Table 2
Reasons for treatment discontinuation.

	TACE group		TAI group	
Ineffectiveness of protocol treatment	10	13%	10	12%
Adverse event caused by protocol treatment				
Elevation of serum creatinine level	1	1%	1	1%
Elevation of alkaline phosphatase level	2	3%	2	2%
Dyspnea	0	0%	1	1%
Hypotension	1	1%	1	1%
Shivers	0	0%	1	1%
Abdominal pain	0	0%	2	2%
Ascites	1	1%	0	0%
Deterioration before subsequent protocol treatment				
Extrahepatic metastasis	4	5%	7	9%
Portal vein thrombosis	6	8%	3	4%
Tumor rupture	2	3%	0	0%
Ascites	9	11%	11	13%
Liver dysfunction	9	11%	11	13%
Poor general condition	2	3%	2	2%
Other disease	1	1%	6	7%
Technical problem preventing subsequent protocol treatment	13	16%	9	11%
Patient's request	10	13%	11	13%
Indication for tumor ablation	1	1%	2	2%
Protocol treatment ongoing	7	9%	2	2%
Total	79		82	

for patients with advanced HCC treated with TAI had not been fully evaluated and because the efficacy of TACE was still being debated at that time in various countries. Moreover, several differences in TACE methods had been noted between clinical practice in East Asian countries, including Japan, and randomized studies conducted in Europe, including differences in the selection of embolization materials, anti-cancer agents and their doses, in treatment intervals, and in patient characteristics such as tumor stage and liver function. In this study, in which our TACE method was introduced, we selected SMANCS as a chemotherapeutic agent for both TACE and TAI. SMANCS is an anti-cancer drug that has been approved by the Japanese government for administration with lipiodol into the artery feeding HCC, and TAI with SMANCS has been widely used instead of TACE in many hospitals because of its favorable antitumor effect and mild toxicity profile.

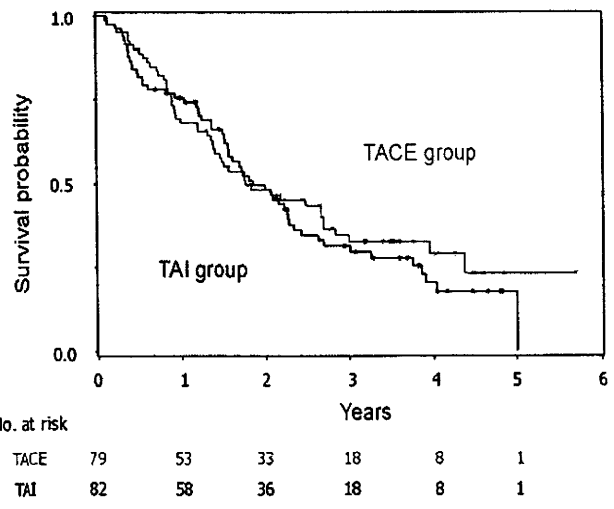

Fig. 2. Survival curves in the TACE group and in the TAI group.

This study did not confirm any significant survival advantage of TACE over TAI. A German group also reported that adding transient occlusion using degradable starch microspheres improved neither tumor response nor survival for patients treated with TAI using cisplatin and doxorubicin in a randomized phase II trial [21]. Llovet and Bruix showed that survival benefits were identified with TACE (doxorubicin or cisplatin) but not with embolization alone in their meta-analysis [11]. The survival benefit of TACE can be ascribed to the combination of embolization and chemotherapy.

It could be argued that the absence of a significant difference in survival rates between the TACE group and TAI group in this study is attributable to our methodological strategy for selecting SMANCS as the anti-cancer agent, because the agent may have produced favorable results in the TAI group. SMANCS is a high molecular weight chemical conjugate of a synthetic copolymer of styrene maleic acid (SMA) and the anti-cancer antibiotic protein, neocarzinostatin (NCS) [22,23]. SMANCS is lipophilic and dissolves in lipiodol to form a stable emulsion (SMANCS-lipiodol), which prevents rapid washout of SMANCS into plasma from trapped lipiodol. Furthermore, because of the enhanced permeability of the tumor vasculature and/or poor lym-

Table 3
Adverse events.

	TACE group						TAI group					
	Grade 3		Grade 4		Grade 1–4		Grade 3		Grade 4		Grade 1–4	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Hematological toxicity												
Leukocytes	1	1	0	0	27	34	0	0	0	0	26	32
Neutrophils	1	0	0	0	14	18	0	0	0	0	15	18
Hemoglobin	1	1	–		25	32	0	0	–		23	28
Platelets	10	13	2	3	54	68	10	12	3	4	57	70
Non-hematological toxicity												
Total bilirubin	21	27	0	0	60	76	15	18	0	0	62	76
Alkaline phosphatase	2	3	0	0	53	67	2	2	0	0	63	77
Aspartate aminotransferase	33	42	0	0	77	97	23	28	0	0	79	96
Alanine aminotransferase	28	35	0	0	73	92	16	20	0	0	77	94
Creatinine	0	0	0	0	13	16	0	0	0	0	16	20
Abdominal pain	0	0	0	0	55	70	2	2	0	0	50	61
Nausea/vomiting	1	1	–		43	54	0	0	–		39	48
Diarrhea	0	0	0	0	2	3	0	0	0	0	4	5
Fever	2	3	0	0	69	87	1	1	0	0	66	80
Shivers	0	0	0	0	12	15	1	1	0	0	14	17
Allergy	0	0	0	0	2	3	0	0	0	0	6	7
Ascites	1	1	–		3	4	0	0	–		0	0
Dyspnea	0	0	0	0	0	0	0	0	1	1	1	1
Hypotension	1	1	0	0	1	1	1	1	0	0	1	1

A 'dash' (–) indicates the grade was not available.

phatic drainage from the tumor interstitium, macromolecular agents like SMANCS are retained more selectively within tumors [24,25]. In fact, experimental studies have shown that tumor-systemic drug concentration ratios as high as 1000 can be achieved using TAI with SMANCS-lipiodol. Thus, the selective delivery of a long-lasting or slow-release anti-cancer agent may have had a sufficient antitumor effect and survival-prolonging efficacy in the TAI group even if embolization had not been used in combination.

The infrequent protocol treatment repetition in this study is another possible reason for the lack of any difference in survival between the two groups, because the average number of protocol treatments was only 2.2 courses in the TACE group and 2.4 in the TAI group, and thus the maximum anti-cancer potential may not have been achieved. We speculated that the choice of SMANCS was partly responsible for the infrequent repetition because hepatic vascular complications, such as the obstruction of the hepatic artery and the arterio-portal shunt, have been reported as adverse reactions specific to SMANCS [26]. These complications are often followed by liver dysfunction, ascites, and technical problems with regard to subsequent protocol treatment, which were the major reasons for treatment discontinuation in this study. The enrollment of many patients with far-advanced HCC in the present phase III study may have been another reason for the small number of treatment repetitions and the subsequent poor survival: the proportion of patients with a pre-treatment AFP level >200 ng/mL was 40% in the phase III study and 24% in the phase II study. Both the antitumor response and the overall survival of the TACE group were poorer than our expectations: the 2-year survival rate in the TACE group was 48.2% in the present study, as opposed to 79% in the phase II study of TACE with SMANCS.

In conclusion, the results of this study suggest that treatment intensification by adding embolization did not increase the survival of HCC patients over SMANCS transarterial chemotherapy alone. The results of this study also showed no significant differences in toxicity, except for an ALP elevation, between the two groups treated with SMANCS. It should be emphasized that the negative results in this study may be attributable to our methodological strategy for selecting SMANCS and the enrollment of many patients with far-advanced HCC. The infrequent treatment repetition and the favorable results of TAI with SMANCS are speculated to be reasons for the lack of any difference in survival between the two groups. Furthermore, the results of this study must be interpreted with caution because current TACE protocols have evolved thanks to the implementation of updated devices including new embolic agents and improved catheters. Additional studies will be required to determine whether the results obtained in this trial are consistent with the results of transarterial treatment with chemotherapeutic agents other than SMANCS and with updated procedures, although it would be difficult to conduct such studies because many consider TACE to be the standard treatment based on the positive results obtained in two recent randomized studies in which doxorubicin or cisplatin was used

[7,8]. There is a more pressing need for the establishment of new and more active treatment strategies that are superior to conventional TACE to improve the dismal prognosis of this disease.

