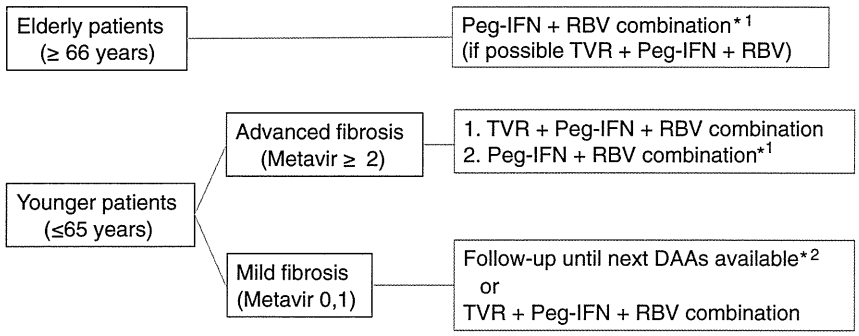

Figure 3 Patients with chronic hepatitis C genotype 1, high viral load; Principles of treatment in retreatment cases, when details of previous treatment are unknown. If IL28B SNP/core amino acid 70 substitutions can be tested, follow the treatment guidelines in treatment-naive patients.

wait for the next generation DAAs. On the other hand, elderly patients are at high risk of developing HCC, so if viral clearance cannot be achieved, low-dose long-term Peg-IFN or IFN therapy, or supportive therapy (e.g. SNMC, UDCA) should be administered with the aims of biochemical improvement and inhibiting hepatocellular carcinogenesis.

Non-elderly patients. As mentioned above, in Japanese studies, retreatment with triple therapy in relapsers following previous Peg-IFN + ribavirin combination therapy is highly efficacious, with an SVR rate of 86%.[9,147] In all non-responders to Peg-IFN + ribavirin combination therapy, the SVR rate was 28%, although better rates can be anticipated in partial responders. Accordingly, the treatment of first choice in relapsers and partial responders to previous therapy is telaprevir + Peg-IFN + ribavirin triple therapy. If triple therapy cannot be tolerated, retreatment with Peg-IFN + ribavirin combination therapy should be considered in patients with advanced fibrosis, although waiting for the next generation DAAs is an option in patients with mild fibrosis.

In null responders to previous therapy, the anticipated therapeutic efficacy for 24 weeks' triple therapy is rather low.[9] Accordingly, telaprevir + Peg-IFN + ribavirin triple therapy should be considered in patients with advanced fibrosis, but for patients with mild fibrosis in general we should wait for the next generation DAAs.

Recommendations:

1 ***Response to the previous therapy is the best indicator of the therapeutic efficacy of retreatment in patients with chronic hepatitis C genotype 1 and a high viral load who failed to respond to previous***

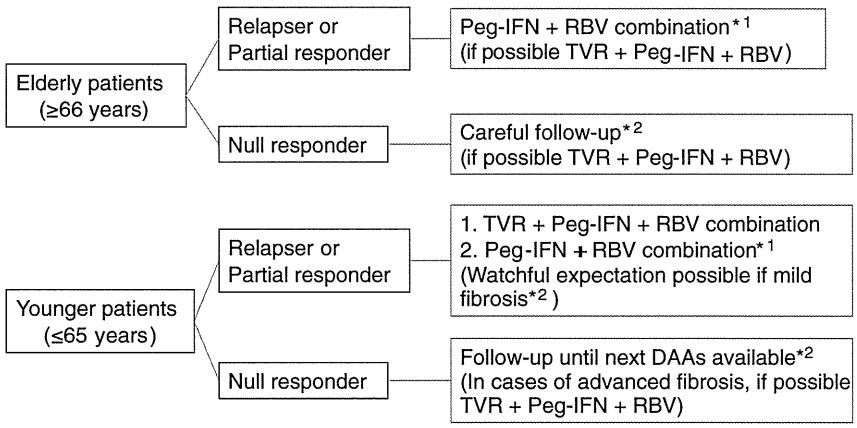

Figure 4 Patients with chronic hepatitis C genotype 1, high viral load; Principles of treatment in retreatment cases, when details of previous treatment are known.

IFN/Peg-IFN + ribavirin combination therapy. In general, follow the therapy protocol in treatment-naive patients for retreatment with combination therapy including ribavirin in patients previously administered IFN or Peg-IFN monotherapy.

2 *Retreatment in elderly patients with genotype 1 and high viral load: for relapsers and partial responders to previous therapy, retreatment should be with Peg-IFN + ribavirin combination therapy in general, although telaprevir + Peg-IFN + ribavirin combination therapy should be considered if it can be tolerated.*
3 *Retreatment in elderly patients with genotype 1 and high viral load: for null responders to previous therapy, as an adequate antiviral effect cannot be expected, careful follow-up should be considered. If ALT levels are abnormal, low-dose long-term Peg-IFN/IFN therapy or supportive therapy should be administered.*
4 *Retreatment in non-elderly patients with genotype 1 and high viral load: for relapsers and partial responders to previous therapy, the treatment of first choice is telaprevir + Peg-IFN + ribavirin combination therapy. If triple therapy cannot be tolerated, retreatment with Peg-IFN + ribavirin combination therapy should be considered in patients with advanced fibrosis, although waiting for the next generation DAAs is an option in patients with mild fibrosis.*
5 *Retreatment in non-elderly patients with genotype 1 and high viral load: for null responders to previous therapy, telaprevir + Peg-IFN + ribavirin triple therapy should be considered in patients with advanced fibrosis, if tolerated, but for patients with mild fibrosis, we should wait for the next generation DAAs.*

3.7 Retreatment—Genotype 1 with low viral load, and Genotype 2

Genotype 1, low viral load

If the previous treatment was IFN or Peg-IFN monotherapy, as a general rule, retreatment should be with Peg-IFN + ribavirin combination therapy. When Peg-IFN-α is contraindicated due to depression or depressive symptoms, IFN-β can be used instead of Peg-IFN.[26] When the previous therapy included ribavirin, telaprevir + Peg-IFN + ribavirin combination therapy should be used. If triple therapy cannot be tolerated, then consider retreatment with Peg-IFN + ribavirin combination therapy, although there is no clear evidence regarding the efficacy of this therapy as retreatment.

