was injected to prevent the sclerosant (5% ethanolamine oleate) from flowing out of the varices into the systemic circulation. After the start of injection of the sclerosant into the varices, the flow of the sclerosant was monitored using x-ray fluoroscopy. The injection of the sclerosant was stopped just as it filled the portosystemic collaterals. However, embolization of the feeder could not be achieved when variceal puncture or accidental retraction of the needle from the varices occurred during injection of the sclerosant. Puncture needles ranged in size from 23 to 25 gauge according to the size of the pore for the biopsy forceps of the endoscope. This treatment was repeated with an interval of 1–2 weeks, and 2–4 sessions were needed to complete one series of treatment and eliminate all varices. Additional treatment with aethoxysclerol was applied at F0 on the basis of the endoscopic findings.

CT Examination

CT was first performed unenhanced to define the liver location, followed by injection of the contrast medium. For the latter, 100 mL of iopamidol 300 (Iopamiron 300, Schering) heated to 37°C was injected using a power injector (Auto Enhance A-250, Nemoto-Kyorindo), at a rate of 4.0 mL/s through a 22-gauge IV catheter inserted into an antecubital vein. Four sets of images were acquired in a craniocaudal direction at 20, 40, 65, and 180 seconds after initiation of contrast medium injection. The first and second acquisitions were used for hepatic artery phase images, the third acquisition for portal venous phase images, and the fourth acquisition for hepatic venous phase images. The third set of images was obtained during 20-second breath-holding, whereas those of other acquisitions were achieved during 10-second breath-holding. This protocol is used routinely in all patients with chronic liver diseases at our institution, and the data of the third acquisition are used for construction of 3D images of the portosystemic collaterals. All scanning was performed using a LightSpeed QX/i CT scanner (GE Healthcare). Specific scanning parameters vary among various scanners and are selected for imaging the details of vascular anatomy. We used the high-quality scanning mode, 1.25-mm slice thickness, and reconstruction intervals of 0.625-mm for portal venous phase images. MDCT was performed with Virtual Place Advance (AZE Ltd.) [25]. There are currently three reformatting techniques available. MPR was used for image reconstruction in this study. In every patient, CT was performed within 1 month before endoscopic injection sclerotherapy and after the final session of endoscopic injection sclerotherapy (median, 29 days; range, 25–34 days).

Evaluation of Portosystemic Collaterals

Portosystemic collaterals were independently assessed on MPR MDCT images before and after endoscopic injection sclerotherapy for esophageal varices by two radiologists (one with 17 and the other with 35 years of experience) who were blinded to the clinical and endoscopic results of endoscopic injection sclerotherapy. The diameter of the main portosystemic collateral vessel, such as the left gastric vein, posterior gastric vein, and paraesophageal vein, before and after endoscopic injection sclerotherapy was measured. The thickest portion of the vessel was measured in all cases. For assessment of changes of the feeding vessel after endoscopic injection sclerotherapy, we used the rate of reduction, which was calculated using the following formula: rate of reduction of the diameter of the feeding vessel (%) = [(diameter of feeding vessel before endoscopic injection sclerotherapy − diameter of feeding vessel after endoscopic injection sclerotherapy) / diameter of feeding vessel before endoscopic injection sclerotherapy] × 100.

Patients were divided into three groups according to the rate of reduction of the diameter of the feeding vessel. Patients with a reduction rate of ≥ 80% were classified as group A (complete eradication group), those with a rate of < 80% but > 40% were classified as group B (narrowing group), and those with a rate of ≤ 40% were classified as group C (no change group). Patients who showed no enhancement of the feeding vessel on MDCT were defined as group A. Moreover, on the basis of the diameter of the paraesophageal vein, which is the draining vessel of esophageal varices, patients were divided into two groups: the large paraesophageal vein group (≥ 3 mm) and the small paraesophageal vein group (< 3 mm). The cutoff diameter of 3 mm represents the median value of the paraesophageal vein. Patients with a paraesophageal vein that was too narrow to be recognized on MDCT were classified in the small paraesophageal vein group.

Follow-Up Study

Relapse after endoscopic injection sclerotherapy was assessed by endoscopy. Follow-up endoscopy was performed at 6-month intervals after treatment. Esophageal varices were evaluated independently at endoscopy by two endoscopists (one with 10 and the other with 15 years of experience). The endoscopic findings of esophageal varices were evaluated according to the classification system of the Japanese Society for Portal Hypertension and Esophageal Varices [24]. A final decision regarding the endoscopic finding was reached by consensus. The appearance of RC1, F1, or bleeding on follow-up endoscopy was regarded as a relapse of esophageal varices. In this prospective study, we defined relapse of esophageal varices as the primary end point and survival as the secondary end point. Data were analyzed in October 2007. The relationship between hemodynamic changes in portosystemic collaterals and prognosis of endoscopic injection sclerotherapy for esophageal varices was analyzed by the results of MPR MDCT images.

Statistical Analysis

All data of portosystemic collaterals are expressed as mean ± SD or median values. The cumulative relapse-free rate and cumulative survival rate among groups by rate of reduction after treatment were determined using the Kaplan-Meier method and statistical software (JMP, version 5, SAS Institute Japan). Significance was tested using the generalized Wilcoxon's test and Student's *t* test. A *p* value of less than 0.05 was regarded as significant.

Results

Portosystemic Collaterals Before Endoscopic Injection Sclerotherapy

Portosystemic collaterals were recognized on MPR MDCT images of all patients with esophageal varices. Table 2 summarizes the portosystemic collaterals evaluated on MPR MDCT images. The left gastric vein, posterior gastric vein, and left gastric vein plus posterior gastric vein were the main feeding vessels for esophageal varices in 83%, 9%, and 8% of patients, respectively. The largest mean diameter of the main feeding vessel was for the left gastric vein followed by the

TABLE 2: Portosystemic Collaterals Identified and Measured on CT

Portosystemic Collateral	No. (%)	Diameter (mm)
Left gastric vein	44 (83)	6.6 ± 2.4 (3.3–15)
Posterior gastric vein	5 (9)	4.1 ± 1.7 (2.7–7.5)
Left gastric vein and posterior gastric vein	4 (8)	6.0 ± 2.3 (2.7–10.3)
Paraesophageal vein	46 (87)	3.8 ± 1.8 (1.8–8.8)
Gastrorenal shunt	43 (81)	3.7 ± 1.4 (1.7–5.2)

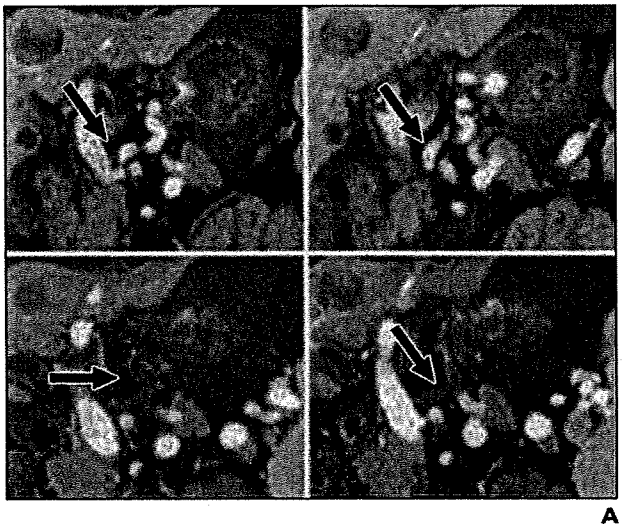
Note—Data for diameter are given as mean ± SD with range in parentheses.

posterior gastric vein. The left gastric vein was recognized as the portosystemic collateral for esophageal varices in 91% of the patients (83% of the patients with left gastric vein alone and 8% with left gastric vein plus posterior gastric vein) (Table 2). Furthermore, paraesophageal vein and gastrorenal shunts were found in 87% and 81% of patients, respectively, each with a mean of diameter of 4 mm.

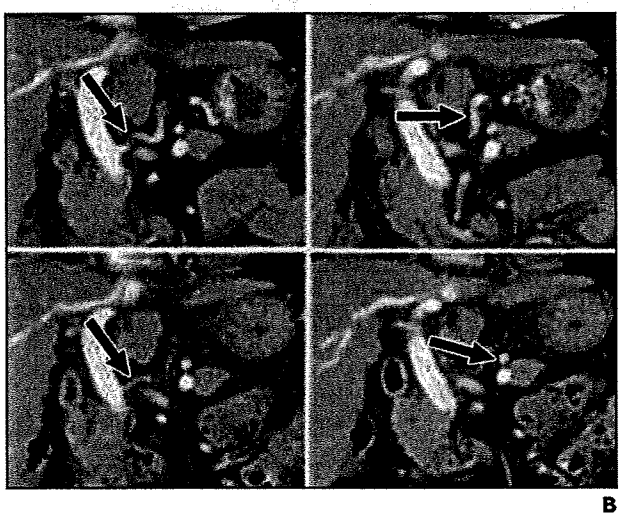
With regard to the relationship between endoscopic findings and portosystemic collaterals, the mean diameter of portosystemic collaterals measured on MPR images was 5.7, 6.4, and 6.6 mm for F1, F2, and F3 esophageal varices, respectively. The portosystemic collaterals tended to be thicker, with higher levels of esophageal varices development. The gastrorenal shunt was also identified as the portosystemic collateral vein, with a median diameter of 3.7 mm. However, there were no differences in relapse-free rates related to the presence or absence or size of the gastrorenal shunt.

Effect of Endoscopic Injection Sclerotherapy on Portosystemic Collaterals

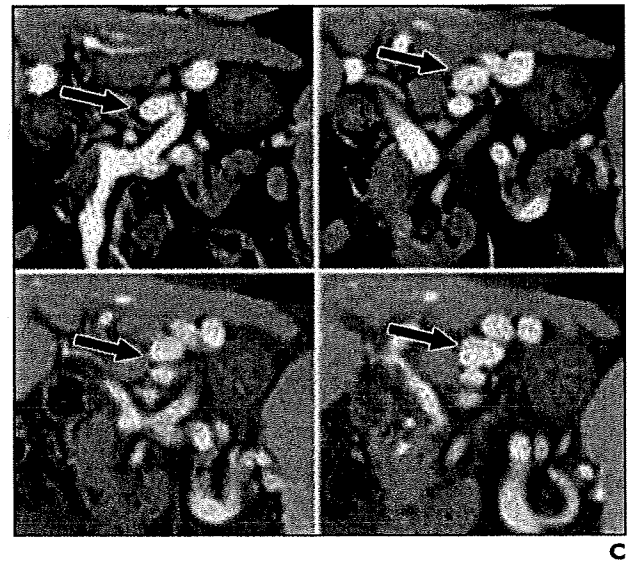
Analysis of the rate of diameter change of portosystemic collaterals after endoscopic injection sclerotherapy allowed classification of patients into groups A ($n = 10$), B ($n = 13$), and C ($n = 30$). Figure 1 shows typical MPR images of portosystemic collaterals of representative patients of the three groups. Figure 1A shows typical MPR images of portosystemic collaterals of a patient from group A, with complete eradication of the left gastric vein after endoscopic injection sclerotherapy. The diameter of the left gastric vein before and after endoscopic injection sclerotherapy was 5 and 0 mm, respectively, with a rate of left gastric vein diameter reduction of 100%. Figure 1B shows typical MPR images of portosystemic collaterals of a patient from group B, with narrowing of the left gastric vein after endoscopic injection sclerotherapy. The diameter of the left gastric vein before and after endoscopic injection sclerotherapy was 5.5 and 3.0 mm, respectively, with a rate of left gastric vein diameter reduction of 46%. Figure 1C shows typical MPR images of portosystemic collaterals of a patient from group C, with no change in the diameter of the left gastric vein after endoscopic injection sclerotherapy. The diameter of the left gastric vein before and after endoscopic injection sclerotherapy was 10 and 10 mm, respectively, with a rate of left gastric vein diameter reduction of 0%.



