, Fukai K, Saisho H. Favorable prognosis of chronic hepatitis C after interferon therapy by long-term cohort study. HEPATOLOGY 2003;38:493–502.
9. Arif A, Levine RA, Sanderson SO, Bank L, Velu RP, Shah A, et al. Regression of fibrosis in chronic hepatitis C after therapy with interferon and ribavirin. Dig Dis Sci 2003;48:1425–1430.
10. Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Goncales FL Jr, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002;26:975–982.
11. Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet 2001;358:958–965.
12. Omata M, Yokosuka O, Takano S, Kato N, Hosoda K, Imazeki F, et al. Resolution of acute hepatitis C after therapy with natural beta interferon. Lancet 1991;338:914–915.
13. Viladomiu L, Genesca J, Esteban JI, Allende H, Gonzalez A, Lopez-Talavera JC, et al. Interferon-alpha in acute posttransfusion hepatitis C: a randomized, controlled trial. HEPATOLOGY 1992;15:767–769.
14. Takano S, Satomura Y, Omata M. Effects of interferon beta on non-A, non-B acute hepatitis: a prospective randomized, controlled-dose study. Gastroenterology 1994;107:805–811.
15. Lampertico P, Rumi M, Romeo R, Craxi A, Soffredini R, Biassoni D, et al. A multicenter randomized controlled trial of recombinant interferon-alpha 2b in patients with acute transfusion-associated hepatitis C. HEPATOLOGY 1994;19:19–22.
16. Hwang SJ, Lee SD, Chan CY, Lu RH, Lo KJ. A randomized controlled trial of recombinant interferon alpha-2b in the treatment of Chinese patients with acute post-transfusion hepatitis C. J Hepatol 1994;21:831–836.
17. Ohnishi K, Nomura F, Nakano M. Interferon therapy for acute post-transfusion non-A, non-B hepatitis: response with respect to anti-hepatitis C virus antibody status. Am J Gastroenterol 1991;86:1041–1049.
18. Simmonds P, Alberti A, Alter HJ, Bonino F, Bradley DW, Brechot C, et al. A proposed system for the nomenclature of hepatitis C virus genotypes. HEPATOLOGY 1994;19:1321–1324.
19. Oketani M, Higashi T, Yamasaki N, Shinmyozu K, Osame M, Arima T. Complete response to twice-a-day interferon-beta with standard interferon-alpha therapy in acute hepatitis C after a needle-stick. J Clin Gastroenterol 1999;28:49–51.
20. Jessner W, Gschwantler M, Steindl-Munda P, Hofer H, Watkins-Riedel T, Wrba F, et al. Primary interferon resistance and treatment response in chronic hepatitis C infection: a pilot study. Lancet 2001;358:1241–1242.
21. Nomura H, Kimura Y, Morita C, Tada H, Okamoto O, Shiraishi G, et al. Usefulness of HCV-RNA assays in efficacy evaluation of interferon treatment for chronic hepatitis C: Amplicor HCV assay and branched DNA probe assay. J Infect 1997;34:349–355.
22. Yamaji K, Hayashi J, Kawakami Y, Furusyo N, Sawayama Y, Kishihara Y, et al. Hepatitis C viral RNA status at two weeks of therapy predicts the eventual response. J Clin Gastroenterol 1998;26:193–199.

Journal of Gastroenterology and Hepatology (2004) **19**, 1312–1317 DOI: 10.1111/j.1400-1746.2004.03459.x

HEPATOLOGY

Factors contributing to ribavirin-induced anemia

HIDEYUKI NOMURA,*,† HIRONORI TANIMOTO,*,† EIJI KAJIWARA,† JUNYA SHIMONO,† TOSHIHIRO MARUYAMA,† NOBUYUKI YAMASHITA,† MASANORI NAGANO,† MASASHI HIGASHI,† TAMOTSU MUKAI,† YUTAKA MATSUI,† JUN HAYASHI,‡ SEIZABURO KASHIWAGI§ AND HIROMI ISHIBASHI¶

**Department of Internal Medicine, Shin-Kokura Hospital, †Kitakyushu Interferon Therapy Study Group, Kitakyushu, ‡Department of Environmental Medicine and Infectious Diseases, Faculty of Medical Sciences, Kyushu University, §Fukuoka Red Cross Blood Center, Fukuoka and ¶Clinical Research Center, National Nagasaki Medical Center, Nagasaki, Japan*

Abstract

Background and Aim: Interferon and ribavirin combination therapy for chronic hepatitis C produces hemolytic anemia. This study was conducted to identify the factors contributing to ribavirin-induced anemia.

Methods: Eighty-eight patients with chronic hepatitis C who received interferon-α-2b at a dose of 6 MU administered intramuscularly for 24 weeks in combination with ribavirin administered orally at a dose of 600 mg or 800 mg participated in the study. A hemoglobin concentration of <10 g/dL was defined as ribavirin-induced anemia.

Results: Ribavirin-induced anemia occurred in 18 (20.5%) patients during treatment. A 2 g/dL decrease in hemoglobin concentrations in patients with anemia was observed at week 2 after the start of treatment. The hemoglobin concentration in patients with ≥2 g/dL decrease at week 2 was observed to be significantly lower even after week 2 than in patients with <2 g/dL decrease ($P < 0.01$). A significant relationship was observed between the rate of reduction of hemoglobin concentrations at week 2 and the severity of anemia ($P < 0.01$). Such factors as sex (female), age (≥60 years old), and the ribavirin dose by body weight (12 mg/kg or more) were significant by univariate analysis.

Conclusions: Careful administration is necessary in patients ≥60 years old, in female patients, and in patients receiving a ribavirin dose of 12 mg/kg or more. Patients who experience a fall in hemoglobin concentrations of 2 g/dL or more at week 2 after the start of treatment should be monitored with particular care.

Key words: adverse reaction, anemia, discontinuation, hemoglobin, interferon, ribavirin.

INTRODUCTION

Cure of chronic hepatitis C in the natural course is rare, and the rate of progression to cirrhosis and hepatocellular carcinoma is also significantly high.[1,2] The eradication of hepatitis C virus (HCV) during the chronic stage is therefore extremely important. With the administration of interferon (IFN), the elimination of serum HCV and cure of chronic hepatitis C have been reported.[3,4] It is also known that the therapeutic effect of IFN differs depending on the HCV genotype and the viral load.[5,6] The number of patients with genotype 1b with high viral load is high in Japan, and eradication of HCV with IFN monotherapy is difficult in these patients.[7] Combination therapy of IFN with ribavirin is reported to be more effective than IFN monotherapy for these patients[6,8–10] and combination therapy has been approved for use in Japan since December 2001.

One adverse reaction observed with ribavirin is hemolytic anemia during treatment. The ribavirin dose is recommended to be reduced by 200 mg if the hemoglobin concentration falls to <10 g/dL. In addition,

Correspondence: Dr Hideyuki Nomura, Department of Internal Medicine, Shin-Kokura Hospital, 1-3-1, Kanada, Kokurakita-ku, Kitakyushu, Fukuoka, 803–8505, Japan. Email: h-nomura@shin-kokura.gr.jp

Accepted for publication 27 December 2003.

treatment is discontinued when the hemoglobin concentration falls to <8.5 g/dL. For safe ribavirin use, it is important to determine the factor(s) associated with hemoglobin reduction in the early stage of treatment. A multicenter examination was therefore conducted in the Kitakyushu area of Japan to clarify the factors related to the induction of anemia during the administration of ribavirin.