Genotype 2, high viral load

If the previous treatment was IFN or Peg-IFN monotherapy, retreatment should be with Peg-IFN + ribavirin combination therapy (24 weeks). When the previous therapy included ribavirin, treatment with Peg-IFN + ribavirin therapy (24–48 weeks) should be considered. SVR rates ≥50% have been reported.[141,148] When Peg-IFN-α is contraindicated due to depression or depressive symptoms, IFN-β can be used instead of Peg-IFN.[26]

Genotype 2, low viral load

If the previous treatment was IFN or Peg-IFN monotherapy, retreatment should be with Peg-IFN + ribavirin combination therapy (24 weeks). When the previous therapy included ribavirin, treatment with Peg-IFN + ribavirin therapy (24–48 weeks) should be considered. High SVR rates comparable to those achieved with initial treatment have been reported.[85,136] As with patients with genotype 2 and a high viral load, if Peg-IFN-α is contraindicated due to depression or depressive symptoms, IFN-β can be used instead of Peg-IFN.[26]

Recommendations:

1 *In patients with genotype 1 and a low viral load, if the previous treatment was IFN or Peg-IFN monotherapy, as a general rule, retreatment should be with Peg-IFN + ribavirin combination therapy. When the previous therapy included ribavirin, telaprevir + Peg-IFN + ribavirin combination therapy should be used. If triple therapy cannot be tolerated, then consider retreatment with Peg-IFN + ribavirin combination therapy in patients with advanced fibrosis.*
2 *In patients with genotype 2, regardless of the viral load, if the previous treatment was IFN or Peg-IFN monotherapy, retreatment should be with Peg-IFN + ribavirin combination therapy (24 weeks). When the previous therapy included ribavirin, treatment with Peg-IFN + ribavirin therapy (24–48 weeks) should be considered.*
3 *In any patient group, in patients unable to tolerate Peg-IFN-α due to depression or depressive symptoms, IFN-β + ribavirin combination therapy should be administered for 28–48 weeks.*

3.8 Treatment of patients with liver cirrhosis

IFN therapy for compensated cirrhosis

The state in which the hepatic functional reserve is preserved, and there is no evidence of liver failure such as jaundice, ascites, hepatoencephalopathy or esophageal varices (Child–Pugh class A) is called compensated

cirrhosis, and when there is evidence of liver failure (Child–Pugh class B, C), it is called decompensated cirrhosis. Patients with liver cirrhosis accompanying severe fibrosis are a high-risk group for hepatocellular carcinogenesis. Even if they avoid developing HCC, the prognosis is poor if they develop liver failure. Accordingly, the objective of treatment for liver cirrhosis is to prevent both HCC and liver failure, and aggressive antiviral therapy is highly necessary in patients with compensated cirrhosis. Viral eradication through IFN therapy in patients with compensated cirrhosis can be expected to reduce the risk of HCC and liver failure.[8] However, patients with advanced hepatic fibrosis are IFN-resistant, and pancytopenia associated with hypersplenism complicating liver cirrhosis impedes IFN therapy.[78,79] When a virological response is not achieved with IFN therapy, a changeover to low-dose long-term IFN therapy should be made with the improving ALT levels and inhibiting hepatocellular carcinogenesis. The safety of telaprevir + Peg-IFN + ribavirin triple therapy has not been established in patients with cirrhosis, and is not approved by national medical insurance for this patient group.

Peg-IFN + ribavirin combination therapy. For some time now, outside of Japan, the standard treatment for patients with compensated cirrhosis has been the same as for chronic hepatitis C, Peg-IFN + ribavirin combination therapy.[149,150] In a trial comparing Peg-IFN-α-2b (1.0 μg/kg per week) monotherapy and combination therapy including ribavirin (800 mg/day), mainly in patients with compensated cirrhosis, higher efficacy was seen with the latter (SVR rates, 9.8% vs 21.6%, $P = 0.06$). The SVR rate was 67% in patients with genotypes 2 and 3, significantly higher than that of 11% in patients with genotypes 1 and 4 ($P = 0.001$). Progression towards liver failure was significantly less in patients achieving SVR than in non-responders (6.2% vs 38.3%, $P = 0.03$).[151] In a clinical trial of Peg-IFN-α-2a 180 μg/kg/week and ribavirin 600–1200 mg/day combination therapy, solely with patients with compensated cirrhosis, a significantly higher SVR rate was seen with genotypes 2 and 3 than with genotypes 1 and 4 (32% vs 58%, $P = 0.04$).[150] In 2011, Peg-IFN-α-2b or Peg-IFN-α-2a + ribavirin combination therapy has been approved in Japan by national medical insurance for the treatment of patients with compensated cirrhosis, irrespective of viral load or genotype. In a Japanese clinical trial of Peg-IFN-α-2b 1.0 μg/kg/week in combination with ribavirin for 48 weeks in patients with compensated HCV cirrhosis, the SVR rate was 22% (15/69) in patients with genotype 1 and a high viral load, and 79% (26/33) in other patients, indicating high efficacy in all groups other than genotype 1 with a high viral load. In a study of 48 weeks of a combination of Peg-IFN-α-2a in two doses, 90 and 180 μg/week, with ribavirin, the SVR rate was 28% (17/61) in the 90-μg group, and 27% (17/63) in the 180-μg group, with no difference seen between groups. In the 90-μg group, the SVR was 21% (10/48) in patients with genotype 1 and 50% (6/12) in those with genotype 2, showing high efficacy against the latter.[152]

In patients with compensated cirrhosis, where the doses of Peg-IFN-α and ribavirin are limited by the high degree of fibrosis, extended courses of combination therapy are required to achieve SVR. The HCV RNA dynamics following commencement of Peg-IFN + ribavirin combination therapy are also a good indicator of SVR in patients with compensated cirrhosis.[153,154] Accordingly, as with chronic hepatitis C, response-guided therapy altering the duration of treatment in accordance with the response to Peg-IFN + ribavirin therapy is useful. If HCV RNA does not become undetectable by treatment week 12 and viral clearance cannot be achieved, as with chronic hepatitis C, consideration should be given to a changeover to low-dose long-term Peg-IFN therapy with the aim of inhibiting hepatocellular carcinogenesis. Adverse reactions to Peg-IFN + ribavirin combination therapy in patients with compensated cirrhosis such as influenza-like-syndrome, depression, lethargy and cytopenia are common, but there are no great differences with chronic hepatitis in terms of safety and tolerability.[149,150] However, pancytopenia associated with hypersplenism may be present in the background, so reduction in the dose of both agents is often required due to severe cytopenias, including anemia, neutropenia and thrombocytopenia.[151,153]

The standard dose for Peg-IFN-α-2b in the treatment of patients with compensated cirrhosis is 1.0 μg/kg/week, and the criteria for dose reduction and discontinuation during treatment are as follows: halve the dose in the case of a neutrophil count <750/μL or platelet count <50 000/μL; and cease both Peg-IFN-α-2b and ribavirin in the case of a neutrophil count <500/μL, platelet count <35 000/μL or Hb <8.5 g/dL.[155] When the pretreatment Hb is ≥14 g/dL, the daily dose of ribavirin is 600 mg for patients weighing ≤60 kg, 800 mg for 61–80 kg and 1000 mg for >80 kg. If the pretreatment Hb is <14 g/dL, the starting dose of ribavirin is reduced by 200 mg, irrespective of weight.