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Review

Expert Opinion

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Pharmacotherapy of chronic hepatitis C virus infection – the IDEAL trial: '2b or not 2b (= 2a), that is the question?'

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Background: There has been no direct comparison of the antiviral efficacy and the adverse effects of peginterferon (PEG-IFN) alfa-2a and PEG-IFN alfa-2b when used in combination therapy with ribavirin for chronic hepatitis C virus (HCV) infection. *Objective*: A head-to-head comparison of the antiviral efficacy and the adverse effects of PEG-IFN alfa-2a and PEG-IFN alfa-2b was made based on the results from the IDEAL trial, a large, multicenter, prospective, randomized, controlled study performed in the United States to provide guidance for the selection of the right PEG-IFN in clinical settings. *Methods*: The results of the IDEAL trial were analyzed. *Results/conclusion*: The antiviral efficacy, as well as the adverse effects, of PEG-IFN alfa-2a and PEG-IFN alfa-2b are similar in US patients with HCV genotype 1 when used in a standard dosing regimen in combination with ribavirin.

Keywords: adverse effects, antiviral efficacy, IDEAL trial, peginterferon alfa-2a, peginterferon alfa-2b, ribavirin

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1. Introduction

Since the first report on the efficacy of interferon (IFN) therapy on non-A, non-B chronic hepatitis was published in 1986 [1], many studies have been performed on the efficacy of antiviral therapy with IFN on chronic hepatitis C virus (HCV) infection for the eradication of HCV. Some studies further reported long-term improvement of liver fibrosis in patients with the eradication of HCV [2-7], and other studies reported improvement of liver steatosis [8] or reduction in the incidence of the development of hepatocellular carcinoma [9-15].

Since the establishment of IFN therapy as a treatment of chronic hepatitis C, two important developments have occurred; one is the emergence of ribavirin used in combination with IFN and the other is the pegylation of IFN to create peginterferon (PEG-IFN). These developments have contributed to the increase in the rate of sustained virologic response (SVR, Table 1), which usually indicates the eradication of HCV.

Currently, combination therapy with PEG-IFN and ribavirin is the standard antiviral therapy for chronic hepatitis C [16]. The selection of the specific regimen of the PEG-IFN/ribavirin combination therapy is determined by the patient HCV genotype and the virological response after the start of therapy. Patients infected with HCV genotypes 1 or 4, which are usually resistant to the therapy, are recommended to undergo a 48-week treatment regimen, whereas patients infected with HCV genotypes 2 or 3, which are usually sensitive to the therapy, are recommended to undergo a 24-week treatment regimen [16-21]. Several additional findings have been reported, which contribute to regimen selection. Efficacy of elongation of the treatment

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Table 1. The definition of virologic responses and abbreviations.

Term	Abbreviation	Definition
Rapid virologic response	RVR	Undetectable serum HCV RNA after 4 weeks of treatment
Early virologic response	EVR	Undetectable serum HCV RNA (complete EVR) or > 2-log drop in HCV RNA concentration (partial EVR) after 12 weeks of treatment
Slow virologic response		Undetectable serum HCV RNA between 12 and 24 weeks after start of treatment
End-of-treatment response	EoTR	Undetectable serum HCV RNA at the end of treatment
Sustained virologic response	SVR	Continued undetectable serum HCV RNA 6 months after the end of treatment
Relapse		Detectable serum HCV RNA within 6 months after the end of treatment after EoTR

duration up to 72 weeks was reported in patients with HCV genotype 1 having slow virologic response (Table 1) [22-24], whereas a 48-week treatment regimen is recommended in patients having an early virologic response (EVR, Table 1). By contrast, it has been reported that for patients with HCV genotypes 2 or 3 and having a rapid virologic response (RVR, Table 1), it may be possible to shorten the treatment duration to as short as 12 weeks [25-29]. In addition, multiple studies report the importance of the adherence to the therapy for achieving SVR [30-33].

One question remains unanswered, however. Which PEG-IFN should be administered in combination with ribavirin: PEG-IFN alfa-2a or PEG-IFN alfa-2b? Physicians may wonder, like Hamlet, '2b or not 2b (= 2a), that is the question'.

Recently, a large prospective, randomized, controlled trial (the IDEAL trial) was conducted, in which antiviral efficacy and adverse effects were compared between patients treated with PEG-IFN alfa-2a and those treated with PEG-IFN alfa-2b. The results of this trial may provide some answers to this question. In this review, we compare the pharmacological characteristics, antiviral efficacy, and adverse effects of PEG-IFN alfa-2a and PEG-IFN alfa-2b as seen from the results of the IDEAL trial and other studies. We will discuss our interpretation of the results and strategy of choosing the kind of PEG-IFN for antiviral therapy for chronic hepatitis C.

2. IFN alfa-2a and IFN alfa-2b (monotherapy and combination therapy with ribavirin)

IFN alfa-2a and IFN alfa-2b are recombinant DNA-derived protein products with substantial amino-acid sequence identity to endogenous IFNs. Both are type I alfa IFN. The first IFN treatment regimen for antiviral therapy against HCV was simply IFN monotherapy. Before ribavirin, a synthetic guanosine nucleoside analog came to be used in combination with IFN, many investigators attempted to increase the rate of SVR with IFN monotherapy. The techniques used included increasing the dose of IFN or lengthening either the entire treatment period or the period of daily administration [34-56]. However, the increase was minimal, especially in patients infected with HCV genotype 1. The rate of SVR in patients with HCV genotype 1 was usually < 15% [57-60]. Although no report directly compared the rate of SVR between patients who received IFN alfa-2a monotherapy and those who received IFN alfa-2b monotherapy, the rate of SVR was similar in the two groups [57-60].

The use of ribavirin in combination with IFN alpha significantly increased the rate of SVR [57,58,61], including cases of retreatment [62-65]. The effect of the addition of ribavirin to IFN alfa on the increase in SVR rate was similar between IFN alfa-2a and IFN alfa-2b; however, no report directly compared the rate of SVR between patients who received combination therapy with IFN alfa-2a plus ribavirin and those who received combination therapy with IFN alfa-2b plus ribavirin.

3. PEG-IFN alfa-2a and PEG-IFN alfa-2b

In the late 1990s, PEG-IFN, a pegylated form of IFN alfa, became available for antiviral treatment of patients with chronic hepatitis C. Conjugation of an inert polyethylene glycol (PEG) molecule to a core protein (IFN alfa in this case) is a well-established method of modifying the pharmacological characteristics of the core protein [66-68]. Indeed, IFN alfa and PEG-IFN alfa differ greatly in their pharmacokinetics (Figure 1). This difference results in a higher SVR rate and fewer adverse effects in patients treated with PEG-IFN compared with those treated with IFN alfa, for both alfa-2a and alfa-2b [69-73].

PEG-IFN alfa-2a and PEG-IFN alfa-2b differ in the size and structure of the interferon and polyethylene glycol molecules, as well as in their pharmacokinetic properties [74-79]. The differences in chemical properties and pharmacokinetics are listed in Table 2. PEG-IFN alfa-2a is produced by forming a covalent bond between a branched 40-kDa PEG molecule and the IFN alfa-2a core protein. PEG-IFN alfa-2b is produced by forming a covalent bond between a linear 12-kDa PEG molecule, monomethoxypolyethylene glycol (mPEG), and the IFN alfa-2b core protein (Figure 2). Each PEG-IFN has a different advantage in yielding antiviral efficacy. PEG-IFN alfa-2a has the longer half-life of the two, whereas PEG-IFN alfa-2b has higher specific antiviral activity. The US Food and Drug Administration (FDA)-approved dosing regimen also differs between the two PEG-IFNs: fixed dosing for PEG-IFN alfa-2a and dosing based on weight for PEG-IFN alfa-2b [80,81]. Although it is presumed