METHODS

Patients

Eighty-eight patients with chronic hepatitis C who started combination therapy with IFN and ribavirin from December 2001 to August 2002 were enrolled in this study. Excluded from the study were patients with cirrhosis, autoimmune hepatitis, alcoholic liver disease, or patients positive for hepatitis B surface antigen by an enzyme-linked immunosorbent assay (Abbott Japan, Tokyo, Japan). Baseline characteristics of patients are given in Table 1. Fifty-six were male and 32 female, with a mean age of 56.6 years, ranging from 27 to 76 years. The proportion of male patients was higher (64%) than female patients. The main serotype was type 1, accounting for 76%. The proportion of patients receiving a per kilogram of body weight dose of <12 mg/kg and ≥12 mg/kg was nearly the same. The proportion of patients with baseline hemoglobin concentrations of <13 g/dL was 22%.

Methods

Patients received 6 million units (MU) of IFN-α-2b (Intron A; Schering Plough, Osaka, Japan) six times per week for the first 2 weeks, followed by three times per week for 22 weeks by intramuscular injection. Ribavirin (Rebetol; Schering Plough) was administered orally for 24 weeks at the daily dose of 600 mg for patients weighing <60 kg and 800 mg for those weighing >60 kg. The dose of ribavirin was reduced by 200 mg if hemoglobin concentrations fell to <10 g/dL. Patients were considered to have ribavirin-induced anemia if hemoglobin concentrations decreased to <10 g/dL. In such cases, a reduction in the dose of ribavirin was required. Both IFN-α-2b and ribavirin were discontinued if the hemoglobin concentration fell below 8.5 g/dL, the leukocyte count fell below 2000/μL, the platelet count fell below 50 000/μL, severe malaise developed, the continuation of treatment was judged not possible by the physician, or the patient desired discontinuation of treatment.

Immediately before the start of treatment, complete blood counts, serum alanine transaminase (ALT), serum creatinine, HCV-RNA, viral loads, and serotype were measured. Viral loads were measured using Amplicor-HCV monitor assay (Roche Molecular Diagnostics, Tokyo, Japan).[11] Complete blood counts, serum ALT, and serum creatinine were also measured at weeks 1, 2, and 4 and monthly thereafter until the completion of the treatment. HCV-RNA was measured at week 12 after the start of treatment and at the completion of treatment using Amplicor-HCV assay version 2.0 (Roche Molecular Diagnostics).[12]

The study protocol was approved by the institutional ethics committees and all patients gave informed consent for participation in this study. The study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki and the International Conference on Harmonization guidelines for good clinical practice.

Table 1 Baseline characteristics of patients

Sex	Male/female	56/32
Age (years)	<60/≥60	46/42
Body weight (kg)	<60/≥60	34/54
Initial ribavirin dose (mg)	600/800	34/54
Serotype	Type 1/type 2	67/21
Ribavirin dose by body weight (mg/kg)	<12/≥12	47/41
Baseline hemoglobin concentration (g/dL)	<13/≥13	19/69

Statistics

Hemoglobin concentrations were compared using an unpaired Student's *t*-test. The analysis of relationship between each factor and anemia was carried out using Mantel–Haenszel analysis. Differences between the groups were tested using Fisher's exact test. Probability values of <0.05 were considered statistically significant. Multiple logistic regression analysis and stepwise regression analysis ($P < 0.1$) were carried out to determine the predictive factors for reduced hemoglobin concentrations. A logistic analysis was carried out for sex (male *vs* female), age (27–59 years *vs* 60–76 years), serotype (type 1 *vs* type 2), ribavirin dose by body weight (<12 mg/kg *vs* ≥12 mg/kg), body weight (<60 kg *vs* ≥60 kg), and baseline hemoglobin concentration (<13 g/dL *vs* ≥13 g/dL).

RESULTS

Change in hemoglobin concentration during treatment with ribavirin

The mean baseline hemoglobin concentration was 14.2 g/dL. The mean hemoglobin concentrations at weeks 1, 2, 4, 8, and 12 after the start of treatment were 14.1, 13.1, 11.8, 11.4, and 11.2 g/dL, respectively. Hemoglobin concentrations decreased from week 1 to week 12 and did not change after week 12 to the completion of treatment. The change in hemoglobin concentration during the first 12 weeks is shown in Table 2. Decreases in hemoglobin concentration at week 1 were not observed in patients either with anemia or without anemia. However, significant decreases were observed at week 2 in both patients with and without anemia

Table 2 Change in hemoglobin concentrations (g/dL) from the start of treatment to week 12

	In patients resulting in			Reduction in hemoglobin at week 2		
	<10 g/dL (n = 18) Mean ± SD	≥10 g/dL (n = 70) Mean ± SD	P-value	≥2 g/dL (n = 17) Mean ± SD	<2 g/dL (n = 71) Mean ± SD	P-value
Pretreatment	13.8 ± 1.3*	14.3 ± 1.4*	0.184	15.4 ± 0.9†,*	13.9 ± 1.4‡,§	<0.001
Week 1	13.3 ± 1.2	14.2 ± 1.3	0.011	14.4 ± 0.9†	14.0 ± 1.4	0.281
Week 2	11.8 ± 1.4*	13.5 ± 1.3*	<0.001	12.1 ± 1.1*	13.4 ± 1.5‡	0.001
Week 4	9.7 ± 1.0*	12.5 ± 1.3*	<0.001	10.5 ± 1.2*	12.1 ± 1.7§	<0.001
Week 8	9.5 ± 0.7*	11.9 ± 1.2*	<0.001	10.3 ± 0.9*	11.7 ± 1.4§	<0.001
Week 12	9.5 ± 1.0*	11.6 ± 1.3*	<0.001	10.3 ± 1.0*	11.4 ± 1.4§	0.003

*P < 0.001 (pretreatment *vs* weeks 2, 4, 8, 12); †P = 0.003 (pretreatment *vs* week 1); ‡P = 0.042 (pretreatment *vs* week 2); §P < 0.001 (pretreatment *vs* weeks 4, 8, 12).

Table 3 Incidence of ribavirin-induced anemia by each factor

						P-value†
Age (years)	27–49	50–59	60–69	70–		
(A)/n	1/20	4/26	11/37	2/5		0.012
(%)‡	5	15	30	40		
Ribavirin dose by body weight (mg/kg)	<12.0	12.0–12.9	13.0–			
(A)/n	5/50	8/25	5/13			0.007
(%)	10	32	38			
Reduction in hemoglobin concentration at week 2 (g/dL)	<1.0	1.0–1.9	2.0–2.9	3.0–		
(A)/n	6/50	4/21	4/9	4/8		0.003
(%)	12	19	44	50		
Baseline hemoglobin concentration (g/dL)	<13.0	13.0–13.9	14.0–14.9	15.0–15.9	16.0–	
(A)/n	5/20	5/19	5/19	3/23	0/7	0.281
(%)	25	26	26	13	0	

†P-value for the relationship between each factor and anemia using Mantel–Haenszel analysis. (A), no. of patients with hemoglobin concentration <10.0 g/dL; (%), percentage with hemoglobin concentration <10.0 g/dL.

(P < 0.001). In particular, 2 g/dL decrease in hemoglobin concentration was observed at week 2 in patients with anemia. A rapid decline in hemoglobin concentration was observed in patients with anemia at weeks 2 and 4. After week 2, the hemoglobin concentration in patients with anemia was significantly lower than in patients without anemia (P < 0.001). Patients with ≥2 g/dL decrease in hemoglobin concentration from baseline at week 2 were already observed to have a significant decline in hemoglobin concentrations at week 1 (P = 0.003). Hemoglobin concentrations in these patients declined rapidly and significantly over weeks 2 and 4 (P < 0.001) and were significantly lower than in patients with <2 g/dL decrease from baseline (P < 0.001).