The criteria for ribavirin dose reduction or discontinuation when a decline in Hb occurs during treatment are:

reduce the daily dose by 200 mg (400 mg if started at 1000 mg) for Hb <10 g/dL; and discontinue if Hb is <8.5 g/dL.[81]

The standard dose for Peg-IFN-α-2a in the treatment of patients with compensated cirrhosis is 90 μg/kg/week. The criteria for dose reduction and discontinuation during treatment are as follows: reduce the dose to 45 μg/mL in the case of a neutrophil count <1000/μL, and to 22.5 μg/mL in the case of a neutrophil count <750/μL; and cease both Peg-IFN-α-2a and ribavirin in the case of a neutrophil count <500/μL, platelet count <50 000/μL or Hb <8.5 g/dL.[156] The starting doses for ribavirin are as for co-administration with Peg-IFN-α-2b. The criteria for ribavirin dose reduction or discontinuation when a decline in Hb occurs during treatment are: reduce the daily dose by 400 mg (600 mg if started at 1000 mg) for Hb <11 g/dL during treatment weeks 1–4, or Hb <10 g/dL during treatment weeks 5–48. For patients with heart conditions or a history of the same, in addition to the above criteria, if a decline in Hb ≥2 g/dL in comparison to the pretreatment level persists for 4 weeks, reduce the daily dose by 400 mg (600 mg if started at 1000 mg). If Hb remains <12 g/dL 4 weeks after the dose reduction, cease ribavirin.[80]

IFN monotherapy. Apart from patients with genotype 1 and a high viral load, IFN monotherapy should be selected for patients unable to tolerate Peg-IFN + ribavirin combination therapy due to adverse reactions such as anemia or depression. At present, IFN-β and human lymphoblastoid IFN (HLBI), an IFN-α formulation, are approved for national medical coverage for the treatment of patients with compensated cirrhosis with HCV genotype 1 and a low viral load, and genotype 2. They are not approved for patients with genotype 1 and a high viral load (≥100 kIU/mL for IFN-β, ≥500 kIU/mL for HLBI). Japanese clinical trials of IFN-β in the treatment of patients with compensated cirrhosis with genotype 1 and a low viral load, and genotype 2, yielded SVR rates in the patients administered 126 doses of 44% (8/18) in the genotype 1 low viral load group (<1 Meq/mL), 19% (3/16) in the genotype 2 high viral load group (≥1 Meq/mL) and 46% (6/13) in the genotype 2 low viral load group.[157] In a Japanese multicenter collaborative trial of HLBI in the treatment of HCV compensated cirrhosis, SVR rates in the group administered HLBI 6 MU consecutive daily for 2 weeks, then 3 MU three times weekly for 46 weeks, were 50% (1/2) in the genotype 1 low viral load group (<100 kIU/mL), 25% (3/12) in the genotype 2 high viral load group (≥100 kIU/mL) and 67% (4/6) in the genotype 2 low viral load group.[158] In both studies, efficacy increased with increased treatment duration. Furthermore, greater efficacy was seen with genotype 2 than genotype 1, and with a low viral load than with a high viral load. The rate of discontinuation due to adverse reactions was similar to that with chronic hepatitis C, and although the incidence of influenza-like syndrome and abnormal laboratory test results was high, no cirrhosis-specific adverse events were reported. In an overseas trial of Peg-IFN monotherapy in the treatment of patients with cirrhosis, SVR rates and biochemical efficacy were both superior to standard IFN therapy. A randomized prospective study comparing standard non-pegylated-IFN-α and Peg-IFN-α-2a reported SVR rates in patients administered non-pegylated-IFN-α-2a 3 MU three times/week, Peg-IFN-α-2a 90 μg/week and 180 μg/week to be 8% (7/88), 15% (14/96) and 30% (26/87), respectively. No difference was seen between groups in terms of tolerability.[159]

HLBI therapy aiming for viral clearance comprises HLBI 6 MU weekly for 2 consecutive weeks, then 3–6 MU three times weekly. The criteria for dose reduction and discontinuation during HLBI treatment are as follows: reduce the dose or increase the interval between doses in the case of a platelet count ≥30 000/μL and <50 000/μL, and discontinue in the case of a white blood cell counts <1500/μL, platelet count <30 000/μL or ALT level ≥500 U/L.[160]

IFN-β therapy is usually commenced at 6 MU, and is administered 3–6 MU consecutive daily until treatment week 6, then 3 MU three times a week. The criteria for dose reduction and discontinuation during IFN-β treatment are as follows: reduce the dose or increase the interval between doses in the case of a white blood cell counts <1500/μL, neutrophil count <750/μL or platelet count <50 000/μL, and discontinue in the case of a white blood cell counts <1000/μL, neutrophil count <500/μL or platelet count <25 000/μL.[133] For both HLBI and IFN-β, if HCV RNA becomes undetectable before treatment week 12, as for chronic hepatitis C, the treatment period should be extended to 48–72 weeks.

Low-dose IFN maintenance therapy. If HCV RNA does not become undetectable before treatment week 12 with Peg-IFN + ribavirin combination therapy or IFN monotherapy, a changeover to low-dose IFN maintenance therapy should be made with the aim of improving ALT levels and inhibiting hepatocellular carcinogenesis. Low-dose IFN or Peg-IFN maintenance therapy is useful in patients with liver cirrhosis in preventing progression

of liver disease and the development of HCC.[19,47,51] It is not effective in all patients, however, and discontinuation of treatment should be considered if improvement is not seen in ALT levels (≤40 IU/L) or AFP levels (≤10 ng/mL) within 6 months.

IFN therapy for decompensated cirrhosis

Patients with decompensated cirrhosis are at high risk of death due to liver failure, and liver transplant is the most effective treatment in suitable cases. However, post-transplant recurrence of hepatitis C causes allograft failure in approximately 30% of recipients within 5 years, so in overseas countries, pretransplant IFN therapy is administered with the aim of HCV eradication or suppression.[161,162] Several studies have demonstrated the efficacy of Peg-IFN (± ribavirin) therapy in patients with HCV genotype 2.[163–165] Patients with decompensated cirrhosis are at high risk of thrombocytopenia, anemia, infections and liver decompensation, however, and treatment discontinuation due to severe cytopenias is common. Serious bacterial infections associated with IFN therapy have been reported to be more common in patients with patients with Child–Pugh C than in Child–Pugh A/B disease.[166]

Treatment of patients with thrombocytopenia

In patients with marked thrombocytopenia associated with hypersplenism, it is difficult to introduce Peg-IFN or ribavirin combination therapy. Measures such as splenectomy or partial splenic embolization (PSE) are employed to increase the platelet count before commencing IFN therapy.[167–169] In Japan, mainly in patients with Child–Pugh A disease, Peg-IFN (± ribavirin) therapy is commenced following splenectomy or PSE. An increase in the platelet count is seen in almost all patients following either procedure, and high SVR rates are seen in patients with HCV genotype 2. However, postoperative complications including overwhelming post-splenectomy infection, portal vein thrombosis and hepatic dysfunction have been reported following both splenectomy and PSE.[168–170] The thrombopoietin receptor agonist, eltrombopag, has been developed overseas as an oral agent that increases platelet counts,[171] but it is not yet available for clinical use in Japan.