A



B



C

Fig. 1—Patients with esophageal varices who underwent endoscopic injection sclerotherapy.
A–C, Typical multiplanar reconstruction MDCT images of portosystemic collaterals in representative patients of groups A (**A**), B (**B**), and C (**C**) show left gastric vein (*arrow*). See text for definition of each group. Images on top row are before endoscopic injection sclerotherapy and images on bottom row are after endoscopic injection sclerotherapy.

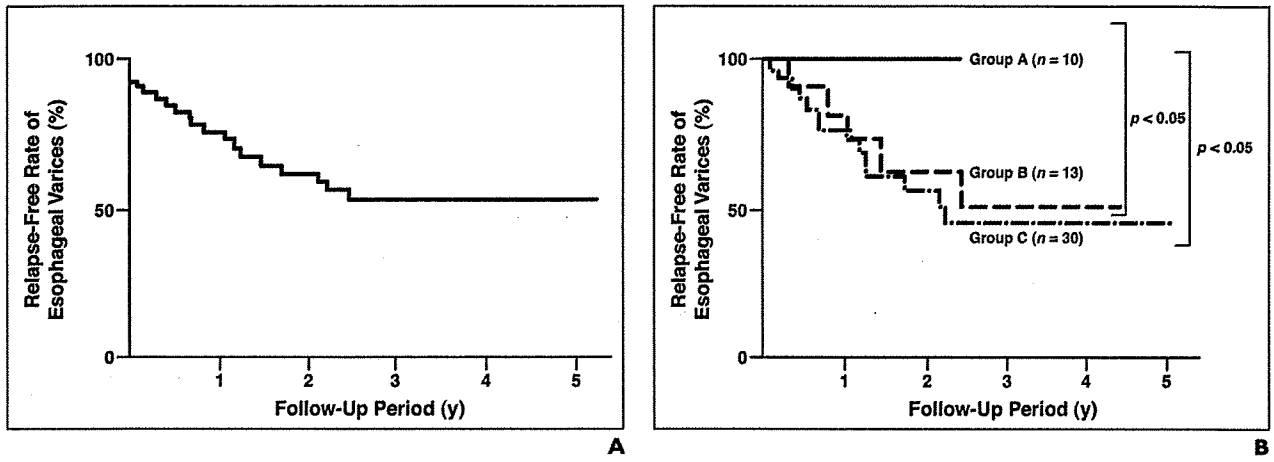


Fig. 2—Cumulative relapse-free rates of esophageal varices after sclerotherapy.
A, Graph shows cumulative relapse-free rates of esophageal varices after sclerotherapy for all patients.
B, Graph shows cumulative relapse-free rates of esophageal varices according to rate of reduction of portosystemic circulation after sclerotherapy.

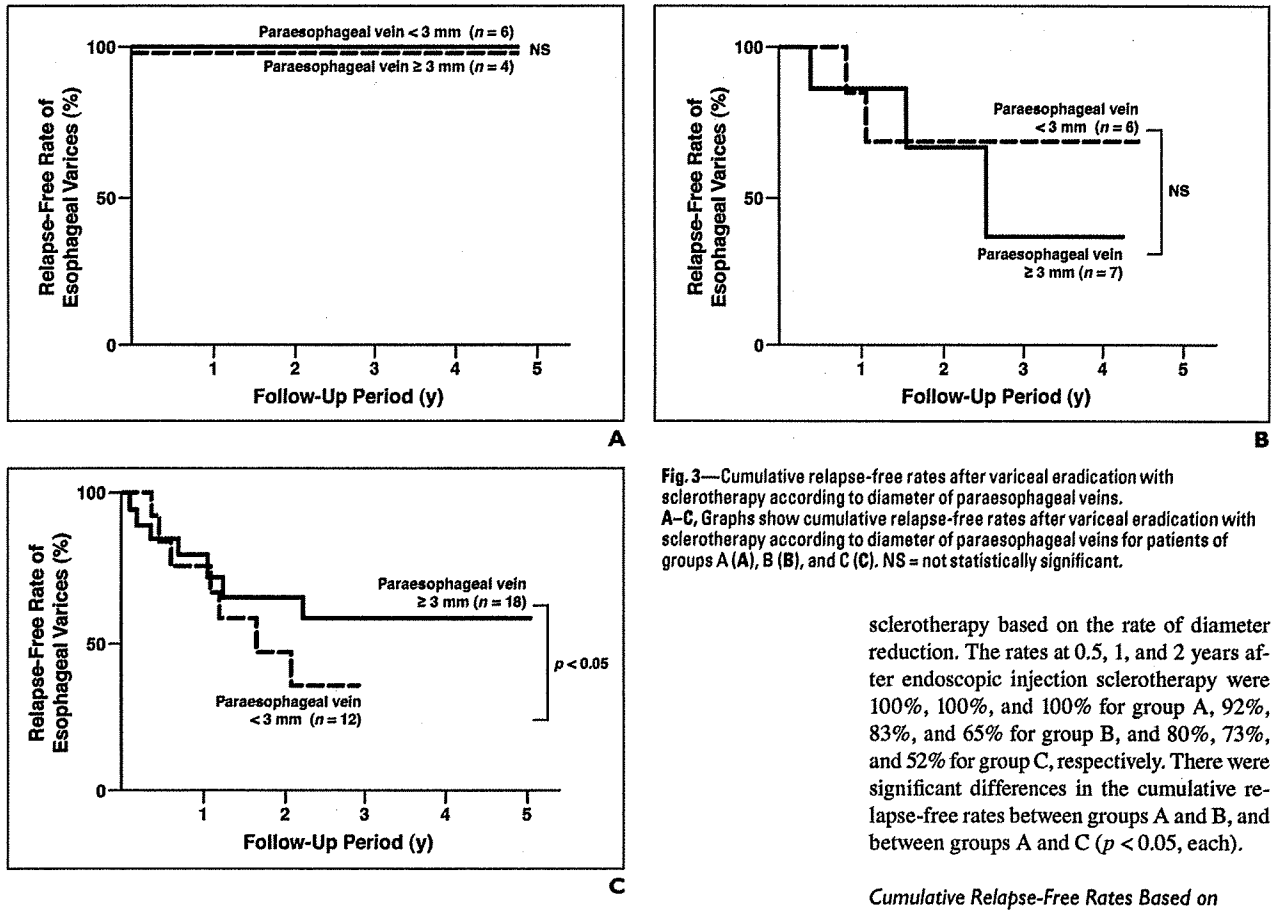


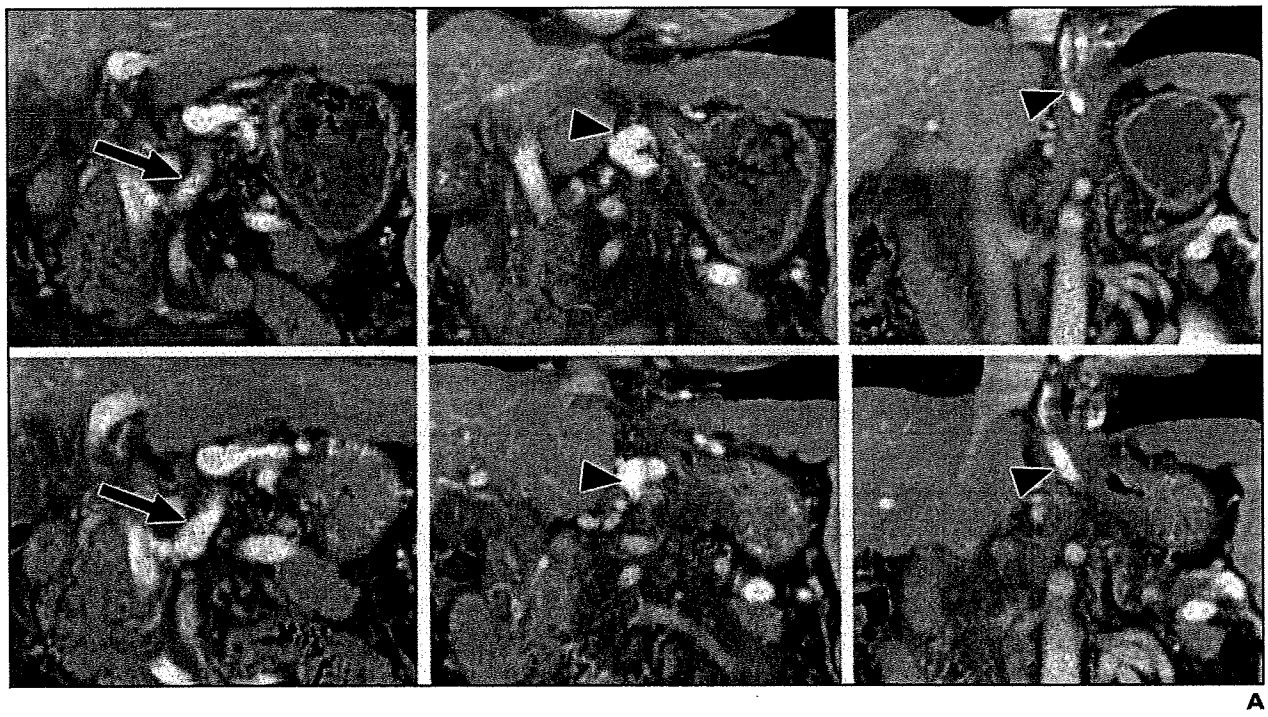
Fig. 3—Cumulative relapse-free rates after variceal eradication with sclerotherapy according to diameter of paraesophageal veins.
A–C, Graphs show cumulative relapse-free rates after variceal eradication with sclerotherapy according to diameter of paraesophageal veins for patients of groups A (**A**), B (**B**), and C (**C**). NS = not statistically significant.

Cumulative Relapse-Free Rates

For all patients, the cumulative relapse-free rates after endoscopic injection sclerotherapy were 87%, 81%, and 61% at 0.5, 1, and 2 years after treatment, respectively (Fig. 2A). The median follow-up period was 22 months. Figure 2B shows the cumulative relapse-free rates after endoscopic injection sclerotherapy based on the rate of diameter reduction. The rates at 0.5, 1, and 2 years after endoscopic injection sclerotherapy were 100%, 100%, and 100% for group A, 92%, 83%, and 65% for group B, and 80%, 73%, and 52% for group C, respectively. There were significant differences in the cumulative relapse-free rates between groups A and B, and between groups A and C ($p < 0.05$, each).

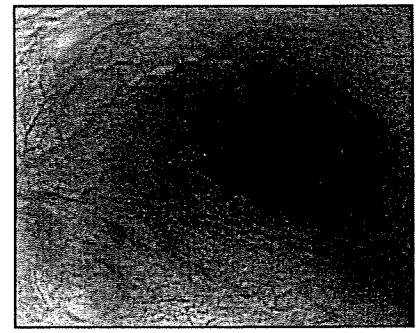
Cumulative Relapse-Free Rates Based on Paraesophageal Vein Diameter

Patients of groups A, B, and C were also divided into large and small paraesophageal vein groups using a cutoff diameter of 3 mm.



