occurred, dose reduction or discontinuation of PEG-IFNα-2a or RBV was performed.

Statistical analysis

All statistical analyses were done using JMP version 9 (SAS). We used the *t* test, Chi-square test, and Fisher's exact test for univariate analysis. To identify factors affecting the SVR rate, we used the logistic regression test. A *p* value of less than 0.05 was considered statistically significant.

Results

Flowchart of the study

A flowchart of the study is shown in Fig. 2. PEG-IFNα-2a monotherapy was initiated in 153 patients, out of which 15 patients necessitated treatment discontinuation due to the patient's hope of recovery or adverse events. The timing of treatment discontinuation was within 4 weeks in three patients, between 5 and 12 weeks in nine patients, and between 13 and 24 weeks in three patients. RVR, cEVR, and LVR were achieved in 18, 70, and 27 patients, respectively, and these 115 patients were randomly assigned to treatment groups according to the response-guided therapy. However, 23 patients remained positive for HCV RNA (non-virological response, NVR) at week 24 and were finally judged as non-SVR.

Of 18 patients with RVR, 10 were assigned to group A (PEG-IFNα-2a monotherapy) and eight to group B (PEG-IFNα-2a/RBV combination); of 70 patients with cEVR, 39 were assigned to group C (weekly PEG-IFNα-2/RBV combination) and 31 to group D (biweekly PEG-IFNα-2/RBV combination); and of 27 patients with LVR, 14 were assigned to group E (PEG-IFNα-2a/RBV combination) and 13 to group F (PEG-IFNα-2a/RBV/FLV combination).

PEG-IFNα-2a monotherapy versus PEG-IFNα-2a/RBV combination therapy in cases with RVR (group A versus group B)

The SVR rate in 18 patients with negative HCV RNA at week 4 after initiation of PEG-IFNα-2a monotherapy (RVR) was 100 % (10/10) in group A (PEG-IFNα-2a monotherapy) and 87.5 % (7/8) in group B (PEG-IFNα-2a/RBV combination), showing no significant difference between the two groups ($p = 0.444$). The rate of treatment discontinuation was 0 % (0/10) in group A. However, treatment discontinuation was required in one patient (12.5 %) in group B due to hemolytic anemia caused by RBV, resulting in non-SVR. Although the rate of RVR by PEG-IFNα-2a monotherapy was only 12 % (18/153), once