Recommendations:

1 *In patients with compensated cirrhosis (Child–Pugh class A) associated with HCV, aggressive IFN therapy should be commenced with the aims of preventing hepatocellular carcinogenesis and liver failure. This patient group requires careful observation during treatment due to the high incidence of adverse reactions such as cytopenias.*
2 *Patients with compensated cirrhosis associated with HCV should be given Peg-IFN + ribavirin combination therapy, irrespective of genotype or viral load. The standard dose is 1.0 μg/kg/week for Peg-IFN-α-2b and 90 μg/week for Peg-IFN-α-2a. The usual treatment period is 48 weeks, although consideration should be given to response-guided therapy and the discontinuation criteria for chronic hepatitis C.*
3 *Patients with compensated cirrhosis associated with HCV genotype 1 and a lower viral load, or genotype 2, not suited to combination therapy with ribavirin, should be administered HLBI or IFN-β monotherapy. HLBI therapy commences with HLBI 6 MU consecutive daily for 2 weeks, then 3–6 MU three times weekly. IFN-β therapy is usually commenced with 6 MU daily for a week, followed by 3 MU daily for 5 weeks, then 3 MU three times a week from treatment week 7. For both HLBI and IFN-β, if HCV RNA becomes undetectable before treatment week 12, the treatment period should be extended to 48–72 weeks.*
4 *If HCV RNA does not become undetectable before treatment week 12 with Peg-IFN + ribavirin combination therapy or IFN monotherapy in patients with compensated cirrhosis associated with HCV, long-term HLBI therapy at a dose of 3 MU three times weekly should be commenced with the aim of inhibiting hepatocellular carcinogenesis. Treatment should be discontinued if improvement is not seen in ALT levels (≤40 IU/L) or AFP levels (≤10 ng/mL) within 6 months.*
5 *The efficacy of IFN therapy is low in patients with decompensated cirrhosis associated with HCV (Child–Pugh class B and C). In particular, patients with Child–Pugh class C do not tolerate IFN therapy well, and serious adverse reactions such as cytopenias and infections have been reported, so IFN therapy is not recommended in this patient group.*
6 *If IFN therapy is being considered in a patient with compensated HCV cirrhosis associated with a platelet count <50 000/μL, one option is to perform splenectomy or PSE before commencing IFN therapy.*

3.9 Management of patients with normal ALT levels

In a study of Peg-IFN + ribavirin combination therapy and hepatocellular carcinogenesis in 809 patients with chronic hepatitis C and normal pretreatment ALT levels (male/female, 269/540; average age, 57 ± 11

years; genotype 1/2, 550/247; mean observation period, 36.2 ± 16.5 months), in the group with platelet counts ≥150 000/μL ($n = 586$) no significant difference was seen in the incidence of HCC according to therapeutic effect, with 1.5% of non-responders developing HCC within 3 years. In the group with platelet counts <150 000/μL ($n = 323$), however, the cumulative incidence of HCC was high at 10.1% in non-responders, with no cases of HCC among the responders or relapsers. These results demonstrated that Peg-IFN + ribavirin therapy significantly inhibits hepatocellular carcinogenesis ($P < 0.001$).[172] The efficacy of Peg-IFN + ribavirin combination therapy is similar in patients with normal and elevated ALT levels.[173,174]

Accordingly, antiviral therapy should be considered even in patients with ALT levels ≤30 IU/mL if their platelet count is <150 000/μL. On the other hand, antiviral therapy does not need to be commenced immediately in patients with an ALT level ≤30 IU/mL and a platelet count ≥150 000/μL, and follow-up while waiting for the next generation DAAs is a reasonable option. ALT levels may rise during the follow-up period, however, and treatment is indicated if the patient has a strong desire to commence antiviral therapy. At present, the available evidence regarding patients with normal ALT levels is mainly related to Peg-IFN + ribavirin combination therapy, although high therapeutic efficacy can also be anticipated with telaprevir + Peg-IFN + ribavirin combination therapy in this patient group.

Recommendation:

Antiviral therapy for patients with normal ALT levels (ALT, ≤30 IU/mL) can be administered in the same way as for patients with elevated ALT levels. Aggressive therapy is particularly desirable in patients with platelet counts <150 000/μL.

4. PROTECTIVE THERAPY

THE AIM OF protective therapy is not HCV clearance, but rather to reduce inflammation and inhibit the progression of fibrotic change in the hepatic tissue. The indications for protective therapy in patients with chronic hepatitis C are: patients with abnormal ALT and AST levels unable to undergo IFN or other antiviral therapy; patients who failed to achieve viral clearance with antiviral therapy; and patients who do not wish to undergo antiviral therapy. UDCA and SNMC are the protective therapies that have been scientifically shown to be useful.

UDCA

Ursodeoxycholic acid is a bile acid formulation, approved for use in doses of 600–900 mg daily by national medical insurance. The main mechanism of action of UDCA in hepatitis is a hepatocytoprotective effect. Other postulated mechanisms of action include protection of the hepatocyte cell membrane by substitution of UDCA for other cytotoxic bile acids, antioxidative stress affects, immunoregulatory effects and anti-apoptotic effects.[175]

Improvement of liver function is seen from UDCA doses of 150 mg/day.[176,177] In a Japanese nationwide multicenter double-blind trial, significantly greater improvement was seen in AST, ALT and γ-glutamyl transpeptidase levels in the groups administered 600 and 900 mg/day than in those given 150 mg/day.[176] Accordingly, the UDCA dose for the treatment of chronic hepatitis C is generally 600 or 900 mg/day. Adverse reactions are mainly gastrointestinal symptoms such as epigastric discomfort, diarrhea and constipation, but these are generally mild. A retrospective study of inhibition of hepatocellular carcinogenesis by UDCA reported that it significantly reduced the incidence of HCC.[178]

SNMC

The main constituent of SNMC is glycyrrhizin, a compound extracted from the liquorice root. The mechanisms of action of SNMC in the treatment of hepatic dysfunction are derived from anti-inflammatory effects related to the steroid-like properties of glycyrrhizin, and hepatocyte cell membrane protective effects. These actions are considered to lead to improved ALT levels. In a Japanese double-blind trial of SNMC 40 mL daily for 1 month, significant improvement in AST and ALT levels was seen in the SNMC group in comparison with the placebo group.[179,180] Doses are 40–100 mL daily or alternate daily, although Japanese dosage comparison trials found significantly greater improvement in ALT levels with 100 mL than with 40 mL.[181,182] In another study, long-term administration of SNMC significantly inhibited progression to liver cirrhosis in comparison with the control group.[183] Adverse reactions to SNMC include hypokalemia and hypertension.

Studies of inhibition of hepatocellular carcinogenesis by SNMC found that the incidence of HCC was significantly lower in the treatment group than in the control group.[183,184] SNMC therapy has also been found to significantly reduce the incidence of HCC in non-responders to IFN therapy.[185,186]

UDCA + SNMC combination therapy

An RCT comparing SNMC monotherapy and UDCA + SNMC combination therapy found significantly greater improvement in ALT levels in the combination therapy group.[187] This combination is useful in reducing inflammation.

Recommendation:

Oral UDCA and i.v. SNMC, or both in combination, are recommended as protective therapy in patients with chronic hepatitis C.

5. THERAPEUTIC PHLEBOTOMY

IRON METABOLISM PLAYS an important role in patients with chronic hepatitis C. Iron is an essential metal, and a constituent of important proteins, including Hb. When iron is present in excess, however, cytotoxic hydroxyl radicals are produced, causing oxidative stress. Therapeutic phlebotomy was devised as a supportive therapy for patients with chronic hepatitis C because oxidative stress associated with iron overload is a factor in progression of liver disease. Restriction of dietary iron is also important in the management of patients undergoing iron reduction therapy. As for protective therapy, therapeutic phlebotomy is indicated in patients with chronic hepatitis C with abnormal ALT and AST levels unable to undergo IFN or other antiviral therapy, patients who failed to achieve viral clearance with antiviral therapy and patients who do not wish to undergo antiviral therapy.