A

B



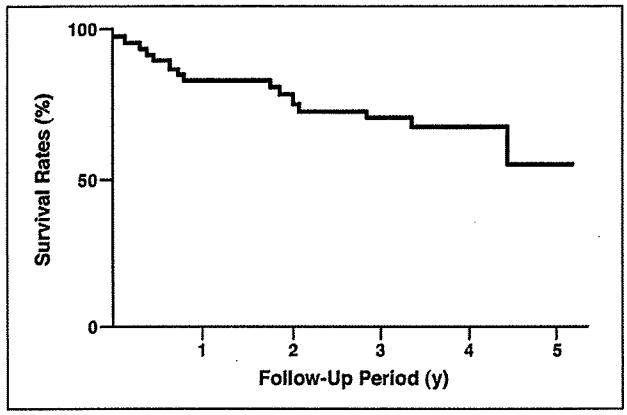
C

Fig. 4—56-year-old man with Child classification B hepatitis C virus–related liver cirrhosis and esophageal varices.
A, Multiplanar reconstruction MDCT images of portosystemic collaterals of this patient (from group C) show large left gastric vein (*arrow*) and large paraesophageal vein (*arrowhead*). Images on top row are before endoscopic injection sclerotherapy and images on bottom row are after endoscopic injection sclerotherapy.
B and **C**, Endoscopic findings in same patient show esophageal varices classified as F2RC1 before endoscopic injection sclerotherapy (**B**) and F0RC0 1 year after endoscopic injection sclerotherapy (**C**).

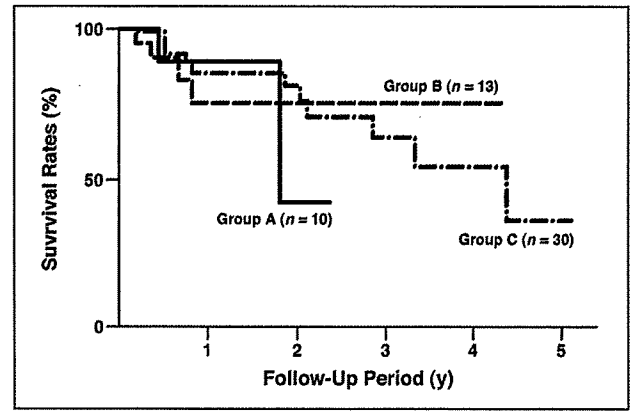
There were no significant differences in the cumulative relapse-free rates between the large paraesophageal vein group and the small paraesophageal vein group after endoscopic injection sclerotherapy for groups A and B (Figs. 3A and 3B). However, for group C, the cumulative relapse-free rates at 0.5, 1, and 2 years after endoscopic injection sclerotherapy were 83%, 78%, and 63% for the large paraesophageal vein group and 75%, 67%, and 36% for the small paraesophageal vein group, respectively (Fig. 3C). Thus, the diameter of the paraesophageal vein significantly influenced the cumulative relapse-free rates only in those patients who showed < 40% reduction in the diameter of feeding vessels after endoscopic injection sclerotherapy ($p < 0.05$). Figure 4 shows the MDCT and endoscopic findings of a representative patient from group C with a large paraesophageal vein. Figure 4 contains images of both before and after endoscopic injection sclerotherapy. Although insufficient embolization of the feeding vessels was evident after endoscopic injection sclerotherapy on the MPR MDCT images, esophageal varices relapse was not recognized on endoscopy 1 year after endoscopic injection sclerotherapy.

Survival Rates

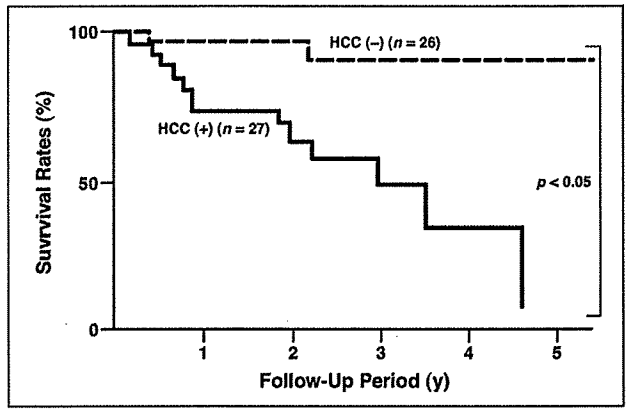
The cumulative survival rates after endoscopic injection sclerotherapy were 91%, 83%, and 78% at 0.5, 1, and 2 years after endoscopic injection sclerotherapy, respectively (Fig. 5A). In this study, the main cause of death was hepatocellular carcinoma (HCC) (60%). The cumulative survival rates after endoscopic injection sclerotherapy according to the rate of reduction of the diameter of feeding vessels (groups A–C) are shown in Figure 5B. There were no significant differences among the three groups with regard to the cumulative survival rates after endoscopic injection sclerotherapy. On the other hand, the cumulative survival rates after endoscopic injection sclerotherapy of patients with HCC (90%, 74%, and 62% at 0.5, 1, and 2 years, respectively) were significantly lower than those of patients without HCC (96%, 96%, and 96%, respectively; $p < 0.05$) (Fig. 5C).



A



B



C

Fig. 5—Cumulative survival rates of patients with esophageal varices after sclerotherapy.
A–C, Graphs show cumulative survival rates of patients with esophageal varices after sclerotherapy for all patients (**A**), patients of groups A, B, and C (**B**), and patients with and without hepatocellular carcinoma (HCC)(**C**). HCC (+) = patients with HCC, HCC (–) = patients without HCC.

Discussion

Esophageal varices, which are present in most patients with liver cirrhosis or portal hypertension, are located within the wall of the lower esophagus, whereas paraesophageal veins are situated outside the wall of the esophagus. These vessels are supplied primarily by the left gastric vein, which divides into anterior and posterior branches. The anterior branch supplies the esophageal varices, and the posterior branch forms the paraesophageal vein [23]. Endoscopic therapy, such as endoscopic injection sclerotherapy and endoscopic ligation, is now a well-accepted procedure for the control and prevention of bleeding from esophageal varices. Whereas endoscopic injection sclerotherapy is performed by intravariceal injection of 5% ethanolamine oleate with iopamidol, endoscopic ligation is performed using a ligation ring, as described by Van Stiegmann and Goff [26]. Endoscopic ligation obliterates mucosal and submucosal varices but not the perforating veins or feeding veins. Furthermore, the procedure does not alter portosystemic hemodynamics. It is reported that endoscopic injection sclerotherapy results in complete eradication of esophageal varices and minimizes the likelihood of recurrence and variceal hemorrhage after therapy [27]. In this regard, it is important to achieve not only endoscopic eradication of esophageal varices but also embolization of the feeding vessels supplied by the portal venous system. In this context, the observed differences in the effects of endoscopic injection sclerotherapy depend on anatomic variability in the portal venous system [28]. Therefore, detailed evaluation of portosystemic collaterals is important before endoscopic injection sclerotherapy.

Conventional CT (i.e., nonhelical CT and single-detector helical CT) provides less information about vascular anatomy of the lower esophagus and upper stomach in patients with esophageal varices compared with axial images or reconstruction images using MDCT. Angiography and PTP are considered the leading techniques in evaluation of vascular anatomy of the lower esophagus and upper stomach in patients with portal hypertension. However, these techniques are more invasive and time-consuming than CT. Recently, MDCT has become more useful for examining the whole portosystemic shunt because of advances in biotechnology and software development. MPR images using MDCT allow rapid assessment of portosystemic collaterals along different planes without losing information about the surrounding structures [22, 23]. Therefore, we evaluated portosystemic collaterals using MPR MDCT images and investigated the relationships between changes in dynamics after endoscopic injection sclerotherapy and clinical course.

In the treatment of esophageal varices by endoscopic injection sclerotherapy, there is a close relationship between the degree of eradication of the feeding vessel and recurrence of esophageal varices. Previous reports showed that the relapse rate in patients who underwent adequate embolization of the feeding vessel to the varices was significantly lower than the rates in those with inadequate embolization [11, 19, 29]. The results of our prospective study using MPR MDCT images emphasize the importance of sufficient eradication of the feeding vessels.

The relapse rate of esophageal varices is higher in patients with inadequate eradication of the feeding vessels than in those with adequate eradication. However, in patients with insufficient embolization of the feeding vessel, such as patients from group C in the present study, the relapse rate of esophageal varices in patients with a large-diameter

paraesophageal vein was significantly lower than that for patients with a small-diameter paraesophageal vein (Fig. 3).

Because of these results, we think that the presence of a large paraesophageal vein enhances vein drainage because flow is from the left gastric vein to the paraesophageal vein, thus making relapse of esophageal varices a less likely event in patients with complete eradication of esophageal varices alone. For esophageal varices with a large paraesophageal vein, even obliteration of esophageal varices on the esophageal mucosa alone, without obliteration of the feeding vessel, might provide a favorable esophageal varices relapse-free rate. In addition, endoscopic ligation, which does not influence the feeding vessel, might result in the same outcome for these esophageal varices. On the other hand, the development of other portosystemic collaterals, such as a gastrorenal shunt, was unrelated to relapse of esophageal varices because those shunts did not always communicate with the left gastric vein and did not enhance drainage of esophageal varices.

We found a close relationship between the outcome of endoscopic injection sclerotherapy for esophageal varices and variability of portosystemic collaterals. MPR MDCT images of portosystemic collaterals before endoscopic injection sclerotherapy are useful for predicting the outcome and might provide useful information for selecting the treatment technique for esophageal varices, such as endoscopic injection sclerotherapy or endoscopic ligation. This issue should be further investigated.

Our results also showed that embolization of the feeding vessel in endoscopic injection sclerotherapy does not always result in improvement of survival rates (Fig. 5). The main cause of death was HCC, and death due to cancer amounted to 60% of deaths in total. In fact, no patients died after rupture of esophageal varices in our study. Because most patients with esophageal varices have liver cirrhosis or HCC, survival depends on the severity of chronic liver disease or the stage of malignancy. Although endoscopic injection sclerotherapy cannot improve prognosis of patients with esophageal varices, we consider the procedure a method that prevents variceal hemorrhage and variceal hemorrhage-related death.

Although MPR MDCT images are of high quality, this technology has several limitations. MDCT requires skilled techniques to obtain adequate source data after bolus IV injection of the contrast material. Enhancement of the portal vein depends considerably on the patient's physique. A large number of source images may be produced, requiring an expensive high-power workstation to handle these data sets. The pulsation artifacts of the heart and aorta also affect visualization of the esophageal varices on MDCT and may reduce image quality. Furthermore, MDCT is not suitable for patients with renal dysfunction [30]. In this regard, a number of studies have evaluated portosystemic collaterals by using endoscopic sonography. This technique is more useful for estimation of the paraesophageal vein and perforating veins around the esophagus measuring < 2 mm in diameter and blood flow than that of MPR images [13, 27, 31]. The combination of MPR MDCT images and endoscopic sonography before endoscopic injection sclerotherapy may provide more useful information. Despite these limitations, evaluation of portosystemic collaterals by MPR images provides important information regarding the prediction of relapse of esophageal varices.

In conclusion, MPR imaging using MDCT provides excellent visualization of portosystemic collateral circulation. Accurate evaluation using MPR MDCT images should help predict esophageal varices relapse after endoscopic injection sclerotherapy.

Acknowledgments

We thank M. Ishifuro and C. Fujioka for their assistance in obtaining MPR MDCT imaging.