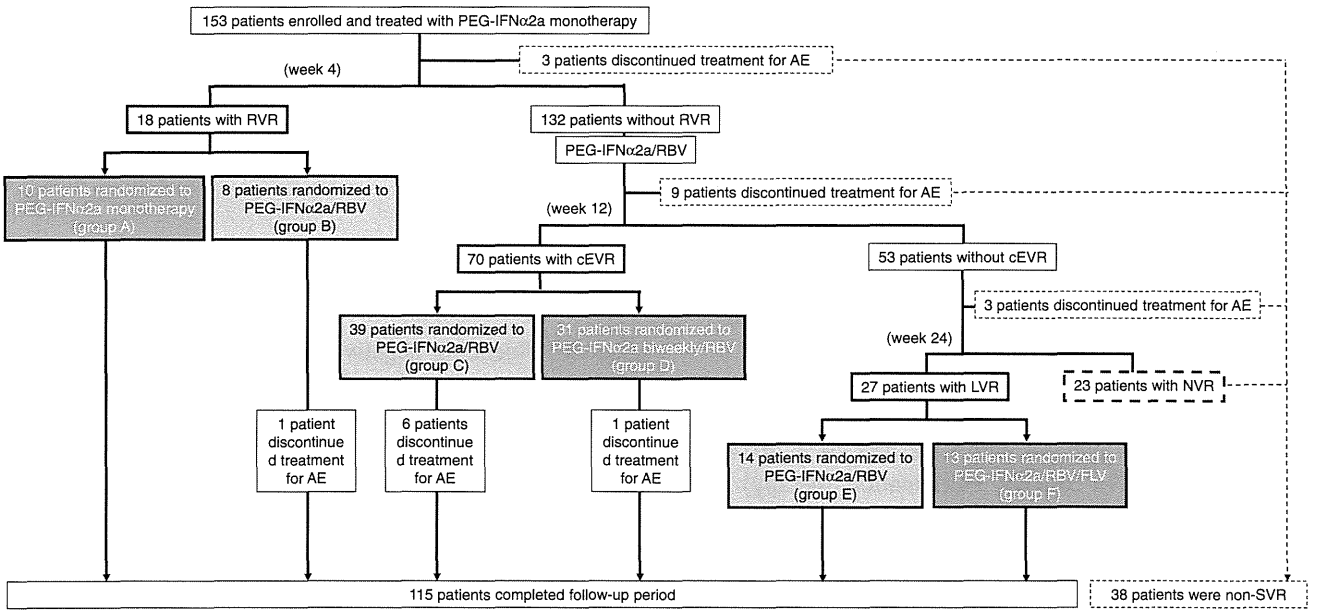

Fig. 2 Flowchart of the study. PEG-IFNα-2a monotherapy was initiated in 153 patients, of whom 15 patients necessitated treatment discontinuation. A total of 115 patients with RVR, cEVR, or LVR were randomly assigned to treatment groups, while 23 patients remained positive for HCV RNA (non-virological response, NVR) at week 24 and were finally judged as non-SVR. Of 18 patients with RVR, 10 were assigned to group A (PEG-IFNα-2a monotherapy) and eight to group B (PEG-IFNα-2a/RBV combination); of 70 patients with cEVR, 39 were assigned to group C (weekly PEG-IFNα-2/RBV combination) and 31 to group D (biweekly PEG-IFNα-2/RBV combination); and of 27 patients with LVR, 14 were assigned to group E (PEG-IFNα-2a/RBV combination) and 13 to group F (PEG-IFNα-2a/RBV/FLV combination)

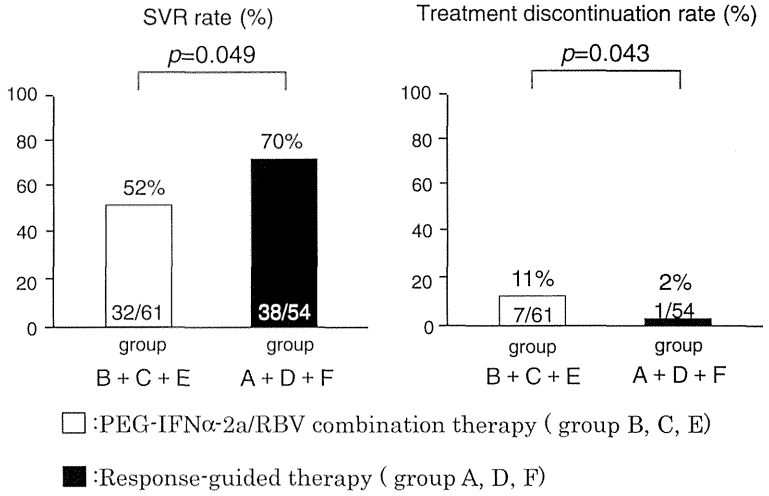

Fig. 3 The SVR and treatment discontinuation rate in the group (A + D + F) of treatment regimens modified according to response-guided therapy and in the group (B + C + E) of PEG-IFNα-2a/RBV combination therapy

RVR is achieved, PEG-IFNα-2a monotherapy without addition of RBV can induce SVR at a high rate with a high tolerability.

Weekly PEG-IFNα-2/RBV combination versus biweekly PEG-IFNα-2/RBV combination therapy in patients with cEVR (group C versus group D)

The SVR rate in 70 patients with cEVR was 54 % (21/39) in group C (weekly PEG-IFNα-2/RBV combination) and 65 % (20/31) in group D (biweekly PEG-IFNα-2/RBV combination). Adverse events leading to treatment discontinuation occurred in six patients (15 %) in group C (a decrease in Hb level, chest pain, fatigue, dizziness, a sense of feeling bad, and a suspicion of HCC) but in only one patient (3 %) in group D (depression), suggesting that the rate of treatment discontinuation tended to be higher in group C than in group D ($p = 0.123$). The difference in the SVR rates between groups C and D may reflect the difference in the rate of treatment discontinuation between the groups.

PEG-IFNα-2a/RBV combination versus PEG-IFNα-2a/RBV/FLV combination therapy in patients with LVR (group E versus group F)

The SVR rate in 27 patients with LVR was 29 % (4/14) in group E (PEG-IFNα-2a/RBV combination therapy) and 62 % (7/13) in group F (PEG-IFNα-2a/RBV/FLV combination therapy), suggesting that the rate tended to be higher in group F than in group E ($p = 0.085$). Thus, addition of an HMG-CoA inhibitor, FLV, increased the SVR rate even in patients with LVR showing delayed negative conversion of HCV RNA. There were no adverse events leading to treatment discontinuation in both groups, and FLV did not augment the adverse events in group F.