Three (3.4%) patients discontinued treatment by week 12 because of decrease in hemoglobin concentrations to below 8.5 g/dL, and an additional two patients discontinued treatment before the completion of treatment. A total of five (6%) patients therefore had hemoglobin concentrations of <8.5 g/dL, who discontinued treatment. The dose of ribavirin was reduced in 18 (20.5%) patients by week 12 because of reduction in hemoglobin concentrations to <10 g/dL. No patient required dose reduction for reduced hemoglobin concentration thereafter. All patients with anemia were therefore observed by week 12.

Factors for ribavirin-induced anemia

The incidence of anemia by each factor is shown in Table 3. The incidence of anemia by age was lowest at 5% in patients <50 years and increased with age. Anemia was observed at a particularly high incidence of 30% in patients ≥60 years old. A significant relationship was observed between age and the incidence of anemia (P < 0.05). A significant relationship was also observed between the ribavirin dose by body weight and the incidence of anemia (P < 0.01), with anemia observed in 10% of patients receiving <12 mg/kg and in 32% of patients receiving 12 mg/kg or more. The incidence of anemia increased with the amount of reduction of hemoglobin concentrations at week 2. In particular, patients with ≥2 g/dL decrease in hemoglobin concentrations at week 2 were observed to have anemia at a rate of 44%. A significant relationship was also observed between the amount of reduction of the hemoglobin

concentration at week 2 and the incidence of anemia ($P < 0.01$). The incidence of anemia in patients with baseline hemoglobin concentrations of <13 g/dL was 25%. In addition, the incidence in patients with baseline hemoglobin concentrations from 13 g/dL to 15 g/dL was nearly the same at 26%. No patient with pretreatment hemoglobin concentrations of ≥16 g/dL was observed to develop anemia during treatment. No relationship was observed between pretreatment hemoglobin concentrations and anemia.

No relationship was also observed between HCV-RNA negativity at week 12 or at the completion of treatment, or pretreatment viral load and anemia.

Univariate and multivariate analysis of factors contributing to development of ribavirin-induced anemia

The results of univariate and multivariate analyses are shown in Table 4. Univariate analysis showed that the factors contributing to the development of anemia during the administration of ribavirin were sex (female, $P = 0.012$), age (≥60 years old, $P = 0.026$), serotype (type 1, $P = 0.857$), dose of ribavirin by body weight (12 mg/kg or more, $P = 0.019$), body weight (<60 kg, $P = 0.612$), and pretreatment hemoglobin concentrations (<13 g/dL, $P = 0.445$). Sex, age, and ribavirin dose by body weight were significant factors, while body weight, serotype, and pretreatment hemoglobin concentrations were not significant. The most important factor contributing to ribavirin-induced anemia by multivariate analysis was sex (female, $P = 0.025$). Stepwise selection revealed sex (female, $P = 0.017$) and dose of ribavirin by body weight (12 mg/kg or more, $P = 0.026$) as significant factors.

Discontinuation of treatment

Treatment was discontinued in five patients who had a reduction of hemoglobin concentrations to <8.5 g/dL, in four patients who had severe malaise, and in two patients who desired discontinuation of treatment, resulting in 11 patients or 12.5% who discontinued treatment. In this study, no patients discontinued treatment because of thrombocytopenia or leukocytopenia. All patients who discontinued treatment because of severe malaise had a reduction in hemoglobin concentrations by ≥4 g/dL from the pretreatment level at the time of discontinuation. Two of these patients had hemoglobin concentrations of <10 g/dL at discontinuation. The other two patients were discontinued because of anorexia and severe insomnia. Two patients desired discontinuation of treatment because of financial reasons.

DISCUSSION

The therapeutic effect of IFN monotherapy in patients with chronic hepatitis C with high viral loads is extremely low. It has been confirmed that the addition of ribavirin to IFN in these patients results in a higher therapeutic effect than with IFN alone.[8–10] The efficacy of pegylated IFN and ribavirin combination therapy has also been reported.[5,6] Several significant adverse reactions are, however, associated with ribavirin. One is hemolytic anemia.[8,9] There are patients who must discontinue combination therapy because of anemia, and it is therefore important to determine the factor(s) associated with anemia caused by ribavirin. It is also important to reduce the dose of ribavirin at as early a stage as possible to allow the safe continuation of treatment in patients who experience a marked fall in hemoglobin concentrations and to reduce the number of patients who must discontinue treatment. To do this, it is important to identify patients who will develop anemia in the early phase of treatment. For use as a predictive factor and for application to every patient who receives ribavirin, the test items must be simple, inexpensive, and quick. In this study we examined the factors of baseline age, sex, complete blood count, viral load and serotype.

Hemoglobin concentrations decreased during week 2 to week 8 and thereafter remained unchanged until the completion of treatment in this study. The reduction of hemoglobin concentrations as a result of ribavirin-induced anemia was the same as reported by van Vliergbergh *et al.*[13] All patients with anemia were observed by week 12. A 2 g/dL decrease of hemoglobin concentrations was observed at week 2 in patients with anemia. A significant relationship was also observed between the amount of reduction of hemoglobin concentrations at week 2 and the incidence of anemia. Hemoglobin concentrations of patients with ≥2 g/dL decrease from baseline at week 2 was significantly lower after 2 weeks.

Table 4 Results of univariate analysis and multiple logistic regression analysis (ribavirin-induced anemia)

Factors	*P*-value		
	Univariate analysis	Multivariate analysis	Stepwise selection
Sex (female)	0.012	0.025	0.017
Age (≥60 years)	0.026	0.052	–
Serotype (type 1)	0.857	0.432	–
Ribavirin dose by body weight (≥12 mg/kg)	0.019	0.155	0.026
Body weight (≥60 kg)	0.612	0.102	–
Baseline hemoglobin concentration (≥13 g/dL)	0.445	0.641	–

Therefore, the incidence of anemia was significantly higher in patients with ≥2 g/dL decrease from baseline at week 2. A decrease in hemoglobin concentrations by ≥2 g/dL at week 2 is predictive of further, more severe reduction in hemoglobin concentrations. It is therefore necessary to consider an earlier reduction in the ribavirin dose in such patients to prevent discontinuation of treatment because of anemia.

The mechanism of ribavirin-induced hemolytic anemia has not been clearly established. Lau *et al.* explain that ribavirin, following uptake into cells, is phosphorylated and converts to ribavirin triphosphates, which then must be dephosphorylated for elimination from cells.[14] However, because red blood cells lack dephosphorylation enzymes, ribavirin accumulates in cells and destroys the cells, causing hemolytic anemia.

The pretreatment hemoglobin concentration could be a significant factor in ribavirin-induced anemia. However, in this study, hemoglobin concentrations in patients with anemia decreased rapidly in the early stage after the start of administration of ribavirin. Hemoglobin concentrations in these patients thereafter decreased and became <10 g/dL. If the pretreatment hemoglobin concentration was >16 g/dL, anemia was not observed in any patient during administration of ribavirin, while if it was <16 g/dL, the incidence of anemia was similar in all grades.

Van Vlierbergh *et al.* have reported that many anemia patients, as high as 67%, were observed in their study.[13] However, they defined anemia as hemoglobin concentrations of <13.3 g/dL for men and <11.7 g/dL for women at week 8 after the start of treatment. We examined the factors of ribavirin-induced anemia for the purpose of more safe administration of ribavirin and to reduce treatment discontinuations. We defined ribavirin-induced anemia as hemoglobin concentrations of <10 g/dL. In the present study, anemia was observed in 18 patients (20%). In their study, seriously ill anemia patients who need to stop treatment cannot be distinguished. The relationship between the ribavirin dose by body weight and the incidence of anemia was not supposed to be observed in their study. Moreover, because the criteria for anemia was different for men and women, no relationship between sex and anemia was observed. In the present study, the first predictive factor of anemia was sex (women). The significant factors of anemia were also sex (women) and the ribavirin dose by body weight (≥12 mg/kg) by stepwise selection.