References

1. Lay CS, Tsai YT, Teg CY, et al. Endoscopic variceal ligation in prophylaxis of first variceal bleeding in cirrhosis patients with high-risk esophageal varices. *Hepatology* 1997; 25:1346–1350
2. D'Amico G, Pagliaro L, Bosch J. Pharmacological treatment of portal hypertension: an evidence-based approach. *Semin Liver Dis* 1999; 19:475–505
3. Garcia-Tsao G. Current management of the complications of cirrhosis and portal hypertension: variceal hemorrhage, ascites, and spontaneous bacterial peritonitis. *Gastroenterology* 2001; 120:726–748
4. Pagliaro L, D'Amico G, Sorensen TI, et al. Prevention of first bleeding in cirrhosis: a meta-analysis of randomized trials of nonsurgical treatment. *Ann Intern Med* 1992; 117:59–70
5. Sarin SK, Lamba GS, Kumar M, Misra A, Murthy NS. Comparison of endoscopic ligation and propranolol for the primary prevention of variceal bleeding. *N Engl J Med* 1999; 340:988–993
6. D'Amico G, Pagliaro L, Bosch J. The treatment of portal hypertension: a meta-analytic review. *Hepatology* 1995; 22:332–354
7. Poynard T, Cales P, Pasta L, et al. Beta-adrenergic antagonist drugs in the prevention of gastrointestinal bleeding in patients with cirrhosis and esophageal varices: an analysis of data and prognostic factors in 589 patients from four randomized clinical trials—Franco-Italian Multicenter Study Group. *N Engl J Med* 1991; 324:1532–1538
8. Ideo G, Bellati G, Fesce E, Grimoldi D. Nadolol can prevent the first gastrointestinal bleeding in cirrhotics: a prospective, randomized study. *Hepatology* 1988; 8:6–9
9. Grosso M, Spalluto F, Anselmetti GC, et al. Percutaneous transjugular intrahepatic portosystemic shunt (TIPS): the preliminary experience and proposal of a new method [in Italian]. *Radiol Med (Torino)* 1992; 84:619–625
10. Sakai T, Iwao T, Oho K, Toyonaga A, Tanikawa K. Influence of extravariceal collateral channel pattern on recurrence of esophageal varices after sclerotherapy. *J Gastroenterol* 1997; 32:715–719
11. Chikamori F, Kuniyoshi N, Shibuya S, Takase Y. Short-term portal hemodynamic effects of endoscopic embolization for esophageal varices. *Dig Surg* 2000; 17:454–458
12. Mizumoto H, Matsutani S, Fukuzawa T, et al. Hemodynamics in the left gastric vein after endoscopic ligation of esophageal varices combined with sclerotherapy. *J Gastroenterol Hepatol* 2001; 16:495–500
13. Ito K, Matsutani S, Maruyama H, et al. Study of hemodynamic changes in portal systemic shunts and their relation to variceal relapse after endoscopic variceal ligation combined with ethanol sclerotherapy. *J Gastroenterol* 2006; 41:119–126
14. Chikamori F, Kuniyoshi N, Kagiyama S, et al. Role of percutaneous transhepatic obliteration for special types of varices with portal hypertension. *Abdom Imaging* 2007; 32:92–95
15. Dagenais M, Pomier-Layrargues G, Dufresne MP, et al. Transhepatic portal vein stenting for treatment of ruptured duodenopancreatic varices in a patient with chronic pancreatitis. *Surgery* 1994; 115:669–673
16. Miyoshi H, Matsumoto A, Umegaki E, et al. Endoscopic evaluation of the therapeutic effect of sclerotherapy for esophageal varices. *Gastrointest Endosc* 1993; 39:37–42
17. Matsumoto H, Suzuki F, Souda K, et al. Improved long-term survival following complete eradication of esophageal varices by sclerotherapy. *Hepatogastroenterology* 1999; 46:172–176
18. Korula J, Balart LA, Radvan G, et al. A prospec-

tive, randomized controlled trial of chronic esophageal variceal sclerotherapy. *Hepatology* 1985; 5:584–589

19. Takase Y, Shibuya S, Chikamori F, Orii K, Iwasaki Y. Recurrence factors studied by percutaneous transhepatic portography before and after endoscopic sclerotherapy for esophageal varices. *Hepatology* 1990; 11:348–352
20. Nordlinger BM, Nordlinger DF, Fulenwider JT, et al. Angiography in portal hypertension: clinical significance in surgery. *Am J Surg* 1980; 139:132–141
21. Foley WD, Mallisee TA, Hohenwalter MD, Wilson CR, Quiroz FA, Taylor AJ. Multiphase hepatic CT with a multirow detector CT scanner. *AJR* 2000; 175:679–685
22. Kim HC, Yang DM, Jin W, et al. Multiplanar reformations and minimum intensity projections using multi-detector row CT for assessing anomalies and disorders of the pancreaticobiliary tree. *World J Gastroenterol* 2007; 13:4177–4184
23. Kang HK, Jeong YY, Choi JH, et al. Three-dimensional multi-detector row CT portal venography in the evaluation of portosystemic collateral vessels in liver cirrhosis. *RadioGraphics* 2002; 22: 1053–1061
24. The Japan Society for Portal Hypertension and Esophageal Varices. *The general rules for study of portal hypertension*, 2nd ed. [in Japanese]. Tokyo, Japan: Kanehara, 2004:37–38
25. Matsumoto A, Kitamoto M, Imamura M, et al. Three-dimensional portography using multislice helical CT is clinically useful for management of gastric fundic varices. *AJR* 2001; 176:899–905
26. Van Stiegmann G, Goff JS. Endoscopic esophageal varix ligation: preliminary clinical experience. *Gastrointest Endosc* 1988; 34:113–117
27. Shibukawa G, Irisawa A, Saito A, et al. Variceal recurrence after endoscopic sclerotherapy associated with the perforating veins in lower esophagus independently. *Hepatogastroenterology* 2004; 51: 744–747
28. Hashizume M, Kitano S, Tanoue K, et al. Sclerotherapy-resistant esophageal varices with enormously enlarged cephalad collateral vessels predictable using portography. *Hepatogastroenterology* 1995; 42:551–556
29. Chikamori F, Nishio S, Kuniyoshi N, Shibuya S, Takase Y. Blood supply routes of recurrent esophageal varices following endoscopic embolization. *Dig Surg* 2000; 17:17–22
30. Nakayama Y, Imuta M, Funama Y, et al. CT portography by multidetector helical CT: comparison of three rendering models. *Radiat Med* 2002; 20: 273–279
31. Obara K. Hemodynamic mechanism of esophageal varices. *Dig Endos* 2006; 18:6–9

免疫抑制・化学療法によるB型肝炎ウイルス再活性化とその対策

早田　哲郎[1)]　西澤　新也[1)]　森原　大輔[1)]
横山　圭二[1)]　櫻井　邦俊[1)]　上田　秀一[1)]
坂本　雅晴[1)]　阿南　　章[1)]　竹山　康章[1)]
入江　　真[1)]　岩田　　郁[1)]　釈迦堂　敏[1)]
佐々木秀法[2)]　高松　　泰[2)]　向坂彰太郎[1)]

1) 福岡大学医学部消化器内科
2) 福岡大学医学部腫瘍・血液・感染症内科

Tetsuro SOHDA[1)], Sinya NISHIZAWA[1)], Daisuke MORIHARA[1)],
Keiji YOKOYAMA[1)], Kunitoshi SAKURAI[1)], Shuichi UEDA[1)],
Masaharu SAKAMOTO[1)], Akira ANAN[1)], Yasuaki TAKEYAMA[1)],
Makoto IRIE[1)], Kaoru IWATA[1)], Satoshi SHAKADO[1)],
Hidenori SASAKI[2)], Yasushi TAKAMATSU[2)] and Shotaro SAKISAKA[1)]

1) *Department of Gastroenterology and Medicine, Faculty of Medicine, Fukuoka University*
2) *Department of Oncology, Hematology and Infectious disease, Faculty of Medicine, Fukuoka University*

福岡大学医学紀要
第36巻第4号別冊
平成21年12月

福岡大医紀（*Med. Bull. Fukuoka Univ.*）：36(4), 235-241, 2009

Immunosuppressive Therapy or Chemotherapy-Induced Hepatitis B Virus Reactivation

Tetsuro SOHDA[1)], Sinya NISHIZAWA[1)], Daisuke MORIHARA[1)], Keiji YOKOYAMA[1)], Kunitoshi SAKURAI[1)], Shuichi UEDA[1)], Masaharu SAKAMOTO[1)], Akira ANAN[1)], Yasuaki TAKEYAMA[1)], Makoto IRIE[1)], Kaoru IWATA[1)], Satoshi SHAKADO[1)], Hidenori SASAKI[2)], Yasushi TAKAMATSU[2)] and Shotaro SAKISAKA[1)]

[1)] *Department of Gastroenterology and Medicine, Faculty of Medicine, Fukuoka University*
[2)] *Department of Oncology, Hematology and Infectious disease, Faculty of Medicine, Fukuoka University*

Abstract：Immunosuppressive therapy or chemotherapy-induced hepatitis B virus (HBV) reactivation sometimes causes severe hepatitis. Physicians who perform these therapies must therefore be aware of the characteristics of HBV reactivation. HBV reactivation also occurs in patients with negative serum markers for hepatitis B surface antigen (HBsAg). Therefore, hepatitis B core antibody in addition to HBsAg must be tested in all patients who are indicated to receive the above therapies. When any markers for HBV are positive, then the physician should consult with a liver disease specialist and consider alternative treatment with nucleoside analogues.

Key words：Immunosuppressive therapy, Chemotherapy, Hepatitis B virus reactivation, Nucleoside analogues

免疫抑制・化学療法によるB型肝炎ウイルス再活性化とその対策

早田　哲郎[1)]　西澤　新也[1)]　森原　大輔[1)]
横山　圭二[1)]　櫻井　邦俊[1)]　上田　秀一[1)]
坂本　雅晴[1)]　阿南　章[1)]　竹山　康章[1)]
入江　真[1)]　岩田　郁[1)]　釈迦堂　敏[1)]
佐々木秀法[2)]　高松　泰[2)]　向坂彰太郎[1)]

[1)] 福岡大学医学部消化器内科
[2)] 福岡大学医学部腫瘍・血液・感染症内科

要旨：免疫抑制・化学療法後のB型肝炎ウイルス再活性化は，致死的重症肝炎を引き起こすことがあり，免疫抑制・化学療法の施行医は，この肝炎発症が治療終了から数ケ月経って発症する事など，本疾患の特徴をよく認識しておく必要がある．また，この肝炎の発症はHBs抗原陰性症例においてもみられるため，免疫抑制・化学療法を予定している患者に対しては，HBs抗原に加えHBc抗体の測定をルーチン化し，これが陽性であれば，原疾患の治療を行う前に，核酸アナログ投与の実施を含めて肝臓専門医にコンサルトをしていただきたい．

キーワード：免疫抑制・化学療法，B型肝炎ウイルス再活性化，核酸アナログ

別冊請求先：〒814-0180　福岡市城南区七隈7丁目45-1　福岡大学医学部消化器内科　早田哲郎
TEL：092-801-1011　内線3355　FAX：092-874-2663　E-mail：tetsuro@fukuoka-u.ac.jp

はじめに

肝機能正常のB型肝炎ウイルス（HBV）キャリアに対し，抗癌剤や免疫抑制剤を用いた場合，HBV の増殖に引き続き肝障害の急性増悪がみられることがあり，これを HBV 再活性化と呼んでいる[1]．以前から，化学療法によってB型肝炎が増悪することは知られていたが，特に，悪性リンパ腫に対する化学療法では，致死的な重症肝炎が起こることが多く，注意が必要であると認識されていた[2]．最近は，化学療法や免疫療法が進歩し，新規に様々な薬物が開発され臨床応用されている．さらに，移植治療も進歩し，強力な免疫抑制作用を持つ薬物の使用頻度が増えている．これに伴い，HBs 抗原陰性例からの HBV 再活性化による重症肝炎の発症が増加しており，問題となっている[3]．

一方，B型肝炎の治療薬である核酸アナログが発売されて久しく，HBV の増殖抑制効果についてはすでに一定のコンセンサスが得られている．また，HBV キャリアに対する抗癌剤治療中に増悪する肝障害に対しても，本剤の有効性が報告されている[4]．この様に，HBV 再活性化を核酸アナログによって予防することも不可能ではなくなってきた．