Group with PEG-IFNα-2a/RBV combination therapy versus group with response-guided therapy (groups B + C + E versus groups A + D + F)

We then divided all of these groups into two groups according to treatment regimens, a group (A + D + F) in which treatment regimen was modified according to response-guided therapy and a group (B + C + E) of PEG-IFNα-2a/RBV combination therapy. The SVR rate in the response-guided therapy group was significantly higher than in the PEG-IFNα-2a/RBV combination therapy group [70 % (38/54) versus 52 % (32/61), $p = 0.049$].

The rate of treatment discontinuation due to adverse events was significantly lower in the response-guided therapy group than in the PEG-IFNα-2a/RBV combination therapy group [11 % (7/61) versus 2 % (1/54), $p = 0.043$] (Fig. 3).

Factors influencing negative conversion of HCV RNA at week 4, 12, and 24

Factors influencing negative conversion of HCV RNA at week 4 were analyzed in 18 patients with negative HCV RNA and 132 patients with positive HCV RNA. Factors identified as significantly different between the negative and positive groups were age and HCV RNA titer before study treatment, but IL-28B polymorphism and Core 70 mutation were not associated with negative conversion at this time point. Comparison between 88 negative and 53 positive HCV RNA patients at week 12 and that between 115 negative and 23 positive HCV RNA patients at week 24 identified IL-28B polymorphism and Core 70 mutation as factors, showing differences with a statistical significance (Table 2).

Table 2 Characteristics of HCV RNA-negative or positive patients at week 4, 12, and 24

At week 4	Negative ($n = 18$)	Positive ($n = 132$)	p value
Age (years)	49.5 ± 14.6	57.6 ± 10.3	0.003
HCV RNA (Log IU/mL)	6.0 ± 0.7	6.4 ± 0.7	0.009
At week 12	Negative ($n = 88$)	Positive ($n = 53$)	p value
Core 70 substitution (wild/mutant)	39/14	13/22	<0.001
IL-28B, rs8099917 (TT/non-TT)	31/8	10/18	<0.001
At week 24	Negative ($n = 115$)	Positive ($n = 23$)	p value
Core 70 substitution (wild/mutant)	48/23	4/11	0.003
IL-28B, rs8099917 (TT/non-TT)	38/14	3/10	0.003

Value are mean ± standard deviation (SD)

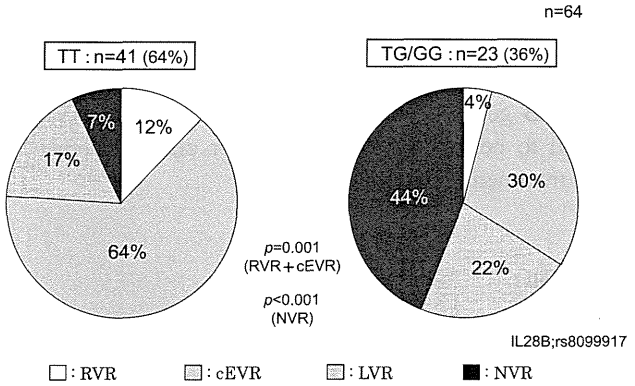

Fig. 4 Treatment response to PEG-IFNα-2a with or without RBV according to the IL-28B single nucleotide polymorphisms (TT versus TG/GG genotype)

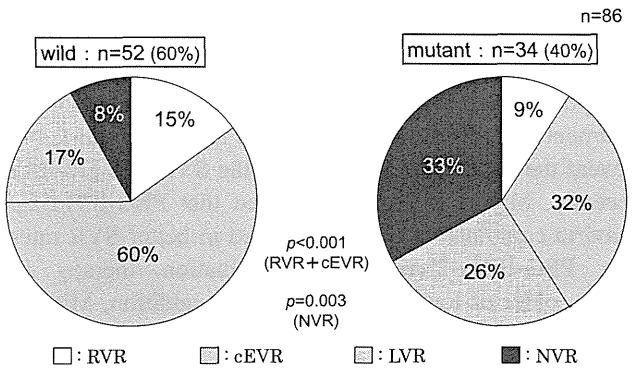

Fig. 5 Treatment response to PEG-IFNα-2a with or without RBV according to the Core 70 mutation (wild-type versus mutant Core 70)