In 1994, a Japanese study reported that therapeutic phlebotomy lowered ALT levels in patients with chronic hepatitis C.[188] A Japanese multicenter RCT also confirmed improvement in ALT levels with therapeutic phlebotomy.[189] Other studies have reported a 50% decrease in ALT levels in 80% of patients, and normalization of ALT levels in 40–70% of patients.[190,191] Histological studies have reported inhibition of progression,[192] and even improvement,[193] of histological changes. Long-term therapeutic phlebotomy has been reported to significantly inhibit hepatocellular carcinogenesis.[190]

In general, therapeutic phlebotomy involves removal of 200–400 mL blood at 1–2-week intervals with the aim of reducing the serum ferritin level to ≤20 ng/mL. If the Hb level drops below 9–10 g/dL, phlebotomies are discontinued to allow recovery of hematopoietic function. After the target has been reached, therapeutic phlebotomies are performed as appropriate with reference to ferritin and Hb levels. Adverse reactions are rare, involving bradycardia and hypotension associated with the vagal reflex.

An additive effect is seen when therapeutic phlebotomy is performed in conjunction with UDCA or SNMC therapy. Greater reduction in ALT levels was seen with UDCA in combination with therapeutic phlebotomy than with UDCA monotherapy.[194] In patients on SNMC therapy, further reduction in ALT levels was seen with the addition of small volume phlebotomies.[195] The combination of therapeutic phlebotomy with another therapy with a different mode of action provides additional improvement in ALT levels.

Recommendations:

Therapeutic phlebotomy is a useful therapeutic modality in patients with chronic hepatitis C. Its use in combination with a protective therapy, oral UDCA or i.v. SNMC should also be considered.

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Original Article

Changes in Plasma Vascular Endothelial Growth Factor at 8 Weeks After Sorafenib Administration as Predictors of Survival for Advanced Hepatocellular Carcinoma

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BACKGROUND: A new predictive biomarker for determining prognosis in patients with hepatocellular carcinoma (HCC) who receive sorafenib is required, because achieving a reduction in tumor size with sorafenib is rare, even in patients who have a favorable prognosis. Vascular endothelial growth factor (VEGF) receptor is a sorafenib target. In the current study, the authors examined changes in plasma VEGF concentrations during sorafenib treatment and determined the clinical significance of VEGF as a prognostic indicator in patients with HCC. **METHODS:** Plasma VEGF concentrations were serially measured in 63 patients with advanced HCC before and during sorafenib treatment. A plasma VEGF concentration that decreased >5% from the pretreatment level at 8 weeks was defined as a "VEGF decrease." An objective tumor response was determined using modified Response Evaluation Criteria in Solid Tumors 1 month after the initiation of therapy and every 3 months thereafter. **RESULTS:** Patients who had a VEGF decrease at week 8 (n = 14) had a longer median survival than those who did not have a VEGF decrease (n = 49; 30.9 months vs 14.4 months; $P = .038$). All patients who had a VEGF decrease survived for >6 months, and the patients who had both a VEGF decrease and an α-fetoprotein response (n = 6) survived during the observation period (median, 19.7 months; range, 6.5-31.0 months). In univariate analyses, a VEGF decrease, radiologic findings classified as progressive disease, and major vascular invasion were associated significantly with 1-year survival; and, in multivariate analysis, a VEGF decrease was identified as an independent factor associated significantly with survival. **CONCLUSIONS:** A plasma VEGF concentration decrease at 8 weeks after starting sorafenib treatment may predict favorable overall survival in patients with advanced HCC. ***Cancer* 2014;120:229-37.**

KEYWORDS: antiangiogenic therapy, biomarker, hepatocellular carcinoma, prognosis, α-fetoprotein.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver (70%-85%) and a major cause of mortality. It is the fifth and seventh most frequent cancer and the second and sixth most frequent cause of cancer death in men and women, respectively.[1] At early stages or at Barcelona Clinic Liver Cancer stage A, a 5-year survival rate of 60% to 70% can be achieved in well selected patients with HCC who undergo surgical therapies (liver resection or transplantation) or locoregional procedures (ie, radiofrequency ablation).[2] However, treatment of advanced HCC that is not amenable to surgical or locoregional therapies remains a challenge in clinical practice.

Sorafenib is an oral, small-molecule tyrosine kinase inhibitor that blocks the synthesis of several intracellular proteins considered to be important for tumor progression, including the platelet-derived growth factor receptor beta, raf kinase, and the vascular endothelial growth factor (VEGF) receptor. VEGF is a homodimetric glycoprotein with a molecular weight of 45 kDa. The VEGF family includes VEGF-A, VEGF-B, VEGF-C, VEGF-D, and a structurally related molecule: placental growth factor. Three high-affinity VEGF tyrosine kinase receptors (VEGFRs) have been identified:

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VEGFR-1, VEGFR-2, and VEGFR-3. VEGFR-2 is the principal receptor that promotes the proangiogenic action of VEGF-A and has been the principal target of antiangiogenic therapies, although additional studies have underlined the importance of signaling through VEGFR-1. In 2 phase 3, placebo-controlled, randomized trials, sorafenib treatment significantly improved the time to tumor progression (TTP) and overall survival (OS) of patients with advanced HCC.[3,4] In those trials, however, no statistically significant pretreatment factors that predicted responses after patients started receiving sorafenib were identified.[5] Therefore, in clinical practice, it is extremely important to identify a predictive post-treatment biomarker that is associated with the treatment efficacy of sorafenib and the prognosis of patients after they start receiving sorafenib.

In general, the efficacy of treating solid tumors with systemic chemotherapy agents is assessed by radiologic findings. In 2010, Lencioni and Llovet published a modification of the Response Evaluation Criteria in Solid Tumors (RECIST).[6] However, the modified RECIST can be used only for typical HCC. Advanced HCCs often have atypical vascular patterns; therefore, evaluating tumor response to sorafenib is difficult with radiologic findings alone. Alternatively, α-fetoprotein (AFP) is the most popular tumor marker for HCC, and it has been reported that early AFP responses are a useful surrogate marker for predicting treatment response and prognosis in patients with advanced HCC who receive cytotoxic and antiangiogenic agents.[7-9] However, approximately 30% of patients with advanced HCC in the Sorafenib HCC Assessment Randomized Protocol (SHARP) trial had normal AFP concentrations.[10] Therefore, the identification of a new biomarker that can complementarily predict the efficacy of sorafenib and the prognosis of patients is necessary.

In a mouse model, an increase in hepatic VEGF levels was observed at 24 hours, 72 hours, and 120 hours after the administration of sorafenib,[11] suggesting that a change in VEGF levels may also occur during sorafenib therapy in humans. Therefore, we evaluated plasma VEGF changes during sorafenib treatment in patients with advanced HCC to determine whether VEGF has potential as a new biomarker for the prediction of treatment efficacy and prognosis after sorafenib administration.