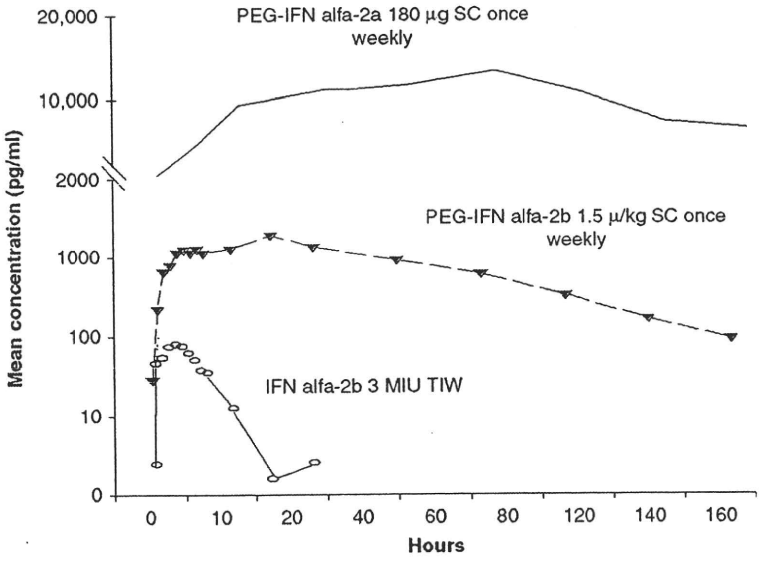

Figure 1. Pharmacokinetics of IFN alfa and PEG-IFN alfa.

that these differences will result in a different antiviral efficacy between the two types of PEG-IFN, no head-to-head results were reported for these two drugs during the period when PEG-IFN monotherapy was the mainstream antiviral therapy for chronic hepatitis C.

4. Previous comparisons of the rate of sustained virologic response between PEG-IFN alfa-2a and PEG-IFN alfa-2b as combination therapy with ribavirin

Combination therapy with PEG-IFN and ribavirin is the current standard antiviral therapy for the treatment of chronic hepatitis C. The use of PEG-IFN in combination with ribavirin has been reported to be superior to combination therapy with standard IFN and ribavirin [82-86], and the addition of ribavirin to PEG-IFN has been reported to be superior to PEG-IFN monotherapy [83,85,87-89]. Many studies have documented a high rate of SVR from combination therapy with PEG-IFN and ribavirin in various patient subpopulations, including patients undergoing the therapy as a retreatment [17-29,90-102].

The ribavirin itself is pharmacologically identical, whether administered in combination with PEG-IFN alfa-2a or PEG-IFN alfa-2b, despite the different names. Therefore, a difference in the antiviral efficacy, if observed, would be due either to the difference between IFN alfa-2a and IFN alfa-2b, the difference in the type of pegylation, or the different dosing regimens or dose reduction rules of PEG-IFN and ribavirin associated with the type of PEG-IFN used. Because similar SVR rates have been observed in patients who received IFN alfa-2a and in those who received IFN alfa-2b, it is presumed that the difference in the type of pegylation and the different dosing regimen would have the strongest impact on the difference in antiviral efficacy. Whether the difference in these factors does in fact cause the observed difference in SVR rate in clinical practice is, therefore, of great interest.

Two earlier studies attempted a direct comparison of antiviral efficacy between PEG-IFN alfa-2a and PEG-IFN alfa-2b in randomized trials [103,104]. However, the number of patients evaluated in these trials was too small (n = 36 and n = 116) and the follow-up period was too short. Furthermore, the trials evaluated heterogeneous interventions and populations. A more recent study focused on patients who were infected with HCV genotype 1 and had a high pretreatment HCV RNA concentration (i.e., difficult-to-treat patients) and reported comparable antiviral efficacy between PEG-IFN alfa-2a plus ribavirin and PEG-IFN alfa-2b plus ribavirin [105]. The authors of this study also reported a higher rate of discontinuation of the therapy due to adverse effects in patients treated by PEG-IFN alfa-2b plus ribavirin. The study contained a fairly large number of patients (n = 380) and was a prospective, randomized trial. The reported observations, however, only extended to 12 weeks after start of treatment, at which time the antiviral efficacy was evaluated by EVR. Although EVR is an established marker of SVR, the final outcome should be evaluated as well. Another study compared the antiviral efficacy of PEG-IFN alfa-2a and PEG-IFN alfa-2b in combination with ribavirin and found a similar rate of SVR between the two groups [106]. Their study was prospective but lacked randomization.

Chou *et al.* [107] attempted an indirect analysis of reported randomized trials to compare the rate of SVR between patients who received PEG-IFN alfa-2a plus ribavirin and those who received PEG-IFN alfa-2b plus ribavirin. They found no statistically significant difference in SVR rate between these

Table 2. Chemical and pharmacokinetic profiles of PEG-IFN alfa-2a and PEG-IFN alfa-2b.

	PEG-IFN alfa-2a	PEG IFN alfa-2b
Size of PEG	40 kDa	12 kDa
Conjugation form	Branched	Linear
Half-life	77 – 100 h	30 – 60 h
Specific activity	7%	28%
Dosing regimen	Fixed dose (180 µg)	Adjustment by weight (1.5 µg/kg)

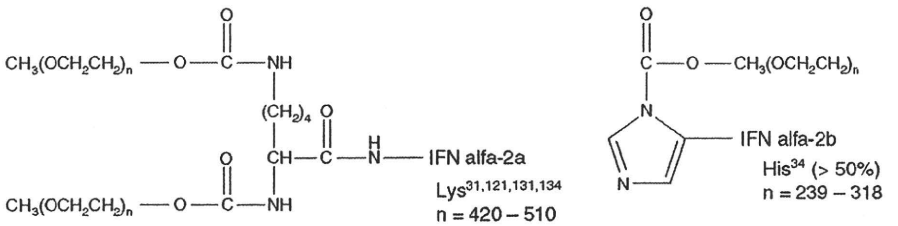

Figure 2. Chemical structures of PEG-IFN alfa-2a and PEG-IFN alfa-2b.

two groups. When only patients with HCV genotype 1 were considered, there was still no difference. Despite these studies, it is clear that a large, well-designed prospective trial is necessary to reach a conclusion on the difference in antiviral efficacy and adverse effects between PEG-IFN alfa-2a plus ribavirin and PEG-IFN alfa-2b plus ribavirin.

5. The IDEAL trial

The IDEAL trial (Individualized Dosing Efficacy vs flat dosing to Assess optimaL peginterferon therapy) was a US, multicenter, prospective, randomized, controlled trial with the purpose of head-to-head comparison of PEG-IFN alfa-2a plus ribavirin and PEG-IFN alfa-2b plus ribavirin for antiviral efficacy against chronic HCV infection. The trial contained a sufficiently large number of patients (n = 3070) and focused on patients with HCV genotype 1 [108]. In this trial, enrolled patients were randomly assigned to one of three groups: weekly 1.0 µg/kg PEG-IFN alfa-2b with daily 800 – 1400 mg ribavirin (low-dose PEG-IFN alfa-2b + ribavirin, n = 1016), weekly 1.5 µg/kg PEG-IFN alfa-2b with daily 800 – 1400 mg ribavirin (standard-dose PEG-IFN alfa-2b + ribavirin, n = 1019), and weekly 180 µg PEG-IFN alfa-2a with daily 1000 – 1200 mg ribavirin (PEG-IFN alfa-2a + ribavirin, n = 1035). Patients in all three groups received 48 weeks of treatment, followed by a 24-week follow-up period (Figure 3) [108]. Ribavirin dosages were modified in response to anemia, an adverse effect of ribavirin, as follows: reduction by 200 or 400 mg in the PEG-IFN alfa-2b groups, and to 600 mg in the PEG-IFN alfa-2a group [108]. The comparison between the latter two groups was a head-to-head comparison between PEG-IFN alfa-2a plus ribavirin and PEG-IFN alfa-2b plus ribavirin with the current standard dosage.

The final results of this trial were recently published [109]. The study patients consisted of 3070 treatment-naïve patients from 118 US centers with chronic HCV genotype 1 infection. The baseline demographics of patients were similar across the three groups. For the two head-to-head comparison groups (standard-dose PEG-IFN alfa-2b + ribavirin and PEG-IFN alfa-2a + ribavirin), they were as follows: male, 60.2 and 59.2%; white ethnicity, 71.8 and 70.8%; black ethnicity, 18.0 and 19.3%; mean age, 47.5 years and 47.6 years; mean weight, 84.0 kg and 82.8 kg; high pretreatment HCV RNA concentration (> 600,000 IU/mL), 82.0 and 82.3%; high fibrosis grade (grade 3 or 4 by METAVIR fibrosis score), 10.9 and 10.6%.