The package insert for ribavirin in Japan calls for the administration of 600 mg to patients weighing <60 kg and 800 mg to patients weighing ≥60 kg. The ribavirin dose may therefore exceed 12 mg/kg in patients weighing <50 kg and in patients weighing between 60 and 66 kg. More female patients tend to weigh <50 kg than men in Japan.

No relationship was observed between HCV-RNA negativity and anemia. In other words, preventing a reduction in hemoglobin concentrations as much as possible and minimizing treatment discontinuation, thereby raising therapeutic efficacy, appear to be important. Instead of changing the ribavirin dose at the level of 60 kg, per kilogram body weight dosing of ribavirin should be considered. The dose of ribavirin should not exceed 12 mg/kg and a more reduced dose should be considered for elderly female patients.

Tsubota *et al.* reported that plasma ribavirin concentration is elevated during week 4 to week 24 and then gradually decreases after discontinuation of treatment.[15] The sustained response rate was higher in patients with high plasma ribavirin concentrations, but the relationship between ribavirin concentrations and anemia was not clarified. Because the cost of assay of plasma ribavirin concentrations is high, it is not feasible to conduct measurement for all patients. Assay results are also not immediately obtainable. In contrast, the measurement of hemoglobin concentration is simple, quick and inexpensive. It is therefore extremely important to predict the patients who may develop anemia by determining hemoglobin concentrations at week 2.

In conclusion, careful administration is necessary in patients ≥60 years old, in female patients, as well as in patients receiving a ribavirin dose of ≥12 mg/kg. Patients who experience a fall in hemoglobin concentrations of 2 g/dL or more at week 2 after the start of treatment should be monitored with particular care.

REFERENCES

1 Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, DOSVIRC Groups. *Lancet* 1997; **22**: 825–32.

2 Takano S, Yokosuka O, Imazeki F, Tagawa M, Omata M. Incidence of hepatocellular carcinoma in chronic hepatitis B and C: a prospective study of 251 patients. *Hepatology* 1995; **21**: 650–5.

3 Imazeki F, Yokosuka O, Fukai K, Saisho H. Favorable prognosis of chronic hepatitis C after interferon therapy by long-term cohort study. *Hepatology* 2003; **38**: 493–502.

4 Arif A, Levine RA, Sanderson SO *et al.* Regression of fibrosis in chronic hepatitis C after therapy with interferon and ribavirin. *Dig. Dis. Sci.* 2003; **48**: 1425–30.

5 Fried MW, Shiffman ML, Reddy KR *et al.* Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N. Engl. J. Med.* 2002; **26**: 975–82.

6 Manns MP, McHutchison JG, Gordon SC *et al.* Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet* 2001; **358**: 958–65.

7 Enomoto N, Takada A, Nakao T, Date T. There are two major types of hepatitis C virus in Japan. *Biochem. Biophys. Res. Commun.* 1990; **16**: 1021–5.

8 Davis GL, Esteban-Mur R, Rustgi V *et al.* Interferon alfa-2b alone or in combination with ribavirin for the treatment of relapse of chronic hepatitis C. *N. Engl. J. Med.* 1998; **339**: 1493–9.

9 McHutchison JG, Gordon SC, Schiff ER *et al.* Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. *N. Engl. J. Med.* 1998; **339**: 1485–92.

10 Poynard T, Marcellin P, Lee SS *et al.* Randomised trial of interferon alpha 2b plus ribavirin for 48 weeks or for 24 weeks versus interferon alpha 2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C

virus. International Hepatitis Interventional Therapy Group (IHIT). *Lancet* 1998; **352**: 1426–32.

11 Lau JYN, Davis GL, Kniffen J *et al.* Significance of serum hepatitis C virus RNA levels in chronic hepatitis C. *Lancet* 1993; **341**: 1501–4.

12 Hayashi K, Fukuda Y, Nakano I *et al.* Prevalence and characterization of hepatitis C virus genotype 4 in Japanese hepatitis C carriers. *Hepatol. Res.* 2003; **25**: 409–14.

13 Van Vlierbergh H, Delanghe JR, De Vos M, Leroux-Roel G, BASL Steering Committee. Factors influencing ribavirin-induced hemolysis. *J. Hepatol.* 2001; **34**: 911–16.

14 Lau JY, Tam RC, Liang TJ, Hong Z. Mechanism of action of ribavirin in the combination treatment of chronic HCV infection. *Hepatology* 2002; **35**: 1002–9.

15 Tsubota A, Akuta N, Suzuki F *et al.* Viral dynamics and pharmacokinetics in combined interferon alfa-2b and ribavirin therapy for patients infected with hepatitis C virus of genotype 1b and high pretreatment viral load. *Intervirology* 2002; **45**: 33–42.

Original Paper

Impact of Hepatologists to Extend Survival of Hepatocellular Carcinoma Patients with Cirrhosis: A Comparison with Non-hepatologists

Kazufumi Dohmen[1,2,3], Masafumi Shirahama[2,3], Hirohisa Shigematsu[2], Koji Irie[4], Hiromi Ishibashi[1]
[1]Clinical Research Center, National Nagasaki Medical Center, Omura; [2]Department of Internal Medicine and [4]Department of Pathology, Saga Prefectural Hospital Koseikan, Saga; [3]Department of Internal Medicine Okabe Hospital, Fukuoka, Japan
Corresponding Author: Dr. Kazufumi Dohmen, Department of Internal Medicine, Okabe Hospital
1-2-1 Myojinzaka Umi-machi Kasuya-gun, Fukuoka 811-2122, Japan
Tel: +81 92 932 0025, Fax: +81 92 933 7253, E-mail: dohmenk@par.odn.ne.jp

KEY WORDS:
Hepatocellular carcinoma; Hepatologist; Specialist; Generalist; Early detection; Therapy; Clinical characteristics; Survival rate

ABBREVIATIONS:
Hepatocellular Carcinoma (HCC); Segmental Transcatheter Arterial Chemoembolization (TACE); Segmental Transcatheter Arterial Chemolipiodolization (TACL); Percutaneous Ethanol Injection (PEI); Percutaneous Acetic Acid Injection (PAI); Microwave Ablation (MA); Radiofrequency Ablation (RFA)

ABSTRACT

Background/Aims: Whether or not generalists and specialist physicians can make an appropriate adaptation of their practice patterns when caring for their patients currently remains a matter of debate. The present study was undertaken to explore whether the clinical characteristics of hepatocellular carcinoma at its time of detection, the initial treatment options and the survival vary between patients with hepatocellular carcinoma associated with cirrhosis who were treated by hepatologists and those who were treated by non-hepatologists.

Methodology: A retrospective study with 626 patients with hepatocellular carcinoma associated with cirrhosis was performed. The patients were stratified into three groups as follows; 1) a hepatologist group: 280 patients followed up and treated consistently by hepatologists, 2) a non-hepatologist group: 126 patients followed up and treated consistently by non-hepatologists, and 3) the other group: 220 patients either followed up by hepatologists and treated by non-hepatologists, or vice versa, or those identified to have tumors incidentally without any follow-up. To confirm the clear difference between generalists and specialists, the gender ratio, age, hepatitis B and C virus markers, serum alpha-fetoprotein level, tumor size, the number of tumors, Child's grade, portal thrombosis at the initial detection, the types of follow-up until the initial detection of hepatocellular carcinoma, the initial treatments chosen, and survival were compared between the hepatologist group and the non-hepatologist group.