We also investigated the correlation between IL-28B polymorphism and HCV RNA-negative conversion within 12 weeks (RVR + cEVR) in 64 patients in whom IL-28B polymorphism was examined. Negative HCV RNA was achieved within 12 weeks in 76 % of 41 patients with IL-28B TT genotype (major) and in 34 % of 23 patients with IL-28B TG or GG genotype (minor), showing a significant difference between them ($p = 0.001$). Especially in cases with NVR, negative HCV RNA was achieved in 7 % of patients with IL-28B major genotype and in 44 % of patients with IL-28B minor genotype ($p < 0.001$), suggesting that IL-28B polymorphism is strongly associated with treatment response (Fig. 4). Similarly, in 86 patients with determined Core 70 mutation status, negative HCV RNA was achieved within 12 weeks in 75 % of 52 patients with wild-type Core 70 and 41 % of 34 patients with mutant Core 70, showing a significant difference between them ($p < 0.001$). In patients with NVR, the rate of becoming HCV RNA-negative within 12 weeks was 8 % in patients with wild-type Core 70 and 33 % in those with mutant Core 70 ($p = 0.003$) (Fig. 5).

The SVR rates at different time points of HCV RNA-negative conversion by IL-28B polymorphism and Core 70 mutation

The SVR rates were investigated in patients with different time points of HCV RNA-negative conversion (RVR in six patients, cEVR in 33, LVR in 13, and NVR in 13) according to the IL-28B genotypes. The SVR rate was 100 % (5/5) in patients with RVR, 65 % (17/26) in patients with cEVR, 57 % (4/7) in patients with LVR, and 0 % (0/3) in patients with NVR with IL-28B major genotype; whereas the rate was 100 % (1/1) in patients with RVR, 43 % (3/7) in patients with cEVR, 83 % (5/6) in patients with LVR, and 0 % (0/10) in patients with NVR with IL-28B minor genotype. Similarly, the SVR rates were investigated in patients with different time points of HCV RNA-negative conversion (RVR in 11 patients, cEVR in 42, LVR in 18, and NVR in 15) according to the Core 70

Table 3 Characteristics of sustained virological response (SVR) and non-SVR patients

	SVR ($n = 70$)	Non-SVR ($n = 83$)	p value
Age (years)	53.1 ± 12.7	59.4 ± 8.7	<0.001
Gender (male/female)	29/41	34/49	0.954
HCV RNA (Log IU/mL)	6.4 ± 0.7	6.4 ± 0.7	0.782
BMI (kg/m^2)	22.7 ± 3.9	22.9 ± 2.8	0.815
Previous IFN (no/yes)	49/21	44/39	0.032
Fibrosis (F0-2/F3-4)	41/9	31/23	0.007
Activity (A0-1/A2-3)	24/27	25/29	0.938
NS5A mutation, n (0-1/2-)	31/10	47/3	0.013
Core 70 substitution (wild/mutant)	30/11	24/27	0.012
IL-28B, rs8099917 (TT/non-TT)	26/9	17/18	0.027
HCV RNA-negative at week 12 (yes/no)	58/12	30/41	<0.001
Treatment group (B,C,E/A,D,F)	32/38	29/16	0.049

Values are mean ± standard deviation (SD)

BMI body mass index

Table 4 Associated factors with sustained virological response (SVR) by multivariate logistic regression analysis

Factor	Odds ratio	95 % CI	p value
Age (per 1 year)	0.94	0.89–0.98	0.005
Previous IFN (no/yes)	1.62	0.62–4.27	0.323
Fibrosis (F0-2/F3-4)	3.38	1.15–10.8	0.026
NS5A mutation, n (2-/0-1)	7.18	1.32–61.0	0.021
Core 70 substitution (wild/mutant)	2.49	1.51–8.28	0.044
IL-28B, rs8099917 (TT/non-TT)	1.85	0.85-8.61	0.563
HCV RNA-negative at week 12 (yes/no)	7.89	2.92–24.0	<0.001

mutation status. The SVR rate was 100 % (RVR), 58 % (cEVR), 44 % (LVR), and 0 % (NVR) in patients with wild-type Core 70; whereas the rate was 67 % (RVR), 55 % (cEVR), 33 % (LVR), and 0 % (NVR) in patients with mutant Core 70. Thus, when the SVR rates were investigated according to the different time points of HCV RNA-negative conversion, there was no association of IL-28B polymorphism or Core 70 mutation with the SVR rates.