MATERIALS AND METHODS

Patient Selection

Between December 2009 and August 2012, 95 consecutive patients with advanced, inoperable HCC received treatment with sorafenib at Musashino Red Cross Hospital. The diagnosis of HCC was based on guidelines established by the Liver Cancer Study Group of Japan[12] and the American Association for the Study of Liver Diseases[13] or by pathologic examination. According to these guidelines, a diagnosis of HCC is confirmed by histology or by characteristic radiologic findings, such as typical arterial enhancement of the tumor followed by a washout pattern in the images in the portal venous phase or the equilibrium phase on dynamic spiral computed tomography (CT) imaging or contrast-enhanced magnetic resonance imaging. Inclusion criteria were predefined as follows: 1) patients were alive 8 weeks after beginning treatment; and 2) patients had plasma VEGF and serum AFP concentrations evaluated at baseline, at 4 weeks, and at 8 weeks. Of 95 patients, 23 were unavailable for a week-8 VEGF measurement for the following reasons: 7 patients stopped sorafenib therapy because of erythema multiforme (grade 2-3) and started other therapies (radiation therapy or cytotoxic chemotherapy) within 1 month after starting sorafenib, 4 patients moved to another location before week 8, 5 patients refused to undergo a plasma VEGF measurement at week 8, and 7 patients were not available for obtaining VEGF concentration results. These 23 patients and 9 other patients who died within 8 weeks were excluded from the study. Hence, in total, 63 patients fulfilled the inclusion criteria. At enrollment, all patients had metastatic or locally advanced HCC that was not amenable to surgery or locoregional therapies, including transcatheter arterial chemoembolization (TACE) and local ablation. Written informed consent was obtained from all patients, and the ethics committee at Musashino Red Cross Hospital approved the study in accordance with the Declaration of Helsinki.

Sorafenib Treatment

The initial daily dose of sorafenib was 800 mg in 28 patients, 400 mg in 28 patients, and 200 mg in 7 patients. A reduced initial dose was allowed for patients who had the following factors: advanced age (≥80 years), gastrointestinal varices with a risk of bleeding, low body weight (<50 kg), and a poor performance status (≥2). In total, 60 patients underwent multiphase-multidetector CT imaging before starting sorafenib, 1 month after starting sorafenib, and every 3 months thereafter. Radiologic responses to therapy were evaluated according to modified RECIST. In all patients, serial measurements of plasma VEGF and serum AFP concentrations were performed before and after the receipt sorafenib and every month thereafter, with an allowance of ± 1 week. The endpoint of the current study was OS. In the follow-up visit after sorafenib administration, the medication was discontinued if progressive disease

(PD) was identified despite treatment, if intolerable adverse events occurred, or if inappropriate liver function was observed. Other palliative treatments or best supportive care were provided subsequently. An AFP response was defined as a decrease ≥20% in the serum AFP concentration during 8 weeks of treatment.

Plasma VEGF Measurements

Serial serum samples were collected prospectively from each patient. Venous blood samples were drawn into a serum separator tube and centrifuged at ×1800*g* for 10 minutes, and plasma samples were stored at −80°C until measurement. Plasma VEGF concentrations were measured quantitatively using an enzyme-linked immunosorbent assay kit (Quantikine Human VEGF Immunoassay; R&D Systems, Minneapolis, Minn) according to the manufacturer's instructions. We defined a decrease in the plasma VEGF level >5% from the pretreatment level at 8 weeks as a "VEGF decrease."

Statistical Analysis

Categorical variables were compared using the chi-square test, and continuous variables were compared using the Mann-Whitney test. All tests of significance were 2-tailed, and P values < .05 were considered statistically significant. OS curves were calculated using the Kaplan-Meier method, and differences between groups were assessed using the log-rank test. OS was determined as the interval between the date of treatment initiation and either death or the last visit. A Cox proportional-hazards model was used to determine the factors associated with OS. In univariate analyses, clinical and biologic parameters (sex, age, etiology, albumin, bilirubin concentrations, Child-Pugh class, plasma VEGF concentrations, and serum AFP concentrations) and tumor factors (vascular invasion and distant metastasis) were included. A logistic regression model was used to identify the factors associated with 1-year survival after the receipt of sorafenib. All statistical analyses were performed using StatView (version 5.0) software (Abacus Concepts, Berkeley, Calif).

RESULTS

Patient Characteristics

In total, 63 patients were enrolled in this study, and their characteristics are listed in Table 1. The diagnosis of HCC was confirmed by histology in 11 patients and by typical radiologic findings based on established guidelines in the remaining 52 patients. In all, 51 patients had previously received other therapeutic modalities, including 22 patients who previously received radiofrequency ablation, 22 who previously underwent TACE, 1 who previously received transcatheter arterial chemoinfusion, and 6 who previously underwent hepatic resection. Twelve patients had received sorafenib as initial therapy for HCC. Among the 63 enrolled patients, 33 were seropositive for hepatitis C virus antibody, 8 were seropositive for hepatitis B surface antigen, and 22 were seronegative for both hepatitis C virus antibody and hepatitis B surface antigen. Eighteen patients had evidence of extrahepatic metastasis, and 18 had major vascular invasion. No patient was lost to follow-up in this study.

TABLE 1. Characteristics of Study Patients With Advanced Hepatocellular Carcinoma (n = 63)

Characteristic	Median [Range]
Age, y	70 [40-85]
Sex: No. of men (%)	53 (84.1)
Baseline AFP, ng/mL	114 [2.0-98440]
Baseline plasma VEGF, pg/mL	288 [60-1580]
Treatment duration, mo	4.1 [0.1-28.3]
Overall survival, mo	9.3 [2.0-30.9]

Abbreviations: AFP, α-fetoprotein; VEGF: vascular endothelial growth factor.

Pretreatment Plasma VEGF Concentration and Prognosis and Extent of Hepatocellular Carcinoma

Pretreatment plasma VEGF concentrations in the 9 patients who died within 8 weeks were significantly higher than in the patients who survived beyond 8 weeks (813 ± 630 pg/mL vs 384 ± 18 pg/mL; $P = .0024$). Consistent with a previous study (the SHARP trial; Llovet et al[3]), our data suggested that the pretreatment plasma VEGF concentration is a useful prognostic factor for sorafenib therapy. However, there was no significant difference in OS between patients who had pretreatment plasma VEGF concentrations ≤450 pg/mL (n = 46) and those who had concentrations >450 pg/mL (n = 17; $P = .731$). The pretreatment plasma VEGF concentration could not predict prognosis for the patients who survived beyond 8 weeks.

We compared the size and extent of HCC between patients who had low plasma VEGF concentrations (≤450 pg/mL) and high plasma VEGF concentrations (>450 pg/mL). No difference was observed in the size or extent of HCC at baseline between patients with lower versus higher pretreatment plasma VEGF concentrations.

Association Between Changes in Plasma VEGF Concentrations and Overall Survival

The median OS assessed by the Kaplan-Meier method was 16.3 months for all 63 patients enrolled in the study

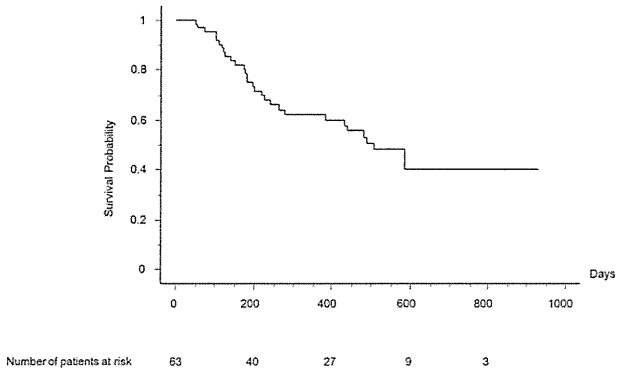

Figure 1. This Kaplan-Meier plot illustrates overall survival for all patients in the study.