最近，厚生労働省「難治性の肝・胆道疾患に関する調査研究」班と「肝硬変を含めたウイルス性肝疾患の治療の標準化に関する研究」班の合同報告として，免疫抑制・化学療法により発症するB型肝炎対策のガイドラインが出された[5]．これを受けて，福岡大学病院においても，以下に示すように，HBV 再活性化における安全対策を強化している．

Ⅰ．HBV 再活性化のメカニズム

HBV キャリアの肝細胞内に存在する HBV は，リンパ球によって常に監視され，通常は極端に増殖することはない．しかし，免疫抑制・化学療法中は，HBV が免疫監視機構から逃れ増殖をはじめる．HBV が非常に増殖した後に免疫抑制・化学療法が中止された場合，免疫監視機構は回復するが，その際，増殖した HBV に対して細胞障害性Tリンパ球を中心とした強い免疫応答が起こり，肝細胞が一気に破壊される．これが HBV 再活性化のメカニズムであり，劇症肝炎を含む重篤な肝障害に進展しやすい．典型的な症例の経過を示す（図1）．

免疫抑制・化学療法による HBV 再活性化は，様々な薬物において報告されている[6]（表1）．薬物によって免疫抑制効果やその継続する期間が異なる．特に，B細胞性リンパ腫の治療薬で CD20 に対するモノクローナル抗体であるリツキシマブは，薬物中止後も強力な免疫抑制効果が約一年間継続すると言われている．また，HBV はウイルス遺伝子上の複製開始部に，glucocorticoid receptor と同じ塩基配列である glucocorticoid responsive element を持つため，副腎皮質ホルモンは直接的に HBV を増殖させるといった特徴がある[7]．

後述する潜在性 HBV 感染症例からも HBV 再活性化は発症することがあるが，その経過をみた Hui らの報告[8]によると，免疫抑制・化学療法後，平均12週で HBV の増殖がみられ，その10週後に HBs 抗原の陽性化が，さらに，その9.5週後に肝障害が出現している．発症のメカニズム上，肝障害出現に先行して必ず HBV の増殖が起こるが，HBV DNA 陽性化から肝障害出現までみると平均18.5週と長期間を要しており，この間に発症予防の対策を講じる時間的な余裕は十分あると考えられる（図2）．

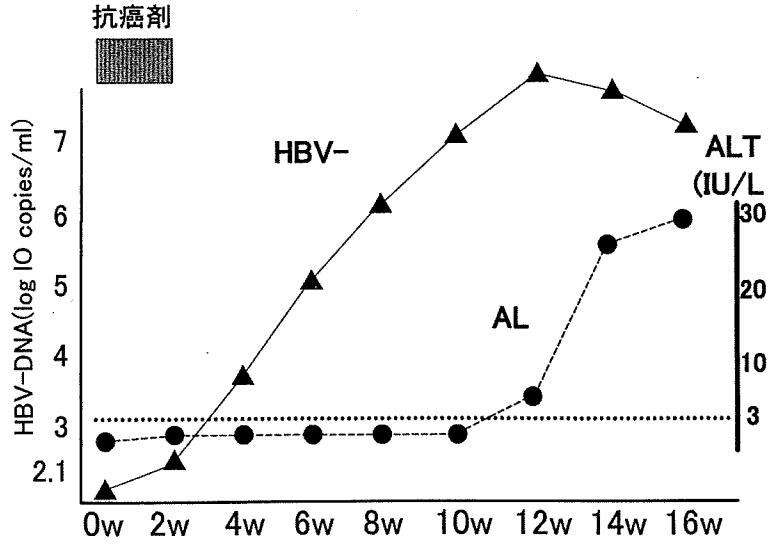


図1　HBV 再活性化の典型的な経過

Ⅱ．潜在性 HBV 感染症例からの HBV 再活性化

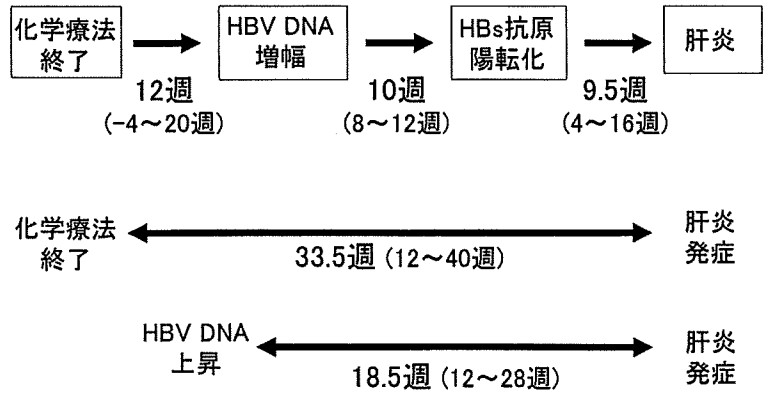
母子感染を含めた新生児から小児期の HBV 感染による無症候性キャリアでは HBV 量が多いため，免疫抑制・化学療法を行う際に注意が必要となることは当然であるが，肝炎発症後に軽快し，肝機能が正常となった後もなお高リスクである．成人の初感染の場合，B型急性肝炎回復後は HBs 抗体陽性となり，いわゆる“治癒”という状態になるが，その場合でも肝細胞内には少量の HBV が残存していることがわかっている（図3）．従って HBV は結核やヘルペス感染症などと同じく，一度感染すると体内から完全に消失することはないと考えられており，最近は“潜在性 HBV 感染”という表現で統一されている[9]．

潜在性 HBV 感染は，血清 HBs 抗原陰性で HBc 抗体 and/or HBs 抗体陽性と定義される．この場合，特殊なウイルス遺伝子変異がない限り血中 HBV DNA は

表1　HBV 再活性化に関係する免疫抑制・化学療法剤

Class	Agents associated with HBV reactivation
Alkylators	Cyclophosphamide
	Ifosfamide
	Chlorambucil
	Carboplatin, Cisplatin
Antimetabolites	Cytarabine
	Fluorouracil
	Gemcitabine
	Mercaptopurine
	Methotrexate
	Thioguanine
Antitumor antibodies	Anthracyclines
	Bleomycin
	Mitomycin C
	Actinomycin D
Corticosteroides	Prednisone/Dexamethasone etc.
Immunotherapy	Rituximab (anti-CD20)
	Alemtuzumab (anti-CD52)
	Infliximab (anti-TNF)
Plant Alkaloids	Vincristine
	Vinblastine
Others	Asparginase
	Procarbazinc
	Docetaxel
	Etoposide
	Fludarabine
	Imatinib Mesylate
	Interferon alpha

Lalazar G, et al：Br J Haematol 136：699-712, 2007 より引用



Hui CK, et al: Gastroenterology 131: 59-68, 2006より引用改変

図2　HBV 再活性化のウイルスマーカーの動きと肝炎発症までの経過

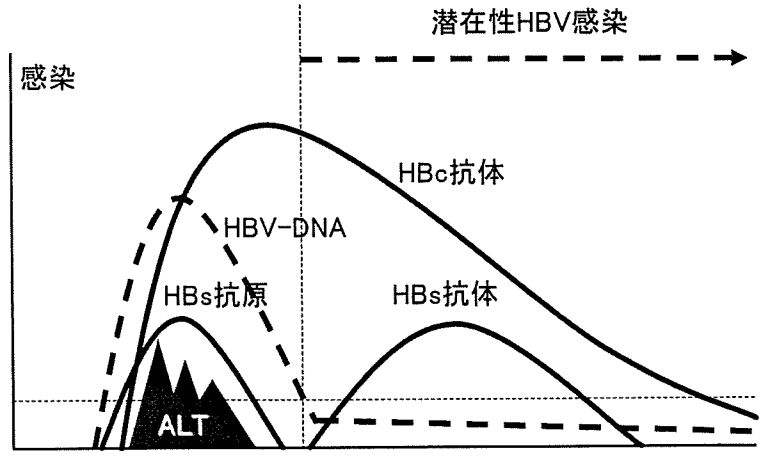


図3　HBV 初感染後のウイルスマーカーの動き

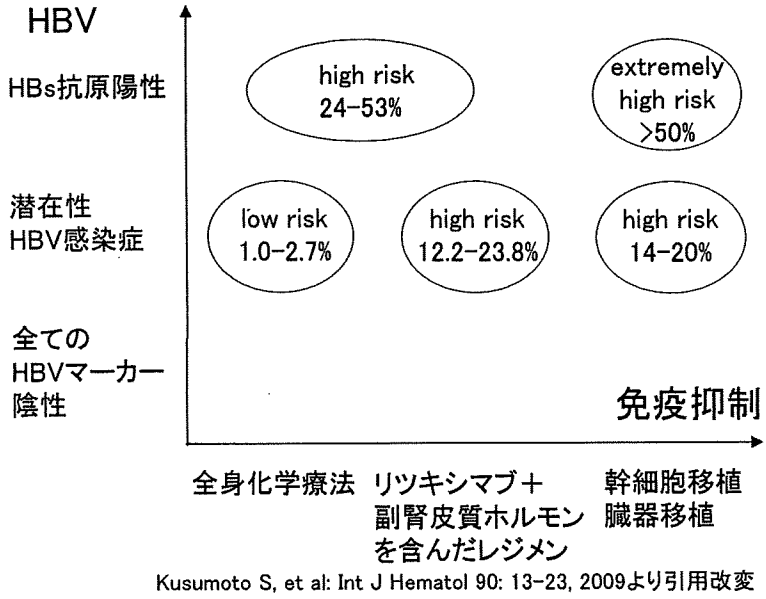


図4　HBV 再活性化のリスク．潜在性 HBV 感染症よりも HBs 抗原陽性キャリアが，また薬物による免疫抑制効果が強いほど，HBV 再活性化のリスクが高い．

検出されず，HBV による肝障害も起こらない．また，不顕性感染から潜在性 HBV 感染状態になったケースが多いため，患者本人も認識しておらず，病歴から絞り込むことはできない．従って，潜在性 HBV 感染のスクリーニングに最も有用なマーカーである HBc 抗体を測定する必要がある．福岡，北九州の赤十字血液センターからの報告によると，全献血者における HBc 抗体陽性の頻度は1.1%であるが，HBc 抗体陽性率は年齢とともに上昇するため，免疫抑制・化学療法を受ける患者の年齢層を考えると，潜在性 HBV 感染症例にはしばしば遭遇すると予想される[10][11]．

最近，この潜在性 HBV 感染症例からの HBV 再活性化の報告が相次いでいる．固形癌に対して通常行われる化学療法は，潜在性 HBV 感染症例における HBV 再活性化のリスクはそれほど高くないが，悪性リンパ腫に対するレジメンでリツキシマブと副腎皮質ホルモンを含んだ R-CHOP 療法は高リスクであることが知られている[12][13]（図4）．その他，クローン病や慢性関節リウマチに使用される抗 TNF 製剤のインフリキシマブやメソトレキセートでも HBV 再活性化の報告がある[14][15]．

Ⅲ．B型急性肝炎と HBV 再活性化の違い

HBV による急性肝障害の代表であるB型急性肝炎は，成人ではほとんどが性行為感染によるものである

表2　HBV 再活性化とB型急性肝炎の臨床像の比較

	再活性化	B型急性肝炎	*P*
年齢	63	33	<0.001
男性	59%	71%	
ALT (IU/L)	929	2,300	<0.001
T.Bil (mg/dL)	10.3	6.4	
Alb (g/dL)	3.2	3.6	<0.001
PT (%)	65.0	75.0	
HBV DNA (log copies/mL)	7.5	5.5	<0.001
劇症化	22%	9 %	0.048
肝関連死	26%	4 %	<0.001