Factors affecting the SVR rate

An univariate analysis in 70 SVR patients and 83 non-SVR patients identified age, previous IFN treatment, fibrosis, NS5A mutation, Core 70 mutation, EVR, IL-28B, and treatment group as factors affecting the SVR rate (Table 3). In this analysis, we examined 83 non-SVR patients: 45 non-SVR patients are presented in Fig. 3, and 38 non-SVR patients (23 patients with NVR and 15 patients who discontinued the Peg-IFN-RBV treatment prior to the enrollment of the randomized trial) are presented in Fig. 2. Multivariate analysis using a logistic regression analysis revealed age (younger), fibrosis (mild), NS5A mutation (two or more mutations), Core 70 status (wild-type), and EVR (RVR + cEVR), to be independent factors affecting the SVR rate, and among them EVR was the most significant factor (odds ratio, 7.89; $p < 0.001$) (Table 4). Therefore, even in patients considered intractable based on the IL-28B genotype or Core 70 mutation status, SVR is expected to be achieved once RVR or cEVR is reached during treatment.

Discussion

The introduction of combined treatment with PEG-IFN and RBV has increased the SVR rate to approximately 40–50 % even in intractable cases with genotype 1b high virus titer chronic hepatitis C after a standard treatment course of 48 weeks [1–4]. In an attempt to further improve the SVR rate, we propose a concept of "response-guided therapy", in which the treatment regimen (such as an extension of a treatment period) is determined according to the viral response to the initial treatment [7–15]. In cases with positive HCV RNA at week 4 or 12, extension of the treatment period from 48 to 72 weeks has been reported to prevent the recurrence and improve the SVR rate [12–14]. Recently, Miyase et al. [34] showed that PEG-IFNα-2a/ribavirin combination therapy resulted in better SVR rates than PEG-IFNα-2b/ribavirin combination therapy in female, older or low-weight patients. In addition, Minami et al. [35] reported that the rate of severe adverse events was not negligible in PEG-IFN/ribavirin combination therapy, and the rate was affected by treatment regimens. Therefore, it is important to establish a treatment regimen of PEG-IFN/RBV combination therapy that has a high efficacy with minimal adverse events. We herein investigated the treatment regimens based on the concept of response-guided therapy to minimize the rate of treatment discontinuation, without changing the treatment period, in consideration of aged patients in Japan.

Factors influencing SVR have been evaluated in many studies that reported IL-28B (a host factor) and Core 70 mutation (a viral factor) as factors predicting the treatment outcome [23, 24, 36–38]. Our present study also demonstrate that the SVR rate was lower in patients with IL-28B minor genotype and those with mutant Core 70, suggesting that IL-28B polymorphism and Core 70 mutation represent factors largely influencing the negative conversion of HCV RNA. Regarding the correlation between treatment response and SVR, Thompson et al. [38] reported that RVR and cEVR rates were lower in patients with the IL-28B minor genotype than in those with the major genotype but the SVR rate was not affected by the IL-28B genotype in patients with RVR or cEVR. In recent studies published after recognition of IL-28B polymorphism, virological response at week 4 and 12 was highly associated with SVR [39, 40]. In our present results, if RVR or EVR is achieved, a high SVR rate can be obtained regardless of the IL-28B polymorphism or Core 70 mutation status.

If RVR is achieved, PEG-IFNα-2a monotherapy exhibits a treatment effect equivalent to that of PEG-IFNα-2a/RBV combination therapy. Conversely, one patient receiving PEG-IFNα-2a/RBV combination therapy developed anemia caused by RBV, resulting in treatment discontinuation and non-SVR. In a phase III clinical trial in Japanese patients, the SVR rate in patients with RVR was 100 % (14/14) in control patients receiving PEG-IFNα-2a monotherapy but was 78 % (18/23) in those receiving PEG-IFNα-2a/RBV combination therapy [41]. Therefore, in terms of preventing treatment discontinuation due to adverse events of RBV, PEG-IFNα-2a monotherapy is recommended in cases with RVR.

In cases with cEVR, the SVR rate in patients who received biweekly PEG-IFNα-2/RBV combination therapy was comparable or even higher as compared to those who received weekly PEG-IFNα-2/RBV combination therapy. This means that biweekly PEG-IFNα-2a in a later treatment period did not reduce the antiviral effects in a subset of cases achieving a good antiviral effect (cEVR). This is partly because the half-life of PEG-IFNα2a is longer than that of PEG-IFNα2b [42–44], thus enabling the maintenance of antiviral effects. Therefore, this biweekly regimen appears possible only with PEG-IFNα2a. Regarding treatment discontinuation, the rate of treatment discontinuation was 3 % (1/31) in patients receiving biweekly PEG-IFNα-2 and 15 % (6/39) in those receiving weekly PEG-IFNα-2, suggesting that the reduced rate of adverse events and subsequent treatment discontinuation by biweekly administration may lead to the increased SVR rate.