Results: There were no statistically significant differences between the two groups with respect to gender ratio, age, hepatitis virus markers and the alpha-fetoprotein level. However, the tumor size, the number of tumors, Child's grade and portal thrombosis at the initial detection were more advanced in the non-hepatologist group, which was most likely due to the poorer follow-up until the detection of hepatocellular carcinoma compared with that in the hepatologist group (p value: 0.0237). Regarding therapy for hepatocellular carcinoma, intensive therapies were more often performed in the hepatologist group and, in addition, non-treated cases were less frequently found in the hepatologist group. Consequently, the 1-, 3- and 5-year survivals of the patients in the hepatologist group were 84.7, 61.1 and 35.1%, respectively, which were significantly longer than those in the non-hepatologist group, which were 80.7, 45.8 and 31.8%, respectively (p value: 0.0434).

Conclusions: Hepatocellular carcinoma patients with cirrhosis who were treated by hepatologists can expect to obtain a longer survival because hepatocellular carcinoma tends to be detected at a smaller size, while such patients also usually receive more appropriate treatment modalities.

INTRODUCTION

Hepatocellular carcinoma (HCC) represents one of the most common and rapidly fatal cancers worldwide with a particularly high prevalence in Japan, Southeast Asia and Southern Africa. Recently, epidemiologic data has shown the incidence of HCC to also be increasing in Europe and the United States (1,2). In Japan, liver cirrhosis is an underlying disease in most cases of HCC, and also an illness for which both non-hepatologists (primary care physicians, internists, general practitioners) as well as hepatologists provide care. Consequently, a sufficient number of patients with liver cirrhosis have been managed consistently by non-hepatologists even after HCC has been detected. On the other hand, substantial variations between subspecialists and generalists are thought to exist in the management and outcome of several diseases. Recent investigations regarding the management of patients with acute myocardial infarction (3), acute diverticulitus (4), *Helicobacter pylori*-related gastroin-

Hepato-Gastroenterology 2004; 51:564-569

testinal disease (5), colorectal cancer (6), nonvariceal upper gastrointestinal bleeding (7,8), hepatitis C (9) and decompensated cirrhosis (10) revealed that specialists were associated with a better outcome due to a more thorough awareness of these diseases.

It seems possible then that better trained subspecialists in clinical management are capable of providing more efficient care. However, whether or not the importance of knowledge concerning HCC associated with cirrhosis between hepatologists and non-hepatologists plays a role in the patient outcome remains uncertain. The clinical application of current knowledge is crucial, given that both the careful follow-up of patients with cirrhosis, in order to detect HCC earlier, and the selection of optimal treatment modalities can possibly lead to an increased survival.

The variations in the outcome of HCC with cirrhosis may be attributable, in part, to patient characteristics, variations in the expertise of the attending physician, and even to controversy regarding preferred treatment techniques for HCC. We thus conducted the present study to investigate whether differences in the knowledge of the latest information and technologies regarding HCC with cirrhosis between hepatologists and non-hepatologists influences early diagnosis, the initial therapeutic options and the survival of patients with HCC with cirrhosis.

METHODOLOGY

Patients

A retrospective study of 626 consecutive patients with a diagnosis of HCC associated with cirrhosis at the Internal Medicine Department, Saga Prefectural Hospital Koseikan and at the Internal Medicine Department, Okabe Hospital between January 1989 and December 2001. All patients were followed for more than 6 months. The diagnosis of HCC was made unequivocally based on the clinical features, ultrasonography, computed tomography, the serum alpha-fetoprotein (AFP) level and/or histological findings when available. For each patient the following data were recorded: sex, age, hepatitis virus markers; hepatitis B surface (HBs) antigen, hepatitis C (HCV) antibody, AFP values, diameter of the tumors, the number of the tumors, the presence or absence of portal thrombosis, Child's grade, the types of follow-up, the types of treatment and survival rate. The AFP level was divided into two categories: 20ng/mL or less and more than 20ng/mL. The largest tumor was regarded as a representative tumor if the patient had two or more tumors. The diameter of the main tumor was measured in its greatest dimension. The tumor size was divided into two groups including a size of 3cm or less or more than 3cm. The number of HCC was divided into two groups including solitary and non-solitary tumors. Portal thrombosis was defined as a protrusion of the tumor into the first and/or second branch or into the main trunk of the portal vein. The degree of cell differentiation was classified according to the system of Edmondson and Steiner (11). Regarding the surveillance program for the early detection of HCC, all patients followed up by the hepatologists and the non-hepatologists were divided into two categories as follows; a closely followed-up group (regular periodic follow-up with monthly AFP measurement and ultrasonography at least every four months), and a non-closely followed-up group (neither performed with AFP measurement nor ultrasonography regularly). Any patients who were discovered incidentally due to related symptoms or by chance were excluded from the study. Types of initial treatment for HCC were categorized into six categories; 1) segmental transcatheter arterial chemoembolization (TACE) or segmental transcatheter arterial chemolipiodolization (TACL), 2) percutaneous ethanol injection (PEI) or percutaneous acetic acid injection (PAI), 3) microwave ablation (MA) or radiofrequency ablation (RFA), 4) surgical resection, 5) continuous or intermittent chemotherapy with a reservoir, and 6) non-treatment. Alcohol consumption was excluded in the current study, because it could not be precisely documented based on the medical records.

Definition of Hepatologist

Clinical physicians were stratified into two groups consisting of hepatologists and non-hepatologists. The hepatologists were defined as those who either had been or became certified by the Japan Society of Hepatology either at the start of the follow-up or during the follow-up for cirrhotic patients, or those who had at least 3 years experience in the hepatology field at an institute certified by the Japan Society of Hepatology. The non-hepatologists were defined as general physicians or specialists in other fields including gastroenterologists, pulmonologists, diabetologists, endocrinologists, and hematologists, etc.

Statistical Analysis

Differences in the means and proportions were evaluated by either the Chi-squared test or Fisher's exact analysis. An estimation of survival was performed by computing the survival curves according to the Kaplan-Meier method and then comparing them using the Cox-Mantel log-rank test (12). A p value of less than 0.05 was considered to be significant.

RESULTS

Variables and Survival between Hepatologist Group and Non-hepatologist Group

The clinical characteristics of the 406 patients included in the study are shown in **Table 1**. Of all the clinical variables examined, the variables reaching statistical significance between the hepatologist group and the non-hepatologist group were tumor size, the number of tumors, Child's grade, portal thrombosis and the types of follow-up, while the gender ratio, age, hepatitis virus markers and the AFP level showed no significant difference. Regarding the histological grade of HCC, a tumor biopsy was less frequently performed in the non-hepatologist group (31.7%) than in the hepatologist group (47.9%), and the difference was statistically significant. Therefore, the difference in the histological grade between both groups could not be compared.

TABLE 1 Patients with HCC Followed up and Treated by Hepatologist or Non-hepatologist

Factors		Hepatologist (n=280) (%)	Non-hepatologist (n=126) (%)	*p* value
Male/Female		179/101	93/33	0.0531
Mean age±SD*		66.0±8.4	65.8±8.1	0.8770
Virus marker	HBsAg (+)	18 (6.4)	10 (7.9)	0.6723
	HCVAb (+)	256 (91.4)	118 (93.6)	0.5519
Alpha-fetoprotein**	≤20ng/mL	108 (42.2)	64 (52.5)	
	>20ng/mL	148 (57.8)	58 (47.5)	0.0769
Diameter of HCC	≤3cm	196 (70.0)	74 (58.7)	
	>3cm	84 (30.0)	52 (41.3)	0.0308
Number of HCC	Solitary	181 (64.6)	64 (50.8)	
	Non-solitary	99 (35.4)	62 (49.2)	0.0115
Child's grade	A	165 (58.9)	59 (46.8)	
	B, C	115 (41.1)	67 (53.2)	0.0241
Portal thrombosis	+	9 (3.2)	12 (9.5)	
	-	271 (96.8)	114 (90.5)	0.0134
Tumor biopsy		134 (47.9)	40 (31.7)	0.0024
Edmondson grade**	Well	68 (50.8)	19 (47.5)	
	Moderately-Poorly	66 (49.2)	21 (52.5)	0.7232
Type of follow-up	Closely	107 (38.2)	33 (26.2)	
	Non-closely	173 (61.8)	93 (73.8)	0.0237
Survival	1-year	84.7%	80.7%	
	3-year	61.1%	45.8%	
	5-year	35.1%	31.8%	0.0434

*Student's *t*-test, all other factors were analyzed by Fisher's exact test.
**The number of cases with sufficient data.