Umemura T, et al：Clin Infect Dis 47：e52–56, 2008 より引用改変

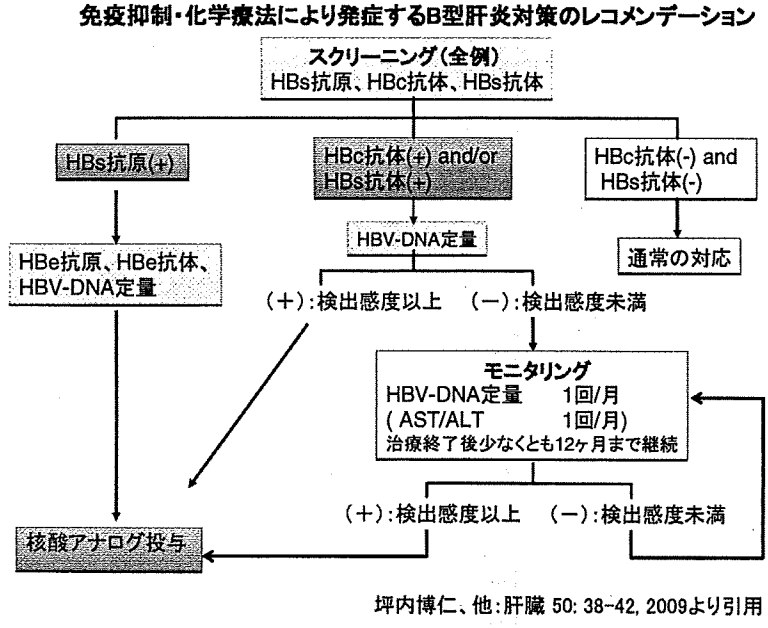


図5　厚生労働省の研究班からのレコメンデーション

表3　消化器内科・肝臓専門医へのコンサルトのタイミング

①化学療法・免疫抑制療法予定患者の検査で，HBs 抗原または HBc 抗体が陽性であった場合

②潜在性 HBV 感染において，治療中および治療後の経過中に HBV-DNA が検出されるようになった場合

が，肝細胞内に侵入し増殖したウイルスに対する正常な免疫応答によって肝障害は起こる．多くの場合，不顕性感染や軽度の急性肝炎で終わることが多い．ウイルス肝炎の中ではB型急性肝炎は劇症化率が高いことで知られているが，B型急性肝炎の中でみると，この劇症化率は1－2％である．これに比べて HBV 再活性化は，HBV 増殖や免疫状態などB型急性肝炎とはかなり異なる様相を呈する．

Umemura らがB型急性肝炎と HBV 再活性化を比較した成績を報告している[16]．HBV の感染経路，HBc 抗体陽性率および基礎疾患を考えると当然であるが，HBV 再活性化症例は有意に平均年齢が高い．ALT のピーク値は HBV 再活性化症例のほうがむしろ有意に低いが，肝予備能を表す検査値は悪化傾向にある．HBV 量は HBV 再活性化症例が100倍高値であり，特筆すべきは，劇症化と肝関連死が HBV 再活性化症例において有意に高いことである．つまり，HBV 再活性化は一旦起こると劇症化しやすく，劇症化すると内科的な救命率

は極めて低いと考えられている（表2）．従って，肝障害を発症させないような予防策が重要になる．

Ⅳ．HBV 再活性化の予防について

HBV 再活性化の予防のポイントは，①潜在性 HBV 感染を慎重に検討することと，②HBV DNA の陽性化を見逃さないことに尽きる．HBV DNA の増加は肝障害出現の数ケ月も前に先行してみられるため，これを見逃さない限り，その後の対策を講じる時間的な余裕は十分ある．潜在性 HBV 感染であれば免疫抑制・化学療法を行いながら，月1回の HBV DNA の測定で経過観察するが，HBs 抗原陽性または HBV DNA が検出される場合は核酸アナログを投与する．厚生労働省の研究班からガイドラインが出されており（図5），これに従えば HBV 再活性化は予防できる．

しかし，このガイドラインは多少煩雑であり，肝臓専門医がコンサルタントとして介入することで，最低限の項目のみに絞った福岡大学病院独自のマニュアルを提案し，これを免疫抑制・化学療法施行医に周知徹底して行う方が，安全管理という観点から見るとリーズナブルであると思われる．そこで，免疫抑制・化学療法前に HBs 抗原と HBc 抗体を測定し，いずれかが陽性であれば肝臓専門医にコンサルトを，さらに経過観察の指示があった場合は HBV DNA が検出された時点で再度肝臓専門医にコンサルトすることを提案する（表3）．核酸アナログの投与は必要に応じて行うが，その終了時期などコンセンサスが得られていない部分もあるため，核酸アナログ投与は肝臓専門医が行うことが望ましいと考える．

最近は，HBc 抗体陰性症例からの HBV 再活性化の報告もある[17]．長い経過によって HBc 抗体が陰性化した HBV キャリアであると考えられるが，このような例外的な症例もあるという認識をもっておく必要はある．また，最も強力な免疫抑制が必要となる造血肝細胞移植や臓器移植の場合は，HBs 抗体と HBV DNA の検査を必須にするなど，独自のプロトコールが必要である．

結　　び

HBV 再活性化は化学療法などの治療後，思いもよらない時に突然起こる重篤な急性肝障害であり，免疫抑制・化学療法に関わる医師，看護師および薬剤師は，HBV 再活性化を常に認識していなければならない．さらに，マニュアルに従ってウイルスマーカーの検査を忘れずに行うことが重要であるが，それをチェックするシステム作りが，HBV 再活性化の確実な予防のために必要である．

文　　献

1）Lok AS, Liang RH, Chiu EK, Wong KL, Chan TK, Todd D：Reactivation of hepatitis B virus replication in patients receiving cytotoxic therapy. Report of a prospective study. Gastroenterology 100：182–188, 1991.

2）Yeo W, Johnson PJ：Diagnosis, prevention and management of hepatitis B virus reactivation during anticancer therapy. Hepatology 43：209–220, 2006.

3）Hui CK, Sun J, Au WY, Lie AK, Yueng YH, Zhang HY, Lee NP, Hou JL, Liang R, Lau GK：Occult hepatitis B virus infection in hematopoietic stem cell donors in a hepatitis B virus endemic area. J Hepatol 42：813–819, 2005.

4）Li YH, He YF, Jiang WQ, Wang FH, Lin XB, Zhang L, Xia ZJ, Sun XF, Huang HQ, Lin TY, He YJ, Guan ZZ：Lamivudine prophylaxis reduces the incidence and severity of hepatitis in hepatitis B virus carriers who receive chemotherapy for lymphoma. Cancer 106：1320–1325, 2006.

5）坪内博仁，熊田博光，清沢研道，持田　智，坂井田　功，田中榮司，市田隆文，溝上雅史，鈴木一幸，輿芝眞彰，森脇久隆，日比紀文，林　紀夫，國土典宏，藤澤知雄，石橋大海，菅原寧彦，八橋　弘，井戸章雄，滝川康裕，井上和明，桶谷　真，宇都浩文，中山伸朗，内木隆文，多田慎一郎，木曽真一，矢野公士，遠藤龍人，田中靖人，梅村武司，熊谷公太郎：免疫抑制・化学療法により発症するB型肝炎対策―厚生労働省「難治性の肝・胆道疾患に関する調査研究」班　劇症肝炎分科会および「肝硬変を含めたウイルス性肝疾患の治療の標準化に関する研究」班合同報告―．肝臓　50：38–42, 2009.

6）Lalazar G, Rund D, Shouval D：Screening, prevention and treatment of viral hepatitis B reactivation in patients with haematological malignancies. Br J Haematol 136：699–712, 2007.

7）Chou CK, Wang LH, Lin HM, Chi CW：Glucocorticoid stimulates hepatitis B viral gene expression in cultured human hepatoma cells. Hepatology 16：13–18, 1992.

8）Hui CK, Cheung WW, Zhang HY, Au WY, Yueng YH, Leung AY, Leung N, Luk JM, Lie AK, Kwong YL, Liang R, Lau GK：Kinetics and risk of de novo hepatitis B infection in HBsAg–negative patients undergoing cytotoxic chemotherapy. Gastroenterology 131：59–68, 2006.

9）Raimondo G, Pollicino T, Cacciola I, Squadrito G：Occult hepatitis B virus infection. J Hepatol 46：160–170, 2007.

10）山崎久義，真鍋寛司，松本浩二，後藤信代，宮崎　卓，友成洋子，徳永和夫，佐藤博行，石井恵美，朝倉　健，清川博之，柏木征三郎：HBc 抗体陽性献血者への通知の効果．血液事業　28：413–419, 2005.

11）Marusawa H, Osaki Y, Kimura T, Ito K, Yamashita

Y, Eguchi T, Kudo M, Yamamoto Y, Kojima H, Seno H, Moriyasu F, Chiba T : High prevalence of anti-hepatitis B virus serological markers in patients with hepatitis C virus related chronic liver disease in Japan. Gut 45 : 284–288, 1999.

12) Kawatani T, Suou T, Tajima F, Ishiga K, Omura H, Endo A, Ohmura H, Ikuta Y, Idobe Y, Kawasaki H : Incidence of hepatitis virus infection and severe liver dysfunction in patients receiving chemotherapy for hematologic malignancies. Eur J Haematol 67 : 45–50, 2001.

13) Kusumoto S, Tanaka Y, Mizokami M, Ueda R : Reactivation of hepatitis B virus following systemic chemotherapy for malignant lymphoma. Int J Hematol 90 : 13–23, 2009.

14) Ojiro K, Naganuma M, Ebinuma H, Kunimoto H, Tada S, Ogata H, Iwao Y, Saito H, Hibi T : Reactivation of hepatitis B in a patient with Crohn's disease treated using infliximab. J Gastroenterol 43 : 397–401, 2008.

15) Gwak GY, Koh KC, Kim HY : Fatal hepatic failure associated with hepatitis B virus reactivation in a hepatitis B surface antigen-negative patient with rheumatoid arthritis receiving low dose methotrexate. Clin Exp Rheumatol 25 : 888–889, 2007.

16) Umemura T, Tanaka E, Kiyosawa K, Kumada H ; Mortality secondary to fulminant hepatic failure in patients with prior resolution of hepatitis B virus infection in Japan. Clin Infect Dis 47 : e52–e56, 2008.

17) Gossmann J, Scheuermann EH, Kachel HG, Geiger H, Hauser IA : Reactivation of hepatitis B two years after rituximab therapy in a renal transplant patient with recurrent focal segmental glomerulosclerosis : a note of caution. Clin Transplant 23 : 431–434, 2009.