Ikeda et al. [19] reported that one of the HMG-CoA reductase inhibitors, FLV, exhibits inhibitory effects on HCV RNA replication in a system of HCV RNA replication clone. In the clinical setting, Sezaki et al. and Rao and Pandya [20–22] reported that combined use of FLV from the treatment initiation period improved the SVR rate [21]. The HCV RNA is replicated using the lipid droplet in hepatocytes [45, 46], and HMG-CoA reductase inhibitors are reported to inhibit the proliferation of HCV RNA by suppressing the synthesis of mevalonic acid through geranylgeranylation [47].

We investigated whether the SVR rate is improved by the addition of FLV only in cases with LVR, because a high SVR rate is expected in patients showing rapid negative conversion of HCV RNA (such as RVR and cEVR cases) without the combined use of FLV. Our results showed that combined use of FLV yielded a higher SVR rate (62 %) as compared to the rate (29 %) obtained without the use of FLV, suggesting that the difference in the recurrence rate may reflect the difference in the SVR rate in patients negative for HCV RNA. Thus, because we used FLV in patients with LVR at high risk of recurrence, but not in those with RVR or cEVR at low risk of recurrence, the difference in anti-HCV activities by FLV was more pronounced. It has been reported that treatment with HMG-CoA reductase inhibitors does not increase the risk of severe hepatotoxicity in patients with chronic hepatitis C [48], which is consistent with our present results showing no adverse events associated with the addition of FLV.

In summary, the SVR rate was 52 % (32/61) in the group receiving PEG-IFNα-2a/RBV combination therapy and 70 % (38/54) in the group receiving modified treatment regimens according to response-guided therapy, showing a significant increase in the latter group. This result may be attributed to the difference in the rate of treatment discontinuation, which was significantly lower in the response-guided therapy group [2 % (1/54)] than in the PEG-IFNα-2a/RBV combination group [11 % (7/61)]. In addition, anti-HCV effects of FLV in patients with LVR at high risk of recurrence may contribute to the improved SVR in the response-guided therapy group. Our results demonstrated the safety and efficacy of PEG-IFNα-2a monotherapy in patients with RVR, biweekly PEG-IFNα-2a/RBV combination therapy in those with cEVR, and PEG-IFNα-2a/RBV/FLV combination therapy in those with LVR.

In conclusion, for the treatment of genotype 1b high virus titer chronic hepatitis C, the selection of an optimal response-guided therapy option, taking into consideration the viral response to initial treatment, the IL-28B polymorphism and Core 70 mutation status, and the safety of individual patients, can improve the SVR rate.

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Ajinomoto Pharma, and Otsuka pharmaceutical. The remaining authors declare no conflict of interest.

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Session 6

切除不能肝細胞癌に対するソラフェニブ療法の減量開始は妥当か —Propensity score matching法による検討—

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背景

切除不能肝細胞癌患者に対するソラフェニブはSHARP試験，Asia-Pacific試験でプラセボ群と比較し，生存期間延長効果が示されている。しかしながら，投与開始用量と治療効果に関する検討は少なく，特に日本人における投与開始用量については一定の見解が定まっていない。そこで，ソラフェニブ減量開始例での抗腫瘍効果，生存期間や有害事象につき推奨用量と比較し，その妥当性を検討した。

方法

本研究グループで2008年1月-2013年7月においてソラフェニブが導入された切除不能肝細胞癌症例465例のうち，600mg/日ないし200mg/日で開始された22症例，さらにBCLC A/Dの6症例を除外した437例(800mg群183例，400mg群254例)を対象とした。背景因子のバイアスを抑えるためpropensity score matching法を用いて両群間での年齢，体重，性別，Child-Pugh score，ECOG-performance statusを調整し，各群139例ずつを抽出した。両群間の全生存期間(OS)，無増悪生存期間(PFS)，抗腫瘍効果，有害事象を比較検討した。

結果

1．患者背景

Propensity score matching法による調整後の背景因子(800mg/400mg群各139例ずつ)を表1に示す。400mg群で投与前AFPが高値であった(p=0.043)以外には，調整した5項目を含め，背景因子に有意差を認めなかった。