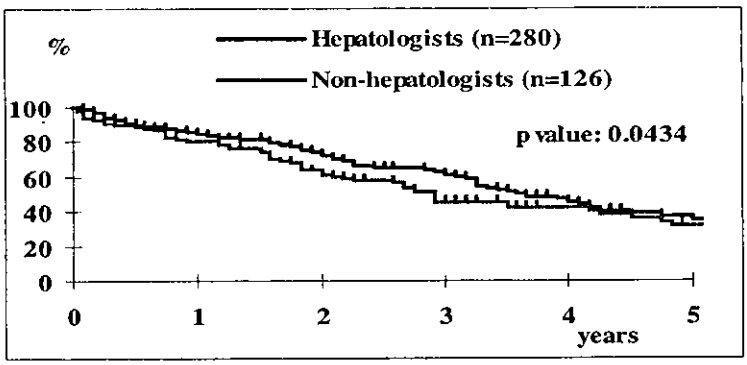

FIGURE 1 Survival rate between the hepatologist group and the non-hepatologist group.

Solitary HCC and HCC measuring 3cm or less in the greatest dimension were detected in 64.6% and 70.0% in the hepatologist group, and in 50.8% and 58.7% in the non-hepatologist group, respectively. These data also proved to be statistically significant (*p* value: 0.0115 in number, 0.0308 in size). Portal thrombosis was found in 3.2% in the hepatologist group but in 9.5% in the non-hepatologist group. This difference was also statistically significant (*p* value: 0.0134). To define the potential significance of a careful follow-up of patients with cirrhosis to find HCC earlier, the ratio of the types between a close follow-up and non-close follow-up was compared between the hepatologist group and the non-hepatologist group. The hepatologist group was more likely to carefully follow up the patients until detecting HCC, compared with the non-hepatologist group, which thus was mostly accounted for the results for less advanced stage of HCC at the initial detection in the hepatologist group. Regarding the type of follow-up, the rates of a close follow-up and non-close follow-up were found to be 38.2% and 61.8% in the hepatologist group and 26.1% and 73.9% in the non-hepatologist group, respectively (*p* value: 0.0237). The 1-, 3- and 5-year survivals in the hepatologist group of 280 patients and the non-hepatologist group of 126 patients were 84.7, 61.1 and 35.1% *versus* 80.7, 45.8 and 31.8%, respectively **(Table 1, Figure 1)**. A significant difference in the survival between both groups was thus observed (*p* value: 0.0434).

Types of Treatment

TACE, TACL and the placement of a catheter were performed by radiologists who were consulted by hepatologists and non-hepatologists at our institutes. A surgical resection was performed by surgeons. Other treatments including PEI, PAI, MA, RFA and chemotherapy with a reservoir and a tumor biopsy under ultrasonography were performed by the hepatologists, and PEI, PAI, MA, RFA and chemotherapy with a reservoir and a tumor biopsy in the patients cared for by non-hepatologists were performed by hepatologist when consulted by non-hepatologists. As for the types of treatment, no significant difference was identified in TACE or TACL, a surgical resection or chemotherapy with a reservoir between the hepatologist group and the non-hepatologist group **(Table 2)**. However, the use of PEI or PAI tended to be performed more often in the hepatologist group compared to that in the non-hepatologist group (51.4% *vs.* 42.1%, *p* value: 0.0867). MA or RFA (33.9% *vs.* 4.0%, *p* value: <0.0001) was likely to be performed more frequently in the hepatologist group while non-treated patients (3.6% *vs.* 11.9%, *p* value: 0.0028) were seen more frequently in the non-hepatologist group. Regarding monotherapy or combination therapy, 38.1% in the non-hepatologist group and 60.7% in the hepatologist group were treated with the combination therapy, respectively (*p* value: <0.0001) **(Table 2)**. The prevalence of monotherapy of TACE alone or TACL alone was found to be more prevalent in the non-hepatologist group (23.0% and 15.1%) compared to that in the hepatologist group (13.2% and 6.8%) (*p* value: 0.0194 in TACE, 0.0101 in TACL).

DISCUSSION

The results of this study demonstrated that cirrhotic patients with HCC who were managed by hepatologists experienced a significantly longer survival than those managed by non-hepatologists. Several studies so far have shown that specialists provide a better outcome than generalists in the management of patients with suspected myocardial chest pain (13), unstable angina (14), acute myocardial infarction (15,16), asthma (17,18), diabetes (19), *Staphylococcus aureus* bacteremia (20), osteoarthritis (21), acute diverticulitis (4,8), *Helicobacter pylori*-related gastrointestinal disease (5), colorectal cancer (6), nonvariceal upper gastrointestinal bleeding (7,8), hepatitis C (9) and decompensated cirrhosis (10). In contrast, other studies have shown that specialists were no bet-

ter than generalists in the management of patients with severe chronic obstructive pulmonary disease (22), hypertension and non-insulin-dependent diabetes mellitus (23). To date, there has been no comparison data on the outcome of HCC patients managed by generalists and hepatologists.

From the results in our study, two factors may explain the observed difference in survival in HCC patients with cirrhosis treated by non-hepatologists and hepatologists. First, the hepatologists may have a better knowledge than non-hepatologists of the importance of a careful follow-up for high-risk patients of HCC. In this study of 406 patients hospitalized with HCC, there was no significant difference in the gender ratio, mean age and hepatitis virus marker between the hepatologist group and the non-hepatologist group. The statistically significant clinical variables between both groups were found to be tumor size, the number of tumors, Child's grade and portal thrombosis. Indeed, several studies suggest that subspecialists tend to work with patients who are younger and healthier (24) or older and in a more severe state (17,25).

However, the results that the disease severity observed between the hepatologist group and the non-hepatologist group in our study was significantly different lead us to carry out this investigation. The longer survival of HCC patients in the hepatologist group could be due to the early detection of HCC because the hepatologists carefully followed up the high-risk group of HCC patients. The early detection of small HCCs in high-risk patients with the timely utilization of examinations such as ultrasonography or the measurement of tumor markers has recently been reported to improve the survival rates (26-28). This study confirms the importance that hepatologists, compared with non-hepatologists, provide better care to detect HCC earlier on their clinical knowledge which possibly leads to more chances to treat HCC (28).

A second explanation could be that the hepatologists have a greater concern about the therapeutic techniques employed for HCC. Owing to the advent of newer technologies, the survival of patients with HCC has increased (29). PEI has been shown to be a highly effective and reproducible treatment for small, nodular-type HCC lesions even when associated with advanced liver cirrhosis (30-32). Recently, Daniele *et al.* reported that a hepatic resection for patients with small HCC had a survival rate similar to that of PEI (33). Furthermore, the combination therapy of TAE and PEI has been shown to significantly reduce local recurrence and contribute to a longer survival for unresectable large HCC due to the enhanced necrotic change of HCC (34,35). Similarly, combination therapy of PEI and PMCT for HCC has been shown to be effective (36). Recently, RFA combined with pretreatment tumor arterial occlusion (37-39) and RFA combined with PEI (40) have also been the promising treatment option even for large HCC. The established patterns of treatment for HCC have gradually changed over time. At the same time, some procedures are too complicated to always be performed and require extensive training (41).