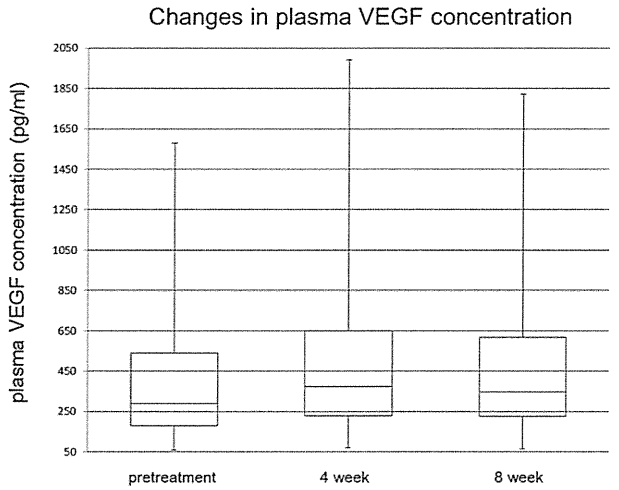

Figure 2. Changes in plasma vascular endothelial growth factor (VEGF) concentrations are illustrated.

(Fig. 1). Plasma VEGF concentrations at baseline, at 4 weeks, and at 8 weeks after the initiation of sorafenib treatment were 288 pg/mL (range, 60-1580 pg/mL), 372 pg/mL (range, 69-1990 pg/mL), and 347 pg/mL (range, 64-1840 pg/mL), respectively (Fig. 2). Plasma VEGF concentrations increased within 4 weeks after the administration of sorafenib in 47 of 63 patients (74.6%). The median survival of patients who had a decrease in their plasma VEGF concentration at week 4 (n = 16) and an increase in their plasma VEGF concentration at week 4 (n = 47) were 19.5 months and 16.8 months, respectively; and there was no significant difference in OS between changes in plasma VEGF at 4 weeks ($P = .645$). However, patients who had a VEGF decrease at week 8 (n = 14) had a longer median survival than those who did not have a VEGF decrease (n = 49; 30.9 months vs 14.4

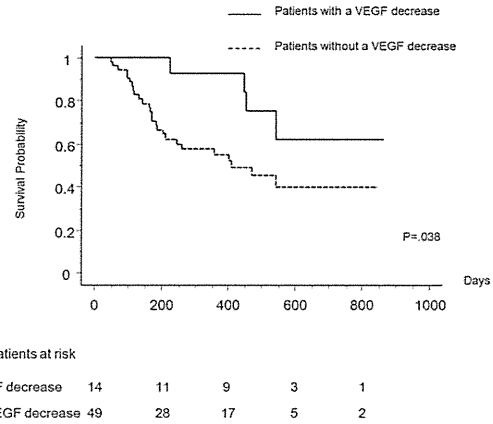

Figure 3. This Kaplan-Meier plot illustrates overall survival according to changes in vascular endothelial growth factor (VEGF) concentration.

months; $P = .038$) (Fig. 3), suggesting that a decrease in VEGF concentration 8 weeks after starting sorafenib treatment is closely associated with a favorable prognosis. The median percentage of decrease in the plasma VEGF concentration was 18.3% (range, 7%-41.7%). There were no differences in any pretreatment patient characteristics, including HCC stage and Child-Pugh score, between patients who did and did not have a VEGF decrease (Table 2).

Relation Between Radiologic Findings or Serum α-Fetoprotein Concentration and Overall Survival

The best radiologic responses to therapy assessed by modified RECIST were classified as a complete response (CR) (n = 4), a partial response (PR) (n = 16), stable disease (SD) (n = 34), and PD (n = 9). Fourteen patients had a VEGF decrease, and their best radiologic responses were a CR (n = 2), a PR (n = 2), SD (n = 9), and PD (n = 1). There was no significant difference in OS between the patients who had an objective response (CR + PR) and those with SD. The survival of patients who had PD was significantly worse than that of the patients without PD (median OS, 5.8 months and 19.4 months, respectively; $P = .0006$). There was no significant difference in OS between patients who had an AFP response and those who did not have an AFP response within the group that did not have PD (ie, those who attained a CR, a PR, or SD [the non-PD group]) (Fig. 4). There also was no significant difference ($P = .111$) between patients who did and did not have an AFP response among those in the non-PD group who had had an elevated AFP at baseline.

TABLE 2. Characteristics of Patients Categorized According to Variation in Vascular Endothelial Growth Factor Levels at 8 Weeks of Sorafenib Treatment

Characteristic	No. of Patients (%)		
	With VEGF Decrease, n = 14	Without VEGF Decrease, n = 49	*P*
Age, y	72	69	.325
Sex: Men	11 (78.6)	42 (85.7)	.679
Body weight, kg	58.3	62.3	.175
Cause of disease			.210
Hepatitis B	0 (0)	8 (16.3)	
Hepatitis C	9 (64.3)	24 (49)	
Other	5 (35.7)	17 (34.7)	
Prior treatment			.797
Yes	11 (78.6)	40 (81.6)	
No	3 (21.4)	9 (18.4)	
Baseline bilirubin, mg/dL	0.8	1.0	.375
Baseline albumin, g/dL	3.4	3.6	.190
Child-Pugh score			.178
5	7 (50)	30 (61.2)	
6	7 (50)	16 (32.7)	
7	0 (0)	3 (6.1)	
Maximum tumor size, cm			.892
≤5	8 (57.1)	22 (44.9)	
>5	6 (42.9)	27 (55.1)	
No. of tumors			.883
≤3	10 (71.4)	34 (69.4)	
>3	4 (28.6)	15 (30.6)	
Extrahepatic disease			.502
Yes	3 (21.4)	15 (30.6)	
No	11 (78.6)	34 (69.4)	
Site of metastatic disease			
Lung	1	7	
Bone	1	4	
Lymph node	1	3	
Lung and bone	0	1	
Major vascular invasion			.739
Yes	3 (21.4)	15 (30.6)	
No	11 (78.5)	34 (69.4)	

Abbreviations: VEGF: vascular endothelial growth factor.

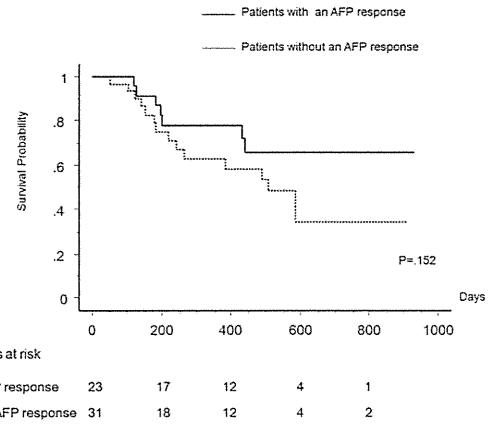

Figure 4. This Kaplan-Meier plot illustrates overall survival according to α-fetoprotein (AFP) response in patients without progressive disease (PD), classified as non-PD (ie, those who had a complete response, a partial response, or stable disease) according to modified Response Evaluation Criteria in Solid Tumors.