2．投与量と治療継続期間

800mg群ではソラフェニブの投与期間中央値は3.1ヵ月(0.1-39.3ヵ月)であり，観察期間中に127例(91.4%)で中止，85例(61.2%)で減量投与が行われ，増量例は認めなかった。一部欠損値を認めるが，一日平均投与量は628mgであった。

一方，400mg群では投与期間中央値は3.9ヵ月(0.1-32.1ヵ月)，観察期間中に121例(87.1%)が中止となり，44例(37.1%)で減量投与，36例(25.9%)で増量投与が行われた。一部欠損値を認めるが，一日平均投与量は395mgであった。

3．生存期間と治療効果

両群でのOSを図1，PFSを図2に示す。OS中央値は800mg群，400mg群で順に9.2ヵ月，9.7ヵ月(p=0.350)，PFS中央値は3.4ヶ月，3.2ヶ月(p=0.729)であり，両群間に有意差を認めなかった。modified RECISTによる最良総合効果はCR/PR/SD/PD/NEが800mg群で2/23/45/44/25，400mg群で2/18/54/45/20(例)であり，奏効率はそれぞれ18.0%，14.4%と有意差を認めなかった(p=0.416)。

4．有害事象

有害事象を表2に示す。肝障害，肺障害，手足症候群，皮疹，消化管出血，高血圧，疲労，発熱，下痢について両群でのGrade 3以上の発現率に有意差は認められなかったが，手足症候群についてはGrade 1以上の発現率が800mg群で高い傾向にあった(p=0.092)。

考察

切除不能肝細胞癌に対するソラフェニブの開始用量と治療効果・安

表1．背景因子の比較

	800mg群 (n=139)	400mg群 (n=139)	p value
年齢	70.0±8.5	70.1±9.1	0.903[a]
性別 男/女	114/25	111/28	0.760[b]
身長	161.4±8.3	159.7±21.0	0.362[a]
体重	60.1±12.1	59.1±14.0	0.528[a]
B/C/B+C/nonB nonC	28/76/1/34	16/75/2/46	0.121[b]
Stage Ⅱ/Ⅲ/Ⅳ	4/58/77	7/49/83	0.438[b]
ECOG PS, 0/1/2	107/30/2	106/29/4	0.803[b]
Child-Pugh score 5/6/7/8点	58/60/19/2	56/66/11/3	0.445[b]
Alb	3.56±0.48	3.59±0.48	0.616[a]
ChE	171±71.6	167±73.0	0.703[a]
AFP	3593±10551	10384±37885	0.043[a]
PIVKA-Ⅱ	8851±33057	20797±96248	0.168[a]
BCLC stage B/C	53/86	51/88	0.901[b]