The antiviral efficacies for all three groups are listed in Table 3. The rate of end-of-treatment response (EoTR, Table 1) in patients who received PEG-IFN alfa-2a plus ribavirin was higher than in patients who received standard-dose PEG-IFN alfa-2b plus ribavirin (64.4 vs 53.2%, $p < 0.0001$). In contrast, the relapse rate after completion of the therapy in patients who received standard-dose PEG-IFN alfa-2b plus ribavirin was lower than in patients who received PEG-IFN alfa-2a plus ribavirin (23.5 vs 31.5%, $p = 0.0024$). As a result, the rate of SVR was similar between the two groups (40.9% for PEG-IFN alfa-2a and 39.8% for PEG-IFN alfa-2b, $p = 0.5687$). The similarity of the rate of SVR between patients treated with PEG-IFN alfa-2a and ribavirin and those treated with standard-dose PEG-IFN alfa-2b (1.5 µg/kg) was maintained within subgroups: female (41.9 vs 44.3%)/male (40.1 vs 36.9%), black ethnicity (26.0 vs 23.0%)/white ethnicity (44.2

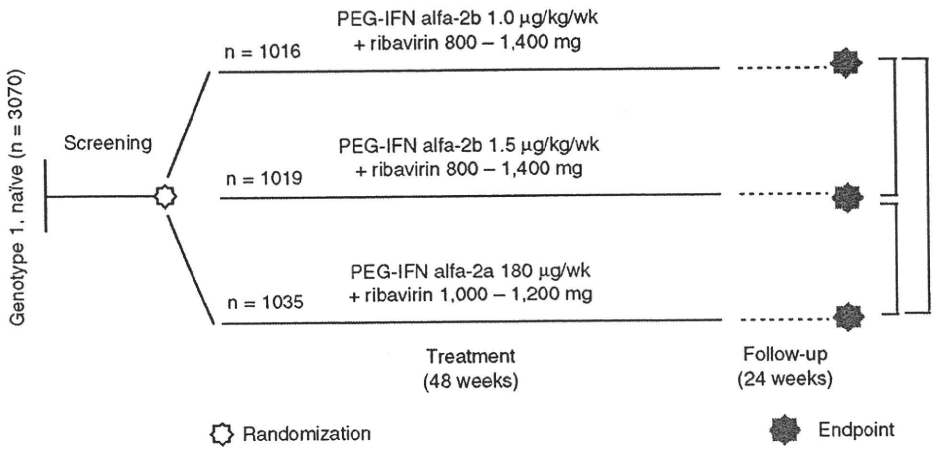

Figure 3. Study design of the IDEAL trial.

Table 3. The rate of rapid virologic response, early virologic response, end-of- treatment response, sustained virologic response, and relapse in three arms of the IDEAL study.

	PEG-IFN alfa-2b 1.0 µg/kg/week + ribavirin 800 – 1400 mg (n = 1016)	PEG-IFN alfa-2b 1.5 µg/kg/week + ribavirin 800 – 1400 mg (n = 1019)	PEG-IFN alfa-2a 180 µg/week + ribavirin 1000 – 1200 mg (n = 1035)
RVR (4 weeks)	7.8%	11.4%	11.9%
EVR (12 weeks)	36.0%	39.9%	45.0%
EoTR (48 weeks)	49.2%	53.2%	64.4%
SVR (24 weeks -up)	38.0%	39.8%	40.9%
relapse rate	20.0%	23.5%	31.5%

vs 43.6%), pretreatment fasting glucose < 5.6 mmol/L (44.1 vs 43.7%)/≥ 5.6 mmol/L (32.9 vs 29.7%), patients without steatosis (49.3 vs 47.6%)/with steatosis (36.4 vs 34.5%), pretreatment HCV RNA concentration > 600,000 IU/mL (35.6 vs 35.3%)/≤ 600,000 IU/mL (65.6 vs 60.7%), and METAVIR fibrosis score 0 to 2 (43.6 vs 42.1%)/3 or 4 (23.6 vs 20.7%). In multivariate analysis, the factors that influenced SVR were low pretreatment HCV RNA concentration (≤ 600,000 IU/mL), non-black ethnicity, minimal fibrosis score (METAVIR 0 to 2), lack of steatosis, pretreatment fasting glucose < 5.6 mmol/L, and pretreatment ALT elevation. The kind of PEG-IFN used (2a or 2b) did not have an impact on SVR.

As with the SVR rate, the rate of adverse effects and the rates of dose modification and discontinuation due to adverse effects were similar between patients treated with PEG-IFN alfa-2a plus ribavirin and those treated with standard-dose PEG-IFN alfa-2b plus ribavirin (Table 4). The percentages of patients who discontinued the therapy due to adverse effects were 13.0 and 12.7%, and the percentage of patients who experienced a dose reduction due to adverse effects were 42.9 and 43.3%, respectively. With regard to hematologic parameters, neutrophil counts fell below 750/mm^3 and 500/mm^3 in 27.0 and 5.9% of patients, respectively, who received PEG-IFN alfa-2a plus ribavirin, and in 22.2 and 2.8% of patients, respectively, who received standard-dose PEG-IFN alfa-2b plus ribavirin. The reduction of neutrophil counts was more marked in patients who received PEG-IFN alpha-2a ($p = 0.01$ and $p = 0.001$, respectively). Hemoglobin level fell below 10 g/dL and 8.5 g/dL in 29.6 and 3.8% of patients, respectively, who received PEG-IFN alfa-2a plus ribavirin, and in 30.7 and 2.5% of patients, respectively, who received standard-dose PEG-IFN alfa-2b plus ribavirin. No difference was found in hemoglobin reduction between the two groups.

6. Other studies comparing PEG-IFN alfa-2a and PEG-IFN alfa-2b in combination with ribavirin

In addition to the IDEAL trial, several other studies have attempted a direct comparison between PEG-IFN alfa-2a and PEG-IFN alfa-2b treatment (Table 5). In a single-center, prospective, randomized, controlled trial conducted in Italy and containing 320 patients including genotypes 1, 2, 3, and 4,

Table 4. The rate of dose modification and discontinuation due to adverse effects in three arms of the IDEAL study.

	PEG-IFN alfa-2b 1.0 μg/kg/week + ribavirin 800 – 1400 mg (n = 1016)	PEG-IFN alfa-2b 1.5 μg/kg/week + ribavirin 800 – 1400 mg (n = 1019)	PEG-IFN alfa-2a 180 μg/week + ribavirin 1000 – 1200 mg (n = 1035)
Dose modification due to adverse effects	33.3%	43.3%	42.9%
Discontinuation due to adverse effects	9.6%	12.7%	13.0%

Table 5. Studies comparing PEG-IFN alfa-2a and PEG-IFN alfa-2b in patients with HCV genotype 1.

Authors (country)	Study name	Method	RCT	No. of sites	No. of cases	Results (SVR rate)	
						PEG 2a	PEG 2b
McHutchison *et al.* (USA)	IDEAL	Prospective	Yes	Multi-center	3070	41%	40%
Ascione *et al.** (Italy)		Prospective	Yes	Single-center	186	55%	40%
Witthoeft *et al.* (Germany)	PRACTICE	Retrospective	No	Multi-center	1128‡	50%	44%
Craxi *et al.* (Italy)	PROBE	Retrospective	No	Multi-center	1351	41%	34%
Rumi *et al.** (Italy)	MIST	Prospective	Yes	Multi- center	222	48%	32%

*Including patients with HCV genotype 4.
‡Matched pair patients.
*All but IDEAL trial were reported as abstracts and have not been published.
PEG 2a: PEG-IFN alfa-2a; PEG 2b: PEG-IFN alfa-2b; RCT: Randomized controlled trial.