It is noteworthy that all patients who had a VEGF decrease and an AFP response survived during the observation period (median, 19.7 months; range, 6.5-31.0 months). In patients without a VEGF response (n = 49), there was no significant difference in OS between those who did and did not have an AFP response ($P = .147$). Of 49 patients who did not have a VEGF decrease at 8 weeks, 19 patients were able to survive beyond 1 year after starting sorafenib. Nine patients without a VEGF decrease at 8 weeks survived for >18 months.

Prognostic Factors After Sorafenib Administration

In univariate analysis, among all patients, a VEGF decease and an AFP response were associated significantly with OS after starting sorafenib. Major vascular invasion and PD, as evidenced by radiologic findings after sorafenib administration, also were significant prognostic factors. To predict which patients would have a highly favorable prognosis, the prognostic factors associated with 1-year survival after starting sorafenib were assessed in univariate and multivariate analyses. In the univariate analysis, a VEGF decrease, PD, and major vascular invasion were associated significantly with survival (Table 3). In the multivariate analysis, which was performed using those factors as covariates, a VEGF decrease was identified as an independent factor associated significantly with survival (Table 3). There was a significant difference in OS among the 3 groups (patients with a VEGF decrease and non-PD, patients without a VEGF decrease but non-PD, and patients without a VEGF decrease and PD; $P = .0013$) (Fig. 5). Only 1 patient who had a VEGF decrease was classified with PD. All 4 patients who had a VEGF decrease and an objective response (CR or PR) were able to survive during the observation period.

Adverse Events During Sorafenib Treatment

The overall incidence of treatment-related adverse events was 100%. The rate of discontinuation of sorafenib as a result of adverse events was 22.2%. Adverse events that led to the discontinuation of sorafenib treatment were liver dysfunction (63.6%), hand-foot skin reaction (18.2%), interstitial pneumonia (9.1%), and rash (9.1%). Dose reductions because of adverse events occurred in 62 patients. The most frequent adverse event leading to dose reductions was liver dysfunction (33.9%). In addition,

TABLE 3. Prognostic Factors Associated With 1-Year Survival After Sorafenib Administration

Risk Factor	OR (95% CI)[a]	*P*
Univariate analysis		
Age, by every 10 y	1.47 (0.75-2.87)	.266
Sex		
Women	1.00	
Men	0.26 (0.50-1.39)	.116
HBV infection		
Negative	1.00	
Positive	0.33 (0.06-2.02)	.231
HCV infection		
Negative	1.00	
Positive	1.23 (0.41-3.74)	.714
Albumin, by every 1 g/dL,	1.34 (0.45-3.99)	.604
Total bilirubin, by every 1 mg/dL	0.79 (0.28-2.25)	.656
Pre-AFP, by every 10 ng/mL	1.00 (1.00-1.00)	.161
Tumor size, cm		
<5	1.00	
≥5	0.42 (0.14-1.32)	.147
No. of tumors		
≤3	1.00	
≥4	0.26 (0.06-1.08)	.064
Major vascular invasion		
Yes	1.00	
No	4.00 (1.12-14.4)	.034
Extrahepatic metastasis		
Yes	1	
No	1.82 (0.56-5.90)	.320
5% VEGF decrease at wk 8		
No	1.00	
Yes	11.1 (1.29-94.6)	.028
PD		
No	1.00	
Yes	0.16 (0.29-0.86)	.033
Objective response: CR + PR		
No	1.00	
Yes	1.63 (0.49-5.42)	.426
AFP response		
No	1.00	
Yes	2.76 (0.80-9.52)	.107
Multivariate analysis[b]		
5% VEGF decrease at wk 8		
No	1.00	
Yes	10.0 (1.02-91.3)	.041
PD		
No	1.00	
Yes	0.20 (0.29-1.39)	.104
Major vascular invasion		
Yes	1.00	
No	3.03 (0.71-12.9)	.134

Abbreviations: AFP, α-fetoprotein; CI, confidence interval; CR, complete response; HBV, hepatitis B virus; HCV, hepatitis C virus; PD, progressive disease; PR, partial response; VEGF, vascular endothelial growth factor.
[a] The ORs for 1-year survival were calculated using logistic regression analysis.
[b] In the multivariate logistic analysis, a 5% VEGF decrease, PD, and portal invasion were included as covariates.

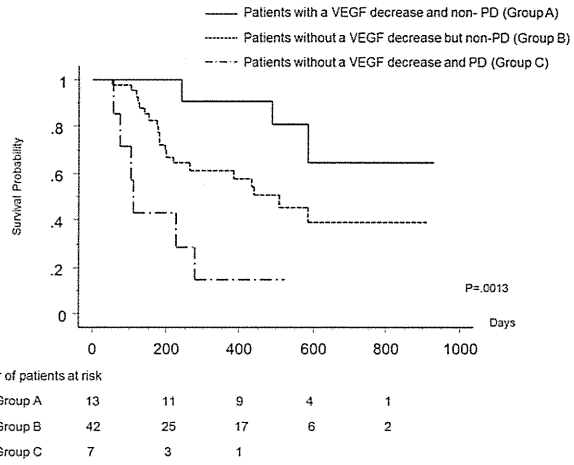

Figure 5. This Kaplan-Meier plot illustrates overall survival according to the combination of vascular endothelial growth factor (VEGF) changes and radiologic findings classified by modified Response Evaluation Criteria in Solid Tumors. Non-PD indicates patients who did not have progressive disease (PD) (ie, those who had a complete response, a partial response, or stable disease).

the incidence of adverse events was not related to plasma VEGF concentrations.

DISCUSSION

In the current study, we demonstrated that plasma VEGF concentrations change dynamically during sorafenib therapy, and changes in VEGF concentration are closely associated with OS in patients who receive treatment with sorafenib. VEGF is the major mediator of angiogenesis in HCC, and several studies have correlated VEGF concentrations with the prognosis of patients who have advanced HCC.[5,14-21]

Recently, a new staging system was proposed that includes the plasma VEGF concentration along with the Cancer of the Liver Italian Program (CLIP) score; this new system—known as the V-CLIP score—classifies patients with advanced HCC more appropriately into a homogeneous prognostic group.[22] Therefore, the concentration of circulating VEGF is included as a candidate prognostic marker for HCC, especially in patients with advanced disease. The objective of our study was to elucidate the important question of whether an on-treatment change in VEGF is a potentially useful new biomarker for predicting prognosis in patients who survive beyond 8 weeks, because such an on-treatment predictor among patients who have relatively longer survival has not yet been elucidated. In this study, plasma VEGF concentrations increased from pretreatment levels within 4 weeks of starting sorafenib in 47 of 63 patients (74.6%). This was followed by a decrease in plasma VEGF levels at 8 weeks in 68.1% of patients. A possible mechanism of this transient increase in VEGF after starting sorafenib may be related to a reactive increase against the inhibition of VEGF activity or hypoxia induced by sorafenib. This