（平成21. 7. 3受付，21. 9. 9受理）

Journal of Viral Hepatitis, 2009, 16, 586–594 doi:10.1111/j.1365-2893.2009.01106.x

Ribavirin dose reduction raises relapse rate dose-dependently in genotype 1 patients with hepatitis C responding to pegylated interferon alpha-2b plus ribavirin

N. Hiramatsu,[1*] T. Oze,[1*] T. Yakushijin,[1] Y. Inoue,[1] T. Igura,[1] K. Mochizuki,[1] K. Imanaka,[2] A. Kaneko,[3] M. Oshita,[4] H. Hagiwara,[5] E. Mita,[6] T. Nagase,[7] T. Ito,[8] Y. Inui,[9] T. Hijioka,[10] K. Katayama,[11] S. Tamura,[12] H. Yoshihara,[13] Y. Imai,[14] M. Kato,[15] Y. Yoshida,[1] T. Tatsumi,[1] K. Ohkawa,[1] S. Kiso,[1] T. Kanto,[1] A. Kasahara,[1] T. Takehara[1] and N. Hayashi[1] [1]*Department of Gastroenterology and Hepatology, Osaka University Graduate School of Medicine, Osaka, Japan;* [2]*Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan;* [3]*NTT West Osaka Hospital, Osaka, Japan;* [4]*Osaka Police Hospital, Osaka, Japan;* [5]*Higashiosaka City Central Hospital, Osaka, Japan;* [6]*National Hospital Organization Osaka National Hospital, Osaka, Japan;* [7]*Suita Municipal Hospital, Osaka, Japan;* [8]*Kansai Rousai Hospital, Hyogo, Japan;* [9]*Hyogo Prefectural Nishinomiya Hospital, Hyogo, Japan;* [10]*National Hospital Organization Osaka Minami Medical Center, Osaka, Japan;* [11]*Osaka Koseinenkin Hospital, Osaka, Japan;* [12]*Minoh City Hospital, Osaka, Japan;* [13]*Osaka Rousai Hospital, Osaka, Japan;* [14]*Ikeda Municipal Hospital, Osaka, Japan; and* [15]*National Hospital Organization Minami Wakayama Medical Center, Wakayama, Japan*

Received November 2008; accepted for publication December 2008

SUMMARY. The impact of ribavirin exposure on virologic relapse remains controversial in combination therapy with pegylated interferon (Peg-IFN) and ribavirin for patients with chronic hepatitis C (CH-C) genotype 1. The present study was conducted to investigate this. Nine hundred and eighty-four patients with CH-C genotype 1 were enrolled. The drug exposure of each medication was calculated by averaging the dose actually taken. For the 472 patients who were HCV RNA negative at week 24 and week 48, multivariate logistic regression analysis showed that the degree of fibrosis ($P = 0.002$), the timing of HCV RNA negativiation ($P < 0.001$) and the mean doses of ribavirin ($P < 0.001$) were significantly associated with relapse, but those of Peg-IFN were not. Stepwise reduction of the ribavirin dose was associated with a stepwise increase in relapse rate from 11% to 60%. For patients with complete early virologic response (c-EVR) defined as HCV RNA negativity at week 12, only 4% relapse was found in patients given ≥12 mg/kg/day of ribavirin and ribavirin exposure affected the relapse even after treatment week 12, while Peg-IFN could be reduced to 0.6 μg/kg/week after week 12 without the increase of relapse rate. Ribavirin showed dose-dependent correlation with the relapse. Maintaining as high a ribavirin dose as possible (≥12 mg/kg/day) during the full treatment period can lead to suppression of the relapse in HCV genotype 1 patients responding to Peg-IFN alpha-2b plus ribavirin, especially in c-EVR patients.

Keywords: chronic hepatitis C, drug exposure, pegylated interferon plus ribavirin, virologic relapse.

INTRODUCTION

Combination therapy of pegylated interferon (Peg-IFN) plus ribavirin is very effective for patients with chronic hepatitis C (CH-C). However, sustained virologic response (SVR) in current therapy occurs in only 40–50% of patients with hepatitis C virus (HCV) genotype 1 [1–4]. Also, SVR is reduced in patients with genotype 1 who require reduction of either Peg-IFN or ribavirin, although dose reduction has little influence on SVR in those with genotype 2 or 3 [1–3,5,6]. Therefore, it is important to clarify the degree to which these medications can be reduced without adversely affecting SVR in patients with CH-C genotype 1.

In an early report on the relationship between drug exposure and antiviral effect in patients with CH-C genotype 1, patients who received ≥80% of their total planned cumulative doses of Peg-IFN and ribavirin for ≥80% of the scheduled duration of therapy had an SVR of 51% compared with only 34% for patients who received lesser amounts of one or both

Abbreviations: CH-C, chronic hepatitis C; c-EVR, complete early virologic response; ETR, end-of-treatment virologic response; Hb, haemoglobin; HCV, hepatitis C virus; IFN, interferon; LVR, late virologic response; Peg-IFN, pegylated interferon; PP, per protocol; Plt, platelet; RVR, rapid virologic response; SVR, sustained virologic response; VR, virologic response; WBC, white blood cell.

Correspondence: Naoki Hiramatsu, MD, PhD, Department of Gastroenterology and Hepatology, Osaka University Graduate School of Medicine, 2-2, Yamadaoka, Suita City, Osaka 565-0871, Japan. E-mail: hiramatsu@gh.med.osaka-u.ac.jp

*Both authors contributed equally to this work.

medications [7]. On the other hand, Shiffman *et al.* [8] recently reported that reducing ribavirin did not affect SVR as long as the dose of Peg-IFN was maintained, while reducing the Peg-IFN dose significantly reduced SVR. The results of these observations are consistent with respect to the effect of Peg-IFN on SVR. However, what is controversial is whether or not reducing the ribavirin dose affects the antiviral effect.

Adding ribavirin to either interferon (IFN) or Peg-IFN monotherapy for patients with CH-C genotype 1 has been shown to reduce the relapse rate in large randomized trials [1,2,9–11]. In detail, adding ribavirin to the usual IFN monotherapy (3MIU, three-times-weekly) in 48-week treatment raised the end-of-treatment virologic response (ETR) rate from approximately 30% to 50% and also lowered the relapse rate from mid-40% to approximately 20% [9–11]. Lindsay *et al.* [12] reported that Peg-IFN alpha-2b (Peg-IFN α-2b) monotherapy (1.5 μg/kg, once-weekly), as compared with IFN alpha-2b (IFNα-2b) monotherapy (3MIU, three-times-weekly), improved ETR (49% vs. 24%), but not the relapse rate (53% vs. 50%). In the trial of Peg-IFN alpha-2a (Peg-IFN α-2a) plus ribavirin *vs* IFN α-2b plus ribavirin or Peg-IFN α-2a alone, the ETR rates were 69%, 52% and 59%, and the relapse rates were 19%, 15% and 52%, respectively [2]. These findings from large-scale trials indicate that the main role of ribavirin is to reduce relapse in the combination therapy with Peg-IFN, although ribavirin affects both ETR and relapse in combination therapy with the usual IFN.

In the present study, we tried to determine whether or not dose reduction of ribavirin (or Peg-IFN) has an effect on virologic relapse in Peg-IFN plus ribavirin treatment for patients with CH-C genotype 1.

PATIENTS AND METHODS

Patients

This study was a multicentre trial conducted by Osaka University Hospital and other institutions participating in the Osaka Liver Forum. A total of 984 patients with CH-C were enrolled in this study between December 2004 and September 2006, and treated with a combination of Peg-IFN α-2b plus ribavirin. The baseline characteristics of the patients are shown in Table 1. All patients were Japanese infected with HCV genotype 1 and a viral load of more than 10^5 IU/mL. Patients were excluded from this study if they had decompensated cirrhosis or other forms of liver disease (alcohol liver disease, autoimmune hepatitis), coinfection with hepatitis B or anti-human immunodeficiency virus. This study was conducted according to the ethical guidelines of the 1975 Declaration of Helsinki and informed consent was obtained from each patient.

Treatment

All patients received Peg-IFN α-2b (PEGINTRON; Schering-Plough, Kenilworth, NJ, USA) plus ribavirin (REBETOL; Schering-Plough) for the duration of the study of 48 weeks. As a starting dose, Peg-IFN α-2b was given subcutaneously once weekly at a dosage of 60–150 μg/kg based on body weight (body weight 35–45 kg, 60 μg; 46–60 kg, 80 μg; 61–75 kg, 100 μg; 76–90 kg, 120 μg; 91–120 kg, 150 μg) and ribavirin was given orally twice a day at a total dose of 600–1000 mg/day based on body weight (body weight <60 kg, 600 mg; 60–80 kg, 800 mg; >80 kg, 1000 mg) according to the manufacturer's drug information available in Japan.

Table 1 Baseline characteristics of patients and drug doses at start of treatment

Factor	Mean ± SD or *n*
n	984
Age (years)	56.3 ± 10.1
Sex (male/female)	555/429
Body weight (kg)	61.8 ± 11.5
History of IFN treatment Naïve/experienced (relapser/nonresponder)*	575/409 (160/182)
White blood cells (/mm^3)	5052 ± 1550
Neutrophils (/mm^3)	2577 ± 1092
Red blood cells (×10^4/mm^3)	442 ± 47
Haemoglobin (g/dL)	14.1 ± 1.4
Platelets (×10^4/mm^3)	15.9 ± 5.5
AST (IU/L)	66 ± 45
ALT (IU/L)	79 ± 61
Serum HCV RNA (kIU/mL)†	1600
Histology (METAVIR)‡	
Fibrosis; 0/1/2/3/4	49/314/197/105/18
Activity; 0/1/2/3	23/329/304/27
Peg-IFN dose (μg/kg/week)	1.45 ± 0.17
Ribavirin dose (mg/kg/day)	11.4 ± 1.6

AST, aspartate aminotransferase; ALT, alanine aminotransferase; HCV, hepatitis C virus. *Viral response to previous treatment was unknown in 57 patients, and 10 patients had discontinued treatment. †Data shown are median values. ‡301 missing.

Dose reduction and discontinuance

Dose modification also followed, as a rule, the manufacturer's drug information according to the intensity of the haematologic adverse effects. The dose of Peg-IFN α-2b was reduced to 50% of the assigned dose when the white blood cell (WBC) count was below 1500/mm^3, the neutrophil count below 750/mm^3 or the platelet (Plt) count below 8×10^4/mm^3, and was discontinued when the WBC count was below 1000/mm^3, the neutrophil count below 500/mm^3 or the Plt count below 5×10^4/mm^3. Ribavirin was also reduced from 1000 mg to 600 mg, 800 mg to 600 mg, or 600 mg to 400 mg when the haemoglobin (Hb)

concentration decreased to less than 10 g/dL, and was discontinued when the Hb concentration decreased to less than 8.5 g/dL. Both Peg-IFN α-2b and ribavirin had to be discontinued if there was a need to discontinue one of the drugs. No ferric medicine or haematopoietic growth factors, such as epoetin alpha, or granulocyte-macrophage colony stimulating factor, were administered.

Virologic assessment and definition of virologic response

Serum HCV RNA level was quantified using the COBAS AMPLICOR HCV MONITOR test, version 2.0 (detection range 6–5000 kIU/mL; Roche Diagnostics, Branchburg, NJ, USA) and qualitatively analysed using the COBAS AMPLICOR HCV test, version 2.0 (lower limit of detection 50 IU/mL; Roche Diagnostics). Complete early virologic response (c-EVR) was defined as the absence of detectable serum HCV RNA at treatment week 12, the late virologic response (LVR) was defined as undetectable serum HCV RNA for the first time at 13–24 weeks of treatment, and the virologic response (VR) was defined as HCV RNA negativity at week 24 and week 48. SVR was defined as the absence of detectable serum HCV RNA at week 72. Patients with less than a 2-log decrease in HCV RNA level at treatment week 12 compared with the baseline had to stop treatment according to the protocol and were regarded as nonresponders. All patients with detectable serum HCV RNA at treatment week 24 were also considered to be nonresponders and were excluded from further treatment.

Assessment of drug exposure

The amounts of Peg-IFN α-2b and ribavirin actually taken by each patient during the full treatment period were evaluated by reviewing the medical records. The mean doses of Peg-IFN α-2b and ribavirin were calculated individually as averages on the basis of body weight at baseline: Peg-IFN α-2b expressed as μg/kg/week, ribavirin expressed as mg/kg/day.

Evaluation of impact of drug exposure on virologic relapse

We evaluated the relationship between the drug exposure of both drugs and relapse by two different methods, univariate and multivariate analysis for relapse and independent evaluation of both drugs for relapse according to the degree of drug exposure. The former was performed with the factors of mean administration doses of both drugs, including the factors at baseline and the timing of HCV RNA negativiation. The latter was examined by classifying Peg-IFN α-2b exposure into five categories (up to 0.6 μg/kg; from 0.6 to less than 0.9 μg/kg; from 0.9 to less than 1.2 μg/kg; from 1.2 to less than 1.5 μg/kg; from 1.5 μg/kg) and ribavirin exposure into five categories (up to 6 mg/kg; from 6 to less than 8 mg/kg; from 8 to less than 10 mg/kg; from 10 to less than 12 mg/kg; from 12 mg/kg).