Ascione *et al.* [110] reported a higher SVR rate in patients treated by PEG-IFN alfa-2a plus ribavirin than in those treated by PEG-IFN alfa-2b (1.5 μg/kg) plus ribavirin (68.7 vs 54.4%, p = 0.0082). A higher SVR rate in patients treated by PEG-IFN alfa-2a plus ribavirin was also observed when only patients with HCV genotype 1 or 4 were considered (54.8 vs 39.8%, p = 0.0398). Another prospective study from Italy in which PEG-IFN alfa-2a and PEG-IFN alfa-2b in combination with ribavirin were directly compared (MIST study) reported a higher rate of SVR in patients treated with PEG-IFN alfa-2a plus ribavirin in 431 patients with HCV genotype 1, 2, 3, and 4 (66 vs 54%, p = 0.02), and when with HCV genotypes 1 and 4 were considered separately (48 vs 32%, p = 0.02) [111]. In the former study, however, the rate of withdrawal of the therapy observed with PEG-IFN alfa-2b plus ribavirin was markedly higher than in patients treated by PEG-IFN alfa-2a plus ribavirin. This is in contrast to the result of the IDEAL trial in the U.S. However, another retrospective study from the US also reported higher treatment persistence in patients treated with PEG-IFN alfa-2a plus ribavirin than in those treated with PEG-IFN alfa-2b plus ribavirin [112]. Further studies will be required on adverse effects and the treatment adherence for the two treatments in different patient populations.

Other reported studies were retrospective, non-randomized comparisons. Two retrospective studies from Italy and from Germany found a higher rate of SVR in real-life settings in patients treated with PEG-IFN alfa-2a plus ribavirin than in those treated with PEG-IFN alfa-2b plus ribavirin [113,114].

Craxi *et al.* [113] studied 1017 naïve patients with HCV genotype 1 who were included in the Italian PROBE study. PEG-IFN alfa-2a and ribavirin were administered to 663 patients, and PEG-IFN alfa-2b and ribavirin to 354 patients. The rate of SVR was 35% for PEG-IFN alfa-2a and 23% for PEG-IFN alfa-2b (p = 0.01). The use of PEG-IFN alfa-2a was shown by multivariate analysis to be one of the independent factors accounting for the higher SVR rate.

Witthoeft *et al.* [114] compared the results observed with PEG-IFN alfa-2a and PEG-IFN alfa-2b by matched pair analysis, including cumulative ribavirin dosage, in patients included in the German PRACTICE study. In 1696 patients with all genotypes, the rate of SVR was 59.3% in patients treated with PEG-IFN alfa-2a plus ribavirin and 53.0% in those treated with PEG-IFN alfa-2b plus ribavirin. In 1128 patients with HCV genotype 1, the SVR rates were 50 and 44%, respectively. The SVR rate was significantly higher in the PEG-IFN alfa-2a group both for all genotypes and for the patients with HCV genotype 1 considered separately (p = 0.008 and p = 0.04, respectively). By contrast, another study from Australia [115] reported a comparable rate of SVR between PEG-IFN alfa-2a and PEG-IFN alfa-2b treatments in patients with HCV genotypes 1, 2, or 3.

Unfortunately, those studies that attempted a direct comparison between PEG-IFN alfa-2a and PEG-IFN alfa-2b have been reported as an abstract form, and final results have not been published. The detailed analyses of the data in these studies that would be published in the future will more clarify

their conclusions. The result of the MIST study will be published in the near future in *Gastroenterology*.

Three studies (one prospective and two retrospective) of patients with HCV and HIV co-infection attempted a direct comparison between PEG-IFN alfa-2a and PEG-IFN alfa-2b in combination with ribavirin [116-118]. All three studies reported no difference in SVR rate between PEG-IFN alpha-2a and PEG-IFN alpha-2b.

7. Conclusion

The differing pharmacokinetics and antiviral activities of PEG-IFN alfa-2a and -2b have long been known. However, whether these differences and the differences in dosing regimen cause differences in treatment outcomes has remained unclear. Data from the IDEAL trial provided one answer to this question. According to the results of this large, prospective, randomized, controlled trial, the final SVR rate and adverse effects of PEG-IFN alfa-2a and PEG-IFN alfa-2b are similar in patients with HCV genotype 1, when used with the standard dosing regimen in combination with ribavirin.

8. Expert opinion

The IDEAL trial showed that the two currently available PEG-IFNs – PEG-IFN alfa-2a and PEG-IFN alfa-2b – in combination with ribavirin, are comparably effective against chronic HCV genotype 1 infection, despite their differing chemical and pharmacokinetic profiles. The IDEAL study protocol was well-designed and contained a sufficiently large number of patients, making it fairly reliable. Although each PEG-IFN has advantages, revealed by detailed analysis, the overall antiviral efficacy appears to be similar from the aspect of the eradication of HCV. The choice of PEG-IFN has weak influence on the SVR rate, in comparison to other factors such as treatment duration or adherence.

Of course, different study populations with differing background characteristics may give different results. The IDEAL trial contained only US patients; the background characteristics of patients in other studies will not be the same. Indeed, four other studies from Italy and Germany reported a result that contradicts the IDEAL study: a higher SVR rate in patients treated with PEG-IFN alfa-2a plus ribavirin than in those treated with PEG-IFN alfa-2b plus ribavirin; however, two of these studies were retrospective and the other two were based on a smaller number of patients than the IDEAL trial. In addition, data were lacking on a direct comparison between PEG-IFN alfa-2a plus ribavirin and PEG-IFN alfa-2b plus ribavirin in Asian patients. Further studies are necessary on this issue in various patient populations. Also, the different dosing regimen and the different dose reduction rules of PEG-IFN and ribavirin may give different results. The dosing regimen and dose reduction rules in the IDEAL trial were based on those approved by the US FDA, and would be different in other countries. The dosing regimen and dose reduction rules in the IDEAL trial were different between PEG-IFN alfa-2a plus ribavirin and PEG-IFN alfa-2b plus ribavirin. The direct comparison between PEG-IFN alfa-2a and PEG-IFN alfa-2b treatment using the same dosing regimen and same dose reduction rules will be necessary for more accurate comparison of antiviral efficacy between these two PEG-IFNs.

Despite these issues, it appears that, to the question posed at the introduction of this review, we can answer '2b or not 2b (= 2a), we can select either one', for initial treatment of a naïve patient with chronic HCV genotype 1 infection. In this situation, physicians may select either kind of PEG-IFN in combination with ribavirin. They may, therefore, select alfa-2a or alfa-2b according to the patient's social factors including availability and cost.

As many practical clinicians treating individual patients have experienced, however, the fact that a patient did not achieve SVR with one PEG-IFN does not necessarily mean that the patient will have no chance to achieve SVR with the other. Despite the similar rate of SVR between patients treated with PEG-IFN alfa-2a and PEG-IFN alfa-2b, their efficacies can be different for individual patients. Many hepatologists have seen cases in which a patient who had failed to achieve SVR with PEG-IFN alfa-2a plus ribavirin experienced successful eradication of HCV with PEG-IFN alfa-2b plus ribavirin, and vice versa. Although the final SVR rates were similar between PEG-IFN alfa-2a plus ribavirin and PEG-IFN alfa-2b plus ribavirin in the IDEAL trial, the EoTR rate and relapse rate were significantly different. These results suggested the different antiviral efficacy between these two PEG-IFNs, despite similar final SVR rates. It is, therefore, not completely futile to attempt to retreat patients who failed to achieve SVR by one PEG-IFN plus ribavirin with the other PEG-IFN plus ribavirin. Several studies, notably the REPEAT and EPIC3 studies [119-121] reported on the data of retreatment of patients who failed to achieve SVR by previous combination therapy with PEG-IFN and ribavirin. Although the SVR rate was low in both studies, the former study contained patients with genotype 1 who failed to achieve SVR with PEG-IFN alfa-2b plus ribavirin, but achieved SVR with PEG-IFN alfa-2a plus ribavirin. Conversely, the latter study contained patients with genotype 1 who failed to achieve SVR with PEG-IFN alfa-2a plus ribavirin, but achieved SVR with PEG-IFN alfa-2b plus ribavirin. However, as the guidelines of the American Association for the Study of Liver Diseases (AASLD) do not recommend retreatment for patients who failed to achieve SVR by PEG-IFN alfa plus ribavirin for the purpose of eradication of HCV [16], the retreatment should be considered for limited cases who cannot wait for the clinical use of new antiviral agents against HCV or who cannot apply for these drugs. In addition, the consideration of retreatment with PEG-IFN plus ribavirin is only for patients who have relapsed; patients who showed no response to one PEG-IFN plus ribavirin should not be retreated with the other PEG-IFN plus ribavirin.

