

Supportive therapies for prevention of hepatocellular carcinoma recurrence and preservation of liver function

Taro Takami, Takahiro Yamasaki, Issei Saeki, Toshihiko Matsumoto, Yutaka Suehiro, Isao Sakaida

Taro Takami, Issei Saeki, Isao Sakaida, Department of Gastroenterology and Hepatology, Yamaguchi University Graduate School of Medicine, Yamaguchi 755-8505, Japan

Takahiro Yamasaki, Toshihiko Matsumoto, Yutaka Suehiro, Department of Oncology and Laboratory Medicine, Yamaguchi University Graduate School of Medicine, Yamaguchi 755-8505, Japan

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Correspondence to: Takahiro Yamasaki, MD, PhD, Department of Oncology and Laboratory Medicine, Yamaguchi University Graduate School of Medicine, 1-1-1 Minami Kogushi, Ube, Yamaguchi 755-8505, Japan. t.yama@yamaguchi-u.ac.jp
Telephone: +81-836-222336
Fax: +81-836-222338

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Abstract

Hepatocellular carcinoma (HCC) is one of the deadliest cancers in the world and is associated with a high risk of recurrence. The development of a wide range of new therapies is therefore essential. In this study, from the perspective of supportive therapy for the prevention of HCC recurrence and preservation of liver function in HCC patients, we surveyed a variety of different therapeutic agents. We show that branched chain amino acids (BCAA) supplementation and late evening snack with BCAA, strategies that address issues of protein-energy malnutrition, are important for liver cirrhotic patients with HCC. For chemoprevention of HCC recurrence, we show that viral control after radical treatment is important. We also reviewed the therapeutic potential of antiviral drugs, sorafenib, peretinoin, iron chelators. Sorafenib is a kinase inhibitor and a standard therapy in the treatment of advanced HCC. Peretinoin is a vitamin A-like molecule that targets the retinoid nuclear receptor to induce apoptosis and inhibit tumor growth in HCC cells. Iron chelators, such as deferoxamine and deferasirox, act to prevent cancer cell growth. These chelators may have potential as combination therapies in conjunction with peretinoin. Finally, we review the potential inhibitory effect of bone marrow cells on hepatocarcinogenesis.

Key words: Hepatocellular carcinoma; Liver cirrhosis; Branched-chain amino acids; Late evening snack; Iron chelators; Bone marrow cells

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Core tip: Hepatocellular carcinoma (HCC) is one of the deadliest cancers in the world and is associated with a high risk of recurrence. Because liver function worsens upon repeated treatment for HCC recurrence, therapies that preserve liver function are essential. Here, we survey a variety of different therapeutic agents and then review the current status and prospects for prevention of HCC recurrence, particularly from the perspective of supportive therapy to preserve liver function. The agents included branched-chain amino acids (BCAA) supplementation, late evening snacking with BCAA, antiviral drugs, sorafenib, peretinoin, iron chelators, and bone marrow cells.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the second leading cause of deaths due to cancer in the world^[1]. The prognosis of HCC has improved recently as a result of progress in a variety of therapies. These therapies include surgical resection, percutaneous-ethanol-injection (PEI), radiofrequency ablation (RFA), trans-arterial chemoembolization (TACE), administration of the drug, sorafenib, and liver transplantation^[2-7]. The greatest problem with HCC is a high risk of recurrence, even when radical treatment is conducted. Recurrent HCC results in a fatal outcome for many patients with hepatic dysfunction. Antiviral therapies, such as nucleic acid analogs and interferon (IFN), have the potential to inhibit HCC recurrence after radical treatment of patients who have hepatitis B virus (HBV)- or hepatitis C virus (HCV)-related liver diseases^[8,9]. Recently, however, the occurrence of both HBs antigen-negative and HCV antibody-negative HCC has actually increased in Japan as the development of antiviral agent and IFN treatments has progressed^[10,11]. It is therefore necessary to develop other therapies to prevent HCC recurrence. Because liver function worsens upon repeated treatment for HCC recurrence, therapies that preserve liver function are essential. In this paper, we review the current status and prospects for prevention of HCC recurrence, particularly from the perspective of supportive therapy to preserve liver function.

First, we review the use of branched chain amino acids and late evening snack (LES), particularly for HCC patients with liver cirrhosis. These treatments are generally intended to address issues of protein-energy malnutrition (PEM) in these patients. We then review

a range of chemoprevention options. These include antiviral therapies (nucleic acid analogs, IFN) for the treatment of hepatitis virus-related HCC, as well as treatment options such as sorafenib, peretinoin, and iron chelators. Finally, we review the potential inhibitory effect of bone marrow cells (BMCs) on hepatocarcinogenesis.

BRANCHED-CHAIN AMINO ACIDS

Most patients with HCC have liver cirrhosis. Generally, liver cirrhotic patients suffer from PEM. These patients commonly exhibit decreased nutrient intake, hypermetabolism, and increased branched-chain amino acids (BCAA) consumption associated with ammonia metabolism in the skeletal muscle, leading to a decrease in plasma BCAA levels^[12-14]. This decrease in plasma BCAA levels reduces protein synthesis in the liver and causes proteolysis in the muscle, which leads to edema and ascites with hypoalbuminemia and decrease in skeletal muscle mass.