a : unpaired t test, b : fisher's exact test

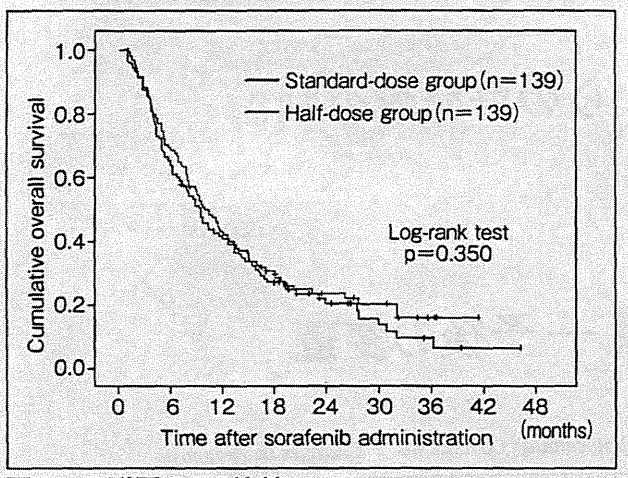

図1．2群間のOS比較

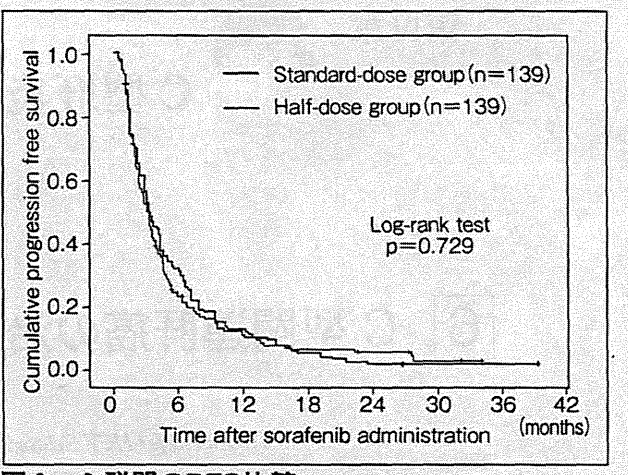

図2．2群間のPFS比較

全性との関連に関して検討した報告は少ない。また，SHARP試験やAsia-Pacific試験での対象患者と比較し[1)2)]，わが国の実臨床でのソラフェニブ投与患者背景(体格，年齢)，診療体制は大きく異なる。日本で800mg/日で開始した症例の80%以上が減量を要したとの報告もあり[3)]，日本人での開始用量につき議論がなされている。本検討では実臨床に即した背景を有する患者を対象とし，背景因子を調整したうえで検討すると400mg開始群は800mg開始群と比較し，OS，PFS，奏効率，有害事象発現率に有意差を認めなかった。この結果から，全身状態や有害事象に応じた用量調節を行うことにより，減量開始でも推奨用量と遜色ない治療効果を得られ，かつ十分な忍容性が認められることが示唆された。実際の用量調整にはより多彩な因子が関与していると考えられ，日本人に対する実臨床での適正開始用量については今後さらなる検討が望まれる。

なお，本発表内容は英文誌に投稿し9月にonline掲載されている[4)]。

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表2．有害事象の比較

	800mg群(n=139)		400mg群(n=139)		p value[a]	
	Any Grade no.(%)	Grade3以上	Any Grade	Grade3以上	Any Grade	Grade3以上
全体	127(91.4)	37(26.6)	127(91.4)	33(23.7)	>0.999	0.580
手足症候群	77(55.4)	8(5.8)	62(44.6)	7(5.0)	**0.092**	>0.999
皮疹	27(19.4)	7(5.0)	24(17.3)	6(4.3)	0.757	>0.999
下痢	43(30.9)	2(1.4)	44(31.7)	1(0.7)	>0.999	>0.999
高血圧	26(18.7)	2(1.4)	19(13.7)	3(2.2)	0.328	>0.999
疲労	69(49.6)	5(3.4)	69(49.6)	4(2.9)	>0.999	>0.999
肝障害	60(43.2)	15(10.8)	61(43.9)	16(11.5)	>0.999	>0.999
消化管出血	9(6.5)	3(2.2)	5(3.4)	0(0.0)	0.206	0.247
肺障害	4(2.9)	3(2.2)	8(5.8)	3(2.2)	0.255	>0.999

a : unpaired t test, b : fisher's exact test

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第Ⅳ章

C型肝炎からの肝発癌の制御

6 C型関連肝癌の治療 — 予後の変遷

Treatment for HCV Related Hepatocellular Carcinoma — Changes in Prognosis

西川 浩樹* 大崎 往夫*

はじめに

肝癌はここ数年，非B非C肝癌の占める割合は漸増傾向にある一方で，C型関連肝癌は減少傾向にある．だがC型肝炎は肝癌の約70％を占めるため，C型肝炎が依然として肝癌の主たる成因であることは明らかである．

本稿ではC型関連肝癌の予後の変遷について述べる．

Ⅰ C型関連肝癌の疫学

図1に大阪赤十字病院における肝細胞癌診断時の成因の推移を示す．かつては70％を超えていたC型関連肝癌が，2012年には全体の70％を大きく下回り，非B非C肝癌が全体の30.2％を占めるという特筆すべき結果であった．一方，本邦における高齢化社会の到来に伴い，初回肝癌診断時の年齢が高齢化してきていることも事実である[1]．当院においても図2に示すように，ここ四半世紀の間に約10歳，肝細胞癌患者の年齢が高齢化している実態が明らかとなった．とくにC型関連肝癌においてはインターフェロン療法などの抗ウイルス療法の進歩により，肝発癌の時期が徐々に遅らされつつあることも肝癌患者の高齢化と関与していると思われる[2]．さらに肝発癌の高リスク群の“囲い込み”および各種画像診断の進歩により，肝癌の早期発見が目立つのも最近の特徴である．とくに肝発癌の高リスク群である背景肝がC型肝硬変の症例において，適切な患者の“囲い込み”により早期発見される症例が徐々に増加してきていることが大きく影響しているものと考えられる．われわれの施設では，2000年以降の症例では図3に示すように約60％の症例が初回診断時のstageがⅠもしくはⅡであった．当院におけるC型関連肝癌の年代別の予後の変遷を図4に示す．年代ごとに有意に予後が改善してきているものと思われる．

Key words：肝細胞癌，C型肝炎，疫学，予後

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