More importantly, the adverse effects of PEG-IFN alfa-2a and PEG-IFN alfa-2b differ between individual patients, although the rates of adverse effects are similar between the

two treatments. In the IDEAL trial, the overall rate of common adverse events was similar between patients treated by PEG-IFN alfa-2a plus ribavirin and those treated by standard-dose PEG-IFN alfa-2b plus ribavirin, but the details of adverse events were heterogenous. The severity of adverse events from PEG-IFN alfa-2a and PEG-IFN alfa-2b can also vary among individuals. Some patients who discontinue the treatment regimen because of adverse effects from one PEG-IFN might have completed the entire treatment regimen with the other, thereby achieving SVR. In consideration of this, the PEG-IFN type should be selected not on the basis of efficacy but rather on the basis of adverse effects, so as to maintain the adherence that is strongly associated with the likelihood of SVR.

In light of these results, switching the PEG-IFN type during the treatment period may be a possible option. Early prediction of the eventual response to the therapy during the treatment will, therefore, become more important. Specifically, early prediction of a lack of SVR will make it possible to switch from PEG-IFN alfa-2a to PEG-IFN alfa-2b, or vice versa, during the course of the treatment. Prediction of the treatment outcome on the basis of RVR or EVR has been reported. This information, as well as the appearance and severity of adverse effects, could determine whether to switch the PEG-IFN type during the early stage of treatment, reducing unnecessary adverse effects and medical cost and maintaining the adherence.

In addition, it will be important to elucidate patient baseline characteristics to determine which patients should be treated initially with PEG-IFN alfa-2a plus ribavirin and which should be treated initially with PEG-IFN alfa-2b plus ribavirin. PEG-IFN alfa-2a and PEG-IFN alfa-2b are, of course, different drugs and their relative suitabilities for individual patients would be expected to differ. It is undoubtedly better for a patient with chronic hepatitis C to achieve SVR with the initial treatment rather than a retreatment and without switching the type of PEG-IFN during treatment.

Finally, the difference in antiviral efficacy between PEG-IFN alfa-2a and PEG-IFN alfa-2b should be evaluated in the future when used in combination with emerging new drugs, such as HCV serine protease or polymerase inhibitors [122-130], which can enhance the treatment efficacy of PEG-IFN. Although the SVR rates were comparable between PEG-IFN alfa-2a and PEG-IFN alfa-2b in combination with ribavirin, the difference in efficacy between the two PEG-IFNs when used in combination with these new drugs has not been determined.

Declaration of interest

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ソナゾイドによる
ルーチン造影超音波
検査

症例に見る
診断から治療までの
流れ

Scheduled Case Study

01-1

肝腫瘍診断における ソナゾイド造影超音波検査の 症例ケーススタディ

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第二世代の超音波造影剤であるソナゾイドは，外殻にシェルを有し，超音波に対して安定したマイクロバブルであり，持続的な造影効果（血管イメージングならびにKupfferイメージング）が得られる。造影CTと同等，もしくはそれを凌駕する造影効果が得られ，ベットサイドでも施行可能であり，簡便かつ安全な検査法である。これまでわれわれは，肝腫瘍のスクリーニングはBモードを中心に行ってきたが，さらに確実に腫瘍を検出，正確な病変範囲を同定，かつ質的診断を高めるため，ソナゾイドを用いた超音波検査をルーチン検査に組み込み施行している。本稿では，当院の肝腫瘍の診断体系を，症例を示しながら説明する。

検査の流れと選択の考え方

肝腫瘍診断の流れは，いままでは図1に示すように，『科学的根拠に基づく肝癌診療ガイドライン 2005年版』や『肝癌診療マニュアル』に沿ったものであった[1,2]。Bモードを中心に行い，必要に応じて定期的にMRIやCTを組み込み，超音波検査の死角を補ってきた。結節

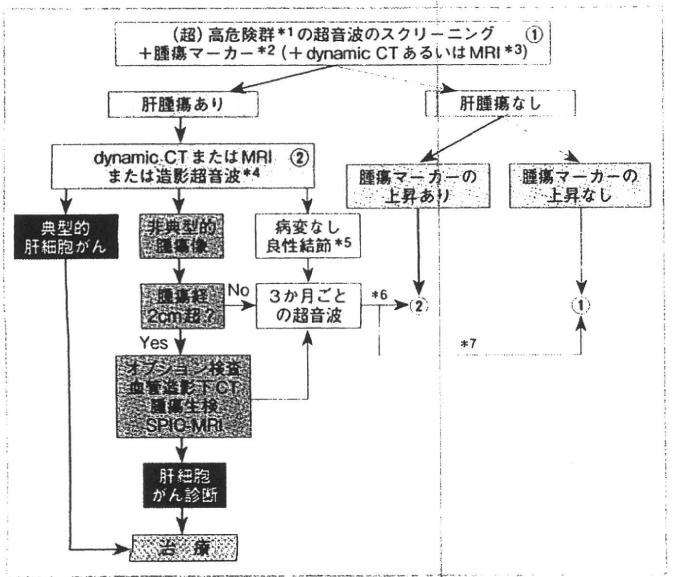

図1　いままでの肝腫瘍診断の流れ

＊1：高危険群はB型肝炎，C型肝炎，肝硬変。超高危険群はB型肝硬変，C型肝硬変。高危険群は原則として6か月に一度，超高危険群は原則として3か月に一度検査を行う。
＊2：腫瘍マーカーはAFP，PIVKA Ⅱ，AFP-L3分画の3種類。AFP-L3分画は肝がんの病名必要。
＊3：dynamic CTあるいはMRIは，超音波検査の死角を補うために定期的（6～12か月くらいの間隔）に行う。
＊4：ヨードアレルギーのある場合はdynamic MRI，腎障害のある場合は造影超音波が推奨される。
＊5：良性結節の場合は，症例に応じて適宜経過観察。
＊6：腫瘍のサイズアップ，もしくは腫瘍マーカーの上昇を認める場合は②に移行する。
＊7：サイズアップがないか消失の場合は①に移行する。

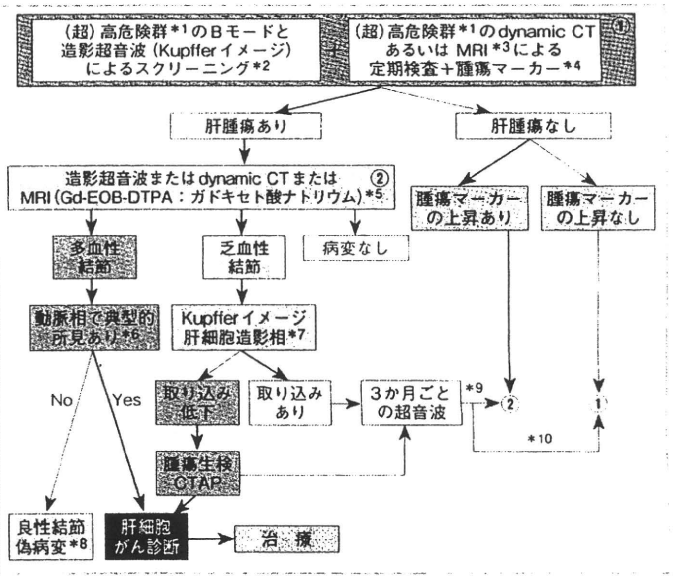

図2　これからの肝腫瘍診断の流れ

＊1：図1の＊1に同じ。
＊2：超音波検査の前にソナゾイドを静注し，Kupfferイメージの撮像のみを行う。同時にBモード（モニタ画像）の撮像もできる。
＊3：図1の＊3に同じ。　＊4：図1の＊2に同じ。
＊5：図1の＊4に同じ。
＊6：肝細胞がんでは動脈相で濃染し，門脈相では低吸収域となる。超音波ではdefect像。
＊7：造影超音波のKupfferイメージはKupffer細胞の多寡を，MRIの肝細胞相はGd-EOB-DTPAは結節内への造影剤の取り込みと排出のバランスを反映して像が構成される。
＊8：シャントなどの偽病変では，一般に後血管相や肝細胞造影相における画像は影響を受けないので鑑別に有用である。
＊9：図1の＊6に同じ。　＊10：図1の＊7に同じ。