Our results indicated that the options of treatment for HCC by non-hepatologists were relatively limited to monotherapy (47.6%) compared to that by the hepatologists (35.4%) whereas combination therapy was adopted more frequently by the hepatologist group (60.7%) than the non-hepatologist group (38.1%). Furthermore, approximately 12 percent of all patients with HCC associated with cirrhosis in the non-hepatologist group were considered to not be eligible for therapy compared with 3.6 percent of those in the hepatologist group, although the fact that more advanced cases of HCC were found in the non-hepatologist group should be taken into account. The non-hepatologists, compared with the hepatologists, remained less likely to adopt optimal and aggressive combined therapies after the efficacy of the combined therapies was established. Generally, subspecialists have a greater knowledge of the disease and implement the latest scientific developments within their special field rapidly (38), whereas non-specialists manifested a delayed response regarding their approach to treatment for any diseases. The difference of survival of HCC patients between the hepatologist group and the non-hepatologist group was believed to be explained by the improved quality of patient care and the aggressive treatment adopted by hepatologists who have advanced training in the field of hepatology.

Increasing specialization and the more frequent use of newly developed procedures by specialists have been cited as major factors increasing healthcare costs (42). In order to limit costs, managed care systems have grown in the United States. They strongly stress the figure that generalists provide equally good, less intensive care for specific conditions at a lower cost than do specialists (43,44). However, the costs and outcomes of patients with specific conditions treated

TABLE 2 Types of Treatment for Patients with HCC Treated by Hepatologists or Non-hepatologists

Types of treatment	Hepatologist (n=280) (%)	Non-hepatologist (n=126) (%)	*p* value
TACE or TACL	204 (72.9)	94 (74.6)	0.8083
PEI or PAI	144 (51.4)	53 (42.1)	0.0867
MA or RFA	61 (33.9)	5 (4.0)	<0.0001
Surgical Resection	15 (5.4)	3 (2.4)	0.2047
Chemotherapy with a reservoir	6 (2.1)	2 (1.6)	>0.9999
Non-treatment	10 (3.6)	15 (11.9)	0.0028
Monotherapy without surgical resection	99 (35.4)	60 (47.6)	0.0212
TACE alone	37 (13.2)	29 (23.0)	0.0194
TACL alone	19 (6.8)	19 (15.1)	0.0101
Combination therapy	170 (60.7)	48 (38.1)	<0.0001

All factors were analyzed by Fisher's exact test.
TACE: Segmental transcatheter arterial chemoembolization;
TACL: Segmental transcatheter arterial Chemolipiodolization;
PEI: Percutaneous ethanol injection; PAI: percutaneous acetic acid injection; MA: Microwave ablation: RFA: Radiofrequency ablation.

by generalists in comparison with that provided by specialists remain controversial. In contrast, in Japan unlike United States managed care systems have not yet been established and consultations for the hepatologist are not associated with the cost of hospitalization. Therefore, no limited access to the hepatologists exists for patients with cirrhosis and HCC. However, in Japan the supply of the hepatologists at the hospital are insufficient to fully follow up and treat the increasing number of patients with cirrhosis and HCC. One of our hospitals in the study has two or three hepatologists and approximately 60-70 new HCC patients a year have been recently identified or referred to (29). In addition, the survival of patients with cirrhosis and HCC has increased over one or two decades due to the development of screening and advanced technology. Consequently, better care by the hepatologists has not been fully provided to a large number of patients with cirrhosis and HCC who are continuing to live longer. As a result, many such patients are still being followed up and treated by non-hepatologists.

This study is unique because there are no published data comparing the outcomes of patients managed by hepatologists *versus* non-hepatologists in the field of HCC although there has been one previous paper on the outcomes of decompensated cirrhosis with a comparison of the results between generalists and specialists (10). This study was limited to our local hospitals to assess the different outcomes by hepatologists or non-hepatologists, nonetheless, it is reasonable to speculate that subspecialists in hepatology play an important and critical role in the care and treatment of patients with HCC associated with cirrhosis. Especially, the countries and areas with a high prevalence of HCC need an increasingly larger number of hepatologists in order to manage HCC more effectively.

In conclusion, hepatologists are associated with an early detection of HCC, optimal treatments and improvement in survivals with HCC. Therefore, the training of a large number of specialists is called for in the countries or areas with an increasing prevalence of HCC.

REFERENCES

1 **El-Serag HB, Mason AC:** Rising incidence of hepatocellular carcinoma in the United States. N Eng J Med 1999; 340:745-750.

2 **El-Serag HB:** Hepatocellular carcinoma: an epidemiologic view. J Clin Gastroenterol 2002; 35(Suppl 2):572-578.

3 **Ayanian JZ, Hauptman PJ, Guadagnoli E, Antman EM, Pashos CL, McNeil BJ:** Knowledge and practices of generalist and specialist physicians regarding drug therapy for acute myocardial infarction. N Eng J Med 1994; 331:1136-1142.

4 **Zarling EJ, Piontek F, Klemka-Walden L, Inczauskis D:** The effect of gastroenterology training on the efficiency and cost of care provided to patients with diverticulitis. Gastroenterology 1997; 112:1859-1862.

5 **Breuer T, Goodman KJ, Malaty HM, Sudhop T, Graham DY:** How do clinicians practicing in the U.S. manage *Helicobacter pylori*-related gastroduodenal diseases? A comparison of primary care and specialist physicians. Am J Gastroenterol 1998; 93:553-561.

6 **Schroy PC, Barrison AF, Ling BS, Wilson S, Geller AC:** Family history and colorectal cancer screening: a survey of physician knowledge and practice pattern. Am J Gastroenterol 2002; 97:1031-1036.

7 **Pardo A, Durandez R, Hernandez M, Pizarro A, Hombrados M, Jimenez A, et al:** Impact of physician specialty on the cost of nonvariceal upper GI bleeding care. Am J Gastroenterol 2002; 97:1535-1542.

8 **Provenzale D, Ofman J, Gralnek I, Rabeneck L, Koff RK, McCrory D:** Gastroenterologist specialist care and care provided by generalists- An evaluation of effectiveness and efficiency. Am J Gastroenterol 2003; 98:21-28.

9 **Shehab TM, Orrego M, Chunduri R, Lok ASF:** Identification and management of hepatitis C patients in primary care clinics. Am J Gastroenterol 2003; 98:639-644.

10 **Bini EJ, Weinshel EH, Generoso R, Salman L, Dahr G, Pena-Sing I, et al:** Impact of gastroenterology consultation on the outcomes of patients admitted to the hospital with decompensated cirrhosis. Hepatology 2001; 34:1089-1095.

11 **Edmondson HA, Steiner PE:** Primary carcinoma of the liver: a study of 100 cases among 48,900 necropsies. Cancer 1954; 7:462-503.

12 **Kaplan EL, Meier P:** Nonparametric estimation for incomplete observations. J Am Stat Assoc 1958; 53:457-481.

13 **Young S, Baigelman W, Coldiron J, Beiser A:** Comparison of efficiency of cardiologists and internists in managing patients with suspected myocardial chest pain. Crit Care Med 1988; 16:1098-1100.

14 **Schreiber TL, Elkhatib A, Grines CL, O'Neill WW:** Cardiologist *versus* internist management of patients with unstable angina: treatment patterns and outcomes. J Am Coll Cardiol 1995; 26:577-582.

15 **Jollis JG, DeLong ER, Peterson ED, Muhlbaier LH, Fortin DF, Califf RM, et al:** Outcome of acute myocardial infarction according to the specialty of the admitting physician. N Eng J Med 1996; 335:1880-1887.