Statistical analysis

Baseline data are expressed as means ± SD or median values. Virologic response was evaluated using per protocol (PP) analysis. To analyse the difference between baseline data including drug exposure and virologic response, univariate analysis using the Mann–Whitney *U*-test or chi-square test and multivariate analysis using logistic regression analysis were performed. The significance of trends in values was determined with the Mantel–Haenszel chi-square test. A two-tailed P value <0.05 was considered significant. The analysis was conducted with SPSS version 15.0J (SPSS Inc., Chicago, IL, USA).

RESULTS

Progress of patients and dose reduction of Peg-IFN α-2b and ribavirin

The progress of patients in this study is shown in Fig. 1. Of the 984 patients, 903 completed 12 weeks of treatment and the c-EVR rate was 49% (445/903), based on PP study. To analyse for relapse, 472 patients with VR were assessed, with 178 (38%) showing Peg-IFN dose reduction without discontinuation and 246 (52%) with ribavirin dose reduction without discontinuation during the full (48 weeks) treatment period. The relapse rate was 26% (125/472) in the patients with undetectable HCV RNA level at the end of treatment. No difference was found in relapse rates between the IFN naïve patients and IFN experienced patients (IFN naïve; 25%, 72/287 *vs* IFN experienced; 29%, 53/185, $P = 0.40$). The SVR rate was 43% (347/812) in the PP study.

Impact of drug exposure during 0–48 weeks on relapse among patients with VR

The mean dose of Peg-IFN α-2b actually taken during the full treatment period by each patient was 1.32 μg/kg/week (range, 0.49–2.16 μg/kg/week; median, 1.38 μg/kg/week) and that of ribavirin was 9.8 mg/kg/day (range, 3.3–16.2 mg/kg/day; median, 10.1 mg/kg/day) in patients with VR.

The result of univariate analysis for relapse among the patients with VR is shown in Table 2a. The degree of fibrosis, the timing of HCV RNA negativiation, Plt value and the mean doses of ribavirin were factors significantly associated with relapse, but those of Peg-IFN α-2b were not. The mean dose of ribavirin as well as the degree of fibrosis and the timing of HCV RNA negativiation was selected as a significant independent factor by multivariate logistic regression analysis (Table 2b).

Next, we analysed the relationship of the relapse rate and the mean ribavirin dose. The overall relapse rate among patients with VR was 26% (125/472). The

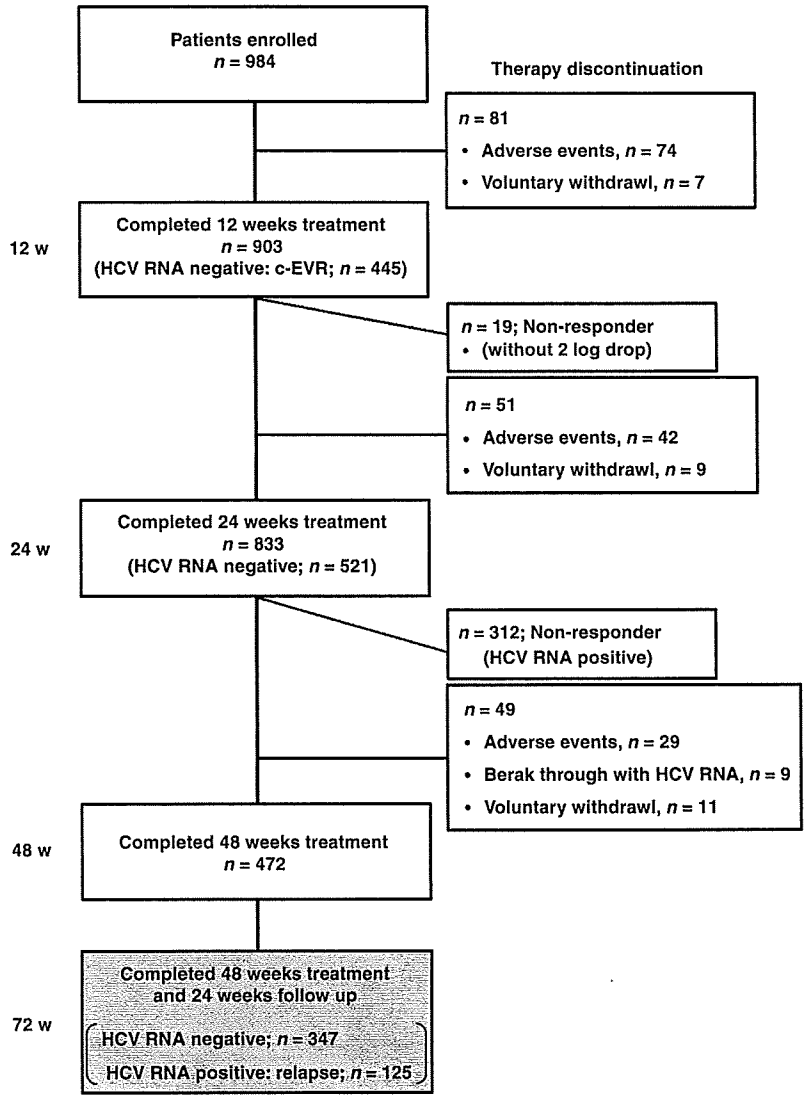


Fig. 1 Flow of patients throughout the study.

relapse rate was 60% (9/15) in patients receiving less than 6 mg/kg/day of ribavirin, and declined to 41% (32/79) at 6–8 mg/kg/day, 27% (34/124) at 8–10 mg/kg/day, 22% (43/193) at 10–12 mg/kg/day and 11% (7/61) in patients given ≥12 mg/kg/day ($P < 0.0001$). Figure 2 shows the relationship of the relapse rate and the mean ribavirin dose for two dosage groups of Peg-IFN α-2b: the group given ≥1.4 μg/kg/week of Peg-IFN and that given <1.4 μg/kg/week (1.4 μg/kg/week was the median value). In both groups, ribavirin was dose-dependently correlated with relapse. More than 12 mg/kg/day of the mean ribavirin exposure could suppress the relapse rate to 20% (4/20) in the group given <1.4 μg/kg/week and strongly suppress it to 7% (3/41) in the group given ≥1.4 μg/kg/week of Peg-IFN.

Impact of drug exposure during 0–48 weeks on relapse according to the timing of HCV RNA negativiation

Relapse rates among patients with c-EVR

The overall relapse rate among patients with c-EVR was 19% (75/391). We separately analysed the relapse rate among the patients with c-EVR according to the degree of exposure to both drugs. Table 3a shows the relapse rates among the patients with c-EVR according to the categories of Peg-IFN α-2b and ribavirin doses during the full treatment period. The relapse rate showed a decline according to the increase in the dose of ribavirin ($P = 0.0002$). The relapse rate was suppressed at an average of 15% (13–16%) in the patients who received 10–12 mg/kg/day of ribavirin, and the average was only 4% for those who received more than 12 mg/kg/day

Table 2 Factors associated with relapse among the patients with virologic response

(a) Univariate analysis

Factor	Nonrelapser	Relapser	*P* value
n	347	125	
Age (years)	53.9 ± 10.7	56.2 ± 9.2	0.07
Sex (male/female)	213/134	66/59	0.09
Serum HCV RNA (kIU/mL)*	1600	1800	0.34
White blood cells (/mm^3)	5335 ± 1517	5075 ± 1428	0.08
Neutrophils (/mm^3)	2797 ± 1143	2625 ± 1021	0.17
Red blood cells (×10^4/mm^3)	450 ± 45	446 ± 50	0.25
Haemoglobin (g/dL)	14.3 ± 1.4	14.2 ± 1.5	0.45
Platelets (×10^4/mm^3)	17.6 ± 5.3	16.4 ± 5.1	0.03
AST (IU/L)	60 ± 42	58 ± 33	0.75
ALT (IU/L)	75 ± 60	71 ± 50	0.98
Histology (METAVIR)†			
Fibrosis: 0–2/3–4	222/20	74/19	0.002
Activity: 0–1/2–3	140/102	52/41	0.75
Peg-IFN dose (μg/kg/week)‡	1.33 ± 0.26	1.27 ± 0.29	0.07
Ribavirin dose (mg/kg/day)‡	10.1 ± 1.9	9.1 ± 2.1	<0.001
Virologic response§: c-EVR/LVR	316/31	75/50	<0.001

(b) Multivariate analysis

Factor	Category	Odds ratio	95% CI	*P* value
Platelets	By 1 × 10^4/mm^3	–	–	NS
Fibrosis¶	0–2/3–4	1/3.192	1.515–6.725	0.002
Ribavirin dose‡	By 1 mg/kg/day	0.790	0.696–0.896	<0.001
Virologic response§	c-EVR/LVR	1/6.290	3.385–11.690	< 0.001

AST, aspartate aminotransferase; ALT, alanine aminotransferase; HCV, hepatitis C virus; c-EVR, complete early virologic response; LVR, late virologic response; NS, not significant difference Peg-IFN, pegylated interferon.
*Data shown are median values. †137 missing. ‡Mean doses during 0–48 weeks. §The timing of HCV RNA negativiation. ¶METAVIR fibrosis score.

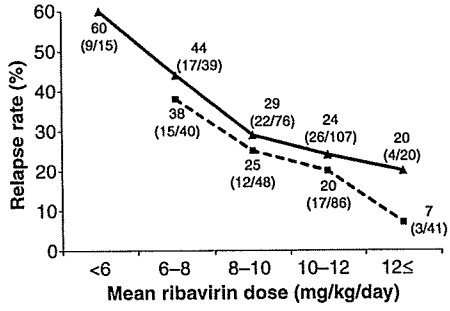


Fig. 2 Relapse rate according to Peg-IFN α-2b and ribavirin doses during treatment of patients who completed treatment, which was stratified with the mean ribavirin doses. (-▲-) Group with the mean Peg-IFN dose <1.4 μg/kg/week; (··■··) Group with the mean Peg-IFN dose ≥1.4 μg/kg/week. The ribavirin dose was dose-dependently correlated with the virologic relapse in both groups ($P < 0.0001$). There was no significant difference between the two Peg-IFN α-2b-dose groups ($P = 0.17$).

of ribavirin. In contrast, the relapse rate was not affected by the dose of Peg-IFN α-2b when the patients were given more than 0.9 μg/kg/week of Peg-IFN α-2b. On the other hand, with respect to patients with rapid virologic response (RVR) defined as the absence of detectable serum HCV RNA at treatment week 4 ($n = 41$), none showed relapse and all attained SVR irrespective of the dose of Peg-IFN α-2b or ribavirin (prevalence of patients: the mean dose of Peg-IFN α-2b; <0.9 : 0.9–1.2 : 1.2–1.5 : 1.5 μg/kg/week ≤ =7 : 17 : 34 : 42%, the mean dose of ribavirin; <8 : 8–10 : 10–12 : 12 mg/kg/day ≤ =15 : 24 : 41 : 20%).

Relapse rates among patients with LVR

Among the patients with LVR, the ribavirin exposure during treatment was also the factor correlated adversely with the relapse rate ($P = 0.03$). However, the overall relapse rate was 62% (50/81), which was much higher than that of the c-EVR patients ($P < 0.0001$) and 45% (5/11) of patients with LVR relapsed even in the group given more than 12 mg/kg/day of the average ribavirin dose (Table 3b).