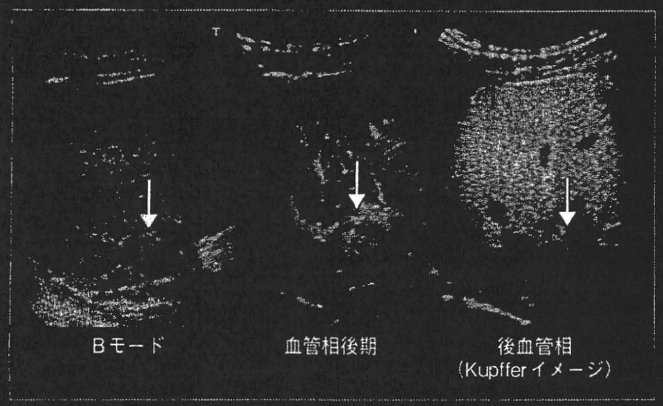

図4　造影超音波像（右肋間走査，67歳，男性）
BモードでS7（切除近傍）に18mm×13mmの低エコーの結節（↓）を認めた。血管相後期では腫瘍全体に均一な造影効果が得られ（↓），Kupfferイメージではdefect像（↓）が得られた。

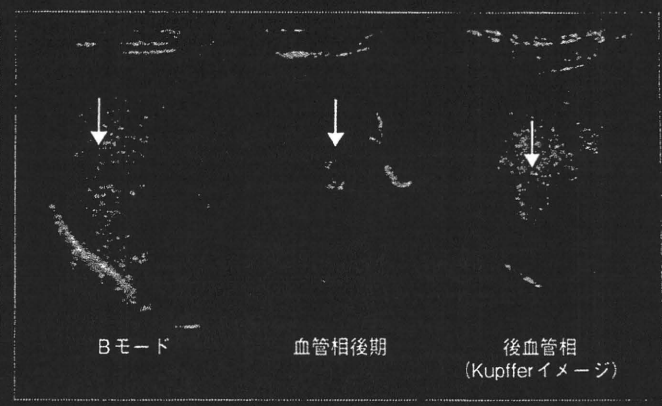

図5　造影超音波像（右肋間走査，67歳，男性）
図4と同一症例。別のレベルの右肋間走査である。Bモードにて辺縁不明瞭な低エコーの小結節（↓）を複数認めた。血管相後期（replenishment）ではこれらは明瞭な造影効果（↓）が得られ，Kupfferイメージで複数の明瞭なdefect像（↓）が得られた。

表1　症例提示

年齢・性別	67歳，男性
既往歴	2000年にB型肝炎キャリアを指摘。 肝細胞がんにて肝S_7切除＋胆嚢摘除術（2008年）
現病歴	2008年4月に肝細胞がんに対する肝切除を受け，以後外来で経過観察中であった。 同年8月，Bモードにて肝切除近傍に低エコー結節を認め，再発を疑い精査となった。

表2　ソナゾイド造影超音波検査の撮像条件

使用装置	AplioXG（東芝社製）
投与量	0.0075mL/kg（添付文書の用量0.015mL/kgの半量）
プローブ	PVT-375BT（コンベックス型）
MI値	0.21～0.34
フレームレート	11～15Hz

が認められた場合は，血流画像を得るためにdynamic CTまたはMRI，または造影超音波検査（レボビスト）を行っていたが，造影超音波はオプション検査の感が強く，腎障害例や造影剤アレルギー例を中心に使用されていた。これらの血流画像で典型的な肝細胞がんの画像が得られれば治療に移行した。また，非典型腫瘍像の場合は，2cmを超える結節ではオプション検査として，血管造影下CT（特に経動脈性門脈造影下CT：CTAP）や肝生検で診断と治療必要度（悪性度）を確定し，治療適応を決めていた。

しかし最近は，ソナゾイドとGd-EOB-DTPA（ガドキセト酸ナトリウム）が使用可能となり，診断体系は大きく変化した。血流画像に加えて安定した機能画像（Kupfferイメージおよび肝細胞イメージ）が得られるようになったからである。

最近の肝腫瘍診断の流れを図2に示す。血流画像と機能画像を適宜組み合わせて，より質の高い診断体系が構築できる。すなわち，患者の拾い上げの部分（存在診断）で，ソナゾイドを投与した後血管相（Kupfferイメージ）が組み込まれている。ただし，ソナゾイドを静注し，血管相を撮像すると，人手と時間もかかりルーチン検査とはなり得ない。このためわれわれは，ルーチン化を目的として血管相は撮像せずKupfferイメージのみに焦点を絞り，処置室で生理食塩水50mLまたは100mLにソナゾイド0.0075～0.015mL/kgを懸濁して，一般の点滴と同じように投与して対応している。患者は，点滴終了後抜針し，超音波検査の待機中に，撮像タイミングとして望まれる30分以上が経過する。もちろん，死角を補う意味で定期的にMRIやCTは組み込んでいる。そして，腫瘍をとらえた場合には，まず血流画像を得るために，造影超音波，そしてdynamic CTまたはMRIを行う。ここで，肝細胞がんに特有の血流画像が得られれば治療に移行するが，乏血性結節の場合には機能画像の情報が重要となる。肝細胞がんは分化度（悪性度）により，微妙に血流画像（動脈血流と門脈血流）と機能画像（Kupffer細胞と肝細胞）の解釈が異なる（**図3**）。ソナゾイドで欠損を示す結節と，Gd-EOB-DTPAで低信号を示す結節に乖離を認める場合もあるが，より精度の高い診断が可能となる。

ソナゾイドが有用であった67歳，男性，B型肝炎キャリア，肝細胞がん切除後の症例を提示する（**表1**）。ソナゾイド造影超音波検査の撮像条件は**表2**のとおりである。Bモードでは，下大静脈