16 **Willison DJ, Soumerai SB, McLaughlin TJ, Gurwitz JH, Gao X, Guadagnoli E, et al:** Consultation between cardiologists and generalists in the management of acute myocardial infarction: implications for quality of care. Arch Intern Med 1998; 158:1778-1783.

17 **Vollmer WM, O'Hollaren M, Ettinger KM, Stibolt T, Wilkins J, Buist AS, et al:** Specialty differences in the management of asthma: a cross-sectional assessment of allergists' patients and generalists' patients in a large HMO. Arch Intern Med 1997; 157:1201-1208.

18 **Zeiger RS, Heller S, Mellon MH, Wald J, Falkoff R, Schatz M:** Facilitated referral to asthma specialist reduces relapses in asthma emergency room visits. J Allergy Clin Immunol 1991; 87:1160-1168.

19 **Levetan CS, Salas JR, Wilets IF, Zumoff B:** Impact of endocrine and diabetes team consultation on hospital length of stay for patients with diabetes. Am J Med 1995; 99:22-28.

20 **Fowler Jr VG, Sanders LL, Sexton DJ, Kong L, Marr KA, Gopal AK, et al:** Outcome of *Staphylococcus aureus* bacteremia according to compliance with recommendations of infectious disease specialists: experience with 244 patients. Clin Infect Dis 1998; 27:478-486.

21 **Mazzuca SA, Brandt KD, Katz BP, Stewart KD:** Therapeutic strategies distinguish community based primary care physicians from rheumatologists in the management of osteoarthritis. J Rheumatol 1993; 20:80-86.

22 **Regueiro CR, Hamel MB, Davis RB, Desbiens N, Connors Jr AF, Phillips RS, et al:** A comparison of generalist and pulmonologist care for patients hospitalized with severe chronic obstructive pulmonary disease: Resource intensity, hospital costs, and survival. Am J Med 1998; 105:366-372.

23 **Greenfield S, Rogers W, Mangotich M, Carney MF, Tarlov AR:** Outcomes of patients with hypertension and non-insulin-dependent diabetes mellitus treated by different systems and specialties. Results from the medical out-

comes study. JAMA 1995; 274:1436-1444.
24 **Horner RD, Matchar DB, Divine GW, Feussner JR:** Relationship between physician specialty and the selection and outcome of ischemic stroke patients. Health Serv Res 1995; 30:275-287.
25 **Greenfield S, Nelson EC, Zubkoff M, Manning W, Rogers W, Kravitz RL, et al:** Variations in resource utilization among medical specialties and systems of care. Results from the medical outcomes study. JAMA 1992; 267:1624-1630.
26 **Gebo KA, Chander G, Jenckes MW, Ghanem KG, Herlong HF, Torbenson MS, et al:** Screening tests for hepatocellular carcinoma in patients with chronic hepatitis C: a systematic review. Hepatology 2002; 36:S84-S92.
27 **Dohmen K, Shirahama M, Miyamoto Y, Torii Y, Irie K, Ishibashi H:** Differences in survival based on the type of follow-up for the detection of hepatocellular carcinoma: an analysis of 547 patients. Hepatol Res 2000; 18:110-121.
28 **Yuen M-F, Cheng C-C, Lauder IJ, Lam S-K, Ooi C-G, Lai C-L:** Early detection of hepatocellular carcinoma increases the chance of treatment: Hong Kong experience. Hepatology 2000; 31:330-335.
29 **Dohmen K, Shigematsu H, Irie K, Ishibashi H:** Trends in clinical characteristics, treatment and prognosis of hepatocellular carcinoma. Hepatogastroenterology 2003; 50: 1872-1877.
30 **Shiina S, Tagawa K, Niwa Y, Unuma T, Komatsu Y, Yoshiura K, et al:** Percutaneous ethanol injection therapy for hepatocellular carcinoma: results in 146 patients. AJR 1993; 160:1023-1028.
31 **Castells A, Bruix J, Bru C, Fuster J, Vilana R, Navasa M, et al:** Treatment of small hepatocellular carcinoma in cirrhotic patients: a cohort study comparing surgical resection and percutaneous ethanol injection. Hepatology 1993; 18:1121-1126.
32 **Orlando A, D'Antoni A, Camma C, Albanese M, Livraghi T, Torzilli G, et al:** Treatment of small hepatocellular carcinoma with percutaneous ethanol injection: a validated prognostic model. Am J Gastroenterol 2000; 95:2921-2927.
33 **Daniele B, De Sio I, Izzo F, Capuano G, Andreana A, Mazzanti R, et al:** Hepatic resection and percutaneous ethanol injection as treatments of small hepatocellular carcinoma. A cancer of the Liver Italian Program (CLIP 08). Retrospective case-control study. J Clin Gastroenterol 2003; 36:63-67.
34 **Tanaka K, Nakamura S, Numata R, Kondo M, Morita K, Kitamura T, et al:** The long term efficacy of combined transcatheter arterial embolization and percutaneous ethanol injection in the treatment of patients with large hepatocellular carcinoma and cirrhosis. Cancer 1998; 82:78-85.
35 **Dohmen K, Shirahama M, Shigematsu H, Miyamoto Y, Torii Y, Irie K, et al:** Transcatheter arterial chemoembolization therapy combined with percutaneous ethanol injection for unresectable large hepatocellular carcinoma: An evaluation of local therapeutic effect and survival rate. Hepatogastroenterology 2001; 48:1409-1415.
36 **Seki T, Tamai T, Nakagawa T, Imamura M, Nishimura A, Yamasaki N, Ikeda K, et al:** Combination therapy with transcatheter arterial chemoembolization and percutaneous microwave coagulation therapy for hepatocellular carcinoma. Cancer 2000; 89:1245-1251.
37 **Rossi S, Garbagnati F, Lentioni R, Allgaier H-P, Marchiano A, Fornari F, et al:** Percutaneous radio-frequency thermal ablation of nonresectable hepatocellular carcinoma after occlusion of tumor blood supply. Radiology 2000; 217:119-126.
38 **Yamasaki T, Kurokawa F, Shirahashi H, Kusano N, Hironaka K, Okita K:** Percutaneous radiofrequency ablation therapy for patients with hepatocellular carcinoma during occlusion of hepatic blood flow: Comparison with standard percutaneous radiofrequency ablation therapy. Cancer 2002; 95:2353-2360.
39 **Yamakado K, Nakatsuka A, Ohmori S, Shiraki K, Nakano T, Ikoma J, et al:** Radiofrequency ablation combined with chemoembolization in hepatocellular carcinoma: treatment response based on tumor size and morphology. J Vasc Interv Radiol 2002; 13:1225-1232.
40 **Kurokohchi K, Watanabe S, Masaki T, Hosomi N, Funaki T, Arima K, et al:** Combination therapy of percutaneous ethanol injection and radiofrequency ablation against hepatocellular carcinomas difficult to treat. Int J Oncol 2002; 21:611-615.
41 **Gunneson TJ, Menon KVN, Wiesner RH, Daniels JA, Hay JE, Charlton MR, et al:** Ultrasound-assisted percutaneous liver biopsy performed by a physician assistant. Am J Gastroenterol 2002; 97:1472-1475.
42 **Eisenberg JM:** Doctors decisions and the cost of medical care. Ann Arbor, Michigan: Health Administration Press; 1986.
43 **Cohen JJ:** Transforming the size and composition of the physician work force to meet the demands of health care reform. N Eng J Med 1993; 329:1810-1812.
44 **Clement DG, Retchin SM, Brown RS, Stegall MH:** Access and outcomes of elderly patients enrolled in managed care. JAMA 1994; 271:1487-1492. [Erratum, JAMA 1994; 272:276].