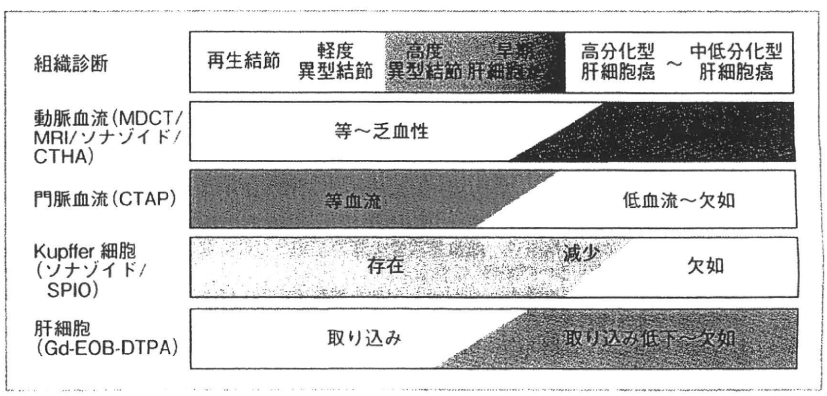

図3　肝硬変に伴う結節性病変の画像所見（概念図）

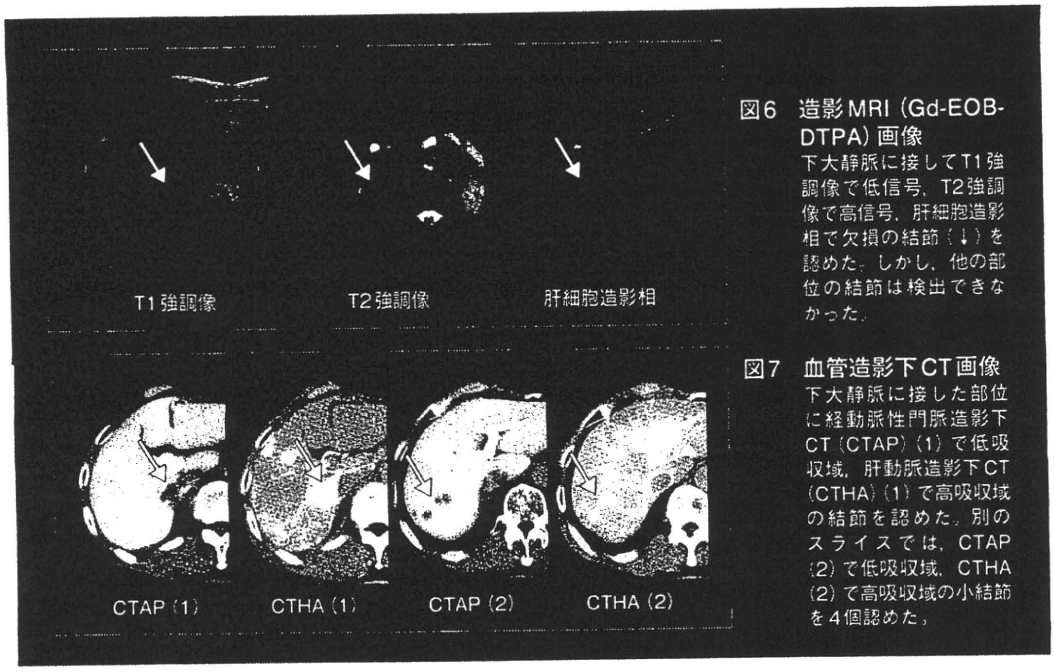

図6　造影MRI（Gd-EOB-DTPA）画像
下大静脈に接してT1強調像で低信号，T2強調像で高信号，肝細胞造影相で欠損の結節（↓）を認めた。しかし，他の部位の結節は検出できなかった。

図7　血管造影下CT画像
下大静脈に接した部位に経動脈性門脈造影下CT（CTAP）（1）で低吸収域，肝動脈造影下CT（CTHA）（1）で高吸収域の結節を認めた。別のスライスでは，CTAP（2）で低吸収域，CTHA（2）で高吸収域の小結節を4個認めた。

近傍の結節は同定できたが（図4），他部位の小結節は不明瞭にしか描出されず確定診断は困難であったが，造影を加えることで結節は明瞭に描出された（図5）。同時期に行ったMRIでは，下大静脈近傍の結節をとらえることはできたが，他の部位の結節は不明であった（図6）。血管造影下CT（CTA）では典型的な肝細胞がんの造影パターンを示し，造影超音波の所見が裏付けられた（図7）。

ソナゾイド造影超音波検査の有用性

ソナゾイドによる造影超音波検査の目的は，肝腫瘍の①質的診断，②存在診断（腫瘍の広がりも含める），③治療効果判定，④治療支援（ラジオ波焼灼療法：RFA，経皮的エタノール局注療法：PEIT）に分けられる。

ウイルス性肝炎など慢性肝疾患の患者に対しては，まず，肝腫瘍のスクリーニングのためKupfferイメージによる存在診断を中心に行い，腫瘍の存在が明らかになった場合，後日，確定診断のために血管相を撮像して質的診断を実施している。

また，血管腫や限局性結節性過形成（FNH）では，腫瘍内の血流がより明瞭に描出され，確定診断につながる。転移性肝がんでは，造影CTでは検出できない微小病変の検出も可能である

ただし，超音波検査で死角となるドームドや深部の腫瘍，また，高分化型肝細胞癌では，Kupffer細胞を有するためKupfferイメージによる存在診断は困難となり，注意を要する。

以上のとおり，ソナゾイドは診断から治療までの幅広いシーンで用いることができ，さらにKupfferイメージによる存在診断では簡便性も高い。よって，ソナゾイドを用いた造影超音波検査は，MRIなどの他の検査に匹敵する有用な検査であり，かつ安全性も考慮すると，それらを凌駕する検査とも言える。

ルーチン化へのアドバイス

当院では，造影超音波検査を，Kupfferイメージによる存在診断と，血管相とKupfferイメージ両者による質的診断の2つに大別している。電子カルテでのオーダは，前者を肝造影メタ・HCC検索，後者を造影エコー（臓器名）と呼んでいる。各検査の実施手順は以下のとおりである。

肝造影メタ・HCC検索オーダ

医師は患者に卵アレルギーの有無を確認し，検査とソナゾイド注射を指示する。外来処置室で（入院の場合は病棟で）ソナゾイドを点滴静注し，抜針して検査室に向かう。検査室では，技師がソナゾイド投与時間を確認した後，手順に従い全肝をスキャンする。必要があれば，後日，血管相も含めた再評価を行う

造影エコー（臓器名）オーダ

こちらも同様に，検査と血管確保用薬剤の注射を指示し，血管確保後に検査室に向かう。検査室では，Bモードで確認できる結節を検索してターゲットを決め，ターゲットの血流動態をドプラで把握する。次に，患者に呼吸や位置決めの練習をしてもらう。最終的にゲインやSTCなどを調整し，造影剤を作成した後，造影検査を開始する。血管相早期（静注開始より15～30秒後），血管相後期（静注開始より20～60秒後），replenishment・MFI（micro flow imaging），後血管相（Kupfferイメージ）をそれぞれ観察する。

まとめ

当院では，診療放射線技師あるいは臨床検査技師が主体となり，数多くの超音波検査を施行している。Kupfferイメージによる存在診断のみであれば，Bモードと同じ感覚でオーダでき，腫瘍が見つかった場合は，後日，血管相を含めた質的診断を追加している。この方法であれば，多くの患者に検査を施行することができる。まずは，簡便なKupfferイメージによる存在診断（当院では肝造影メタ・HCC検索）オーダを始めていくことが，ルーチン化への第一歩であると確信している。

最後に，造影超音波検査の普及を阻む第一の要因に，対応機器が高額なことがある。CTやMRIでの検査が困難な中小規模病院でこそ，造影超音波検査が生かされると思う。メーカー各社にはできるかぎり価格を抑えてもらい，多くの施設で造影超音波検査が行われることを念じてやまない。

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特集II　肝細胞癌治療後の抗ウイルス療法は予後を改善するか

B型肝炎ウイルス陽性肝細胞癌の治療後の核酸アナログ投与*

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Key Words：hepatitis B, hepatocellular carcinoma (HCC), nucleoside analogues, nucleotide analogues, recurrence

はじめに

ウイルス性肝炎の治療の進歩は目覚しいものがある．とくにB型肝炎ウイルス(hepatitis B virus：HBV)に対する抗ウイルス療法は各種核酸アナログの登場により新たな展開を示している[1]．B型慢性肝炎の治療目標は肝硬変への進展，および発癌を抑制することである．HBV量が増加するに従って肝硬変，肝細胞癌への進展率が増加し，核酸アナログ製剤を使用することにより，これらの進展を抑制できることは，すでに台湾のデータより報告された[2-4]．肝細胞癌が発生する前の肝炎，肝硬変においては，核酸アナログによるウイルス量の抑制が発癌を抑制することが示されているが[5]，肝細胞癌治療後の核酸アナログの適応については，まだコンセンサスが得られていないのが現状である．本稿では，B型慢性肝炎を背景とした肝細胞癌の根治治療後症例において，核酸アナログの肝細胞癌の再発抑制効果，肝予備能の改善効果について検討しデータを示す．

対象と方法

対象は，1989～2007年に当院で経験したHBV陽性肝細胞癌232例中，肝切除もしくは局所治療を受け，局所がコントロールされたと判断され，HBVのマーカーが経時的に測定されていた76例であり，これらをretrospectiveに解析した．平均年齢は59歳(21～84歳)，男女比は62：14，核酸アナログ投与例は31例，非投与例は45例で，観察期間中央値は4.5年(0.9～17.3年)である．生存率の解析はKaplan-Meier法，差の解析はBreslow-Gehan-Wilcoxon検定，多変量解析はCoxの比例ハザードモデル(変数増加法)を用いた．また2群間の比較は，連続変数に関してはt検定，Mann-Whitney U検定を，名義変数はχ^2検定を用いた．血液生化学データの項目で変動の多いALT, AST, γ-GTP, ALP, LDH, AFPはわれわれが以前から提唱している積分平均値を使用した[5]．それ以外の項目は経過観察開始時のものを使用した．

核酸アナログ投与例と非投与例の背景因子は表1に示すとおりであるが，差を認めるのは観察開始時のHBV DNA量であり，核酸アナログ投与例のほうが有意に高い値を示している．核酸アナログの投与基準は各主治医の判断に任せ，

* Nucleot(s)ide analogues lowers tumor recurrence rate after initial treatment for hepatitis B virus-related hepatocellular carcinoma.

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