BCAA granules consist of leucine, isoleucine, and valine, which are essential amino acids in humans. The Japanese Nutritional Study Group recommends administration of BCAA to liver cirrhotic patients who have serum albumin levels of 3.5 g/dL or less, a Fisher ratio of 1.8 or less, and a BCAA-to-tyrosine ratio of 3.5 or less^[15]. In contrast, in the guidelines set by the American Society for Parenteral and Enteral Nutrition (ASPEN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), oral administration of BCAA is recommended only in patients with liver cirrhosis who have hepatic encephalopathy^[16,17].

A wide variety of effects of BCAA on chronic liver disease has been confirmed in previous fundamental research and clinical studies. Improvement of insulin resistance^[18,19], improvement of hypoalbuminemia and reduction of oxidative stress^[20,21], activation of immune function^[22,23], promotion of liver regeneration^[24,25], and inhibitory effects on hepatocarcinogenesis^[26-28] have been reported. With regards to the mechanism of action, it has been reported that BCAA activates the insulin signal cascade through upregulation of phosphatidylinositol 3-kinase^[29]. This serves to decrease circulating insulin levels and reduce the expression of insulin-like growth factors (IGF)-1 and IGF-2 as well as IGF-1 receptors to inhibit the IGF/IGF-1 receptor axis^[29].

Given the biological properties referred to above, the following effects of BCAA on HCC can be anticipated: (1) inhibition of hepatocarcinogenesis associated with chronic liver disease; (2) prevention of a reduction in residual liver function caused by HCC treatment; and (3) prevention of recurrence after HCC treatment.

Muto *et al.*^[26] performed a multicenter, randomized controlled trial (RCT) that included 622 decompensated liver cirrhotic patients. They reported that oral administration of BCAA inhibited hepatocarcinogenesis

Table 1 Cohort studies (5 reports) and randomized controlled trial (3 reports) were available

Ref.	Group	Patient number	Therapy for HCC	Male/Female	Age (yr)	Child-Pugh A/B/C	Maximum tumor size (mm)	Study design
Togo <i>et al</i> ^[41]	BCAA	21	Surgery	17/4	66.5 ± 4.5	15/7/0	ND	RCT
2005	control	22		17/5	64.3 ± 9.1	17/5/0	ND	
Ichikawa <i>et al</i> ^[42]	BCAA	26	Surgery	18/8	64.7 ± 9.8	21/5/0	ND	RCT
2012	control	30		20/10	64.5 ± 11.4	25/5/0	ND	
Nishikawa <i>et al</i> ^[43]	BCAA	115	RFA	64/51	69.3 ± 9.4	83/30/2	19.5 ± 6.0	cohort
2013	control	141		85/58	70.9 ± 7.8	88/52/1	19.6 ± 6.6	
Yoshiji <i>et al</i> ^[44]	BCAA	51	RFA	32/19	63.6 ± 15.3	41/10/0	ND	RCT
2013	control	42		25/17	62.2 ± 14.8	33/9/0	ND	
Saito <i>et al</i> ^[45]	BCAA	13	RFA	8/5	73.4 ± 2.2	83/30/2	ND	cohort
2014	control	27		16/11	70.0 ± 1.9	88/52/1	ND	
Nishikawa <i>et al</i> ^[46]	BCAA	40	TACE	27/13	69.9 ± 8.8	6.4 ± 0.4	33.4 ± 16.7	cohort
2012	control	59		32/27	73.2 ± 10.1	5.4 ± 0.1 (score)	35.9 ± 14.7	
Takeda <i>et al</i> ^[47]	BCAA	34	Sorafenib	27/7	72 (55-88)	16/18/0	ND	cohort
2014	control	44		37/7	68 (46-89)	30/14/0	ND	
Imanaka <i>et al</i> ^[48]	BCAA	55	Sorafenib	45/10	72.2 ± 7.8/73.1 ± 6.4	37/18/0	ND	cohort
2015	control	201		167/34	72.4 ± 8.8/67.2 ± 13.0 (Child-Pugh A/B)	179/22/0	ND	

BCAA: Late evening snack using branched-chain amino acid; RFA: Radiofrequency ablation, TACE: Trans-catheter arterial chemoembolization, ND: Not done; RCT: Randomized control trial.

in obese patients [\geq body mass index (BMI) 25 kg/m²] who had HCV-related liver cirrhosis.

Currently, there are many options for the treatment of HCC. Appropriate treatments such as surgical resection, PEI, RFA, TACE, hepatic arterial infusion chemotherapy (HAIC), molecular target-based therapy by sorafenib, and radiation therapy may be chosen depending on residual liver function and tumor stage. Improvements in prognosis have been observed using these approaches^[1,30-40]. However, because recurrence of HCC can occur in liver cirrhosis patients after radical treatment, it is important to maintain residual liver function and to seek ways to inhibit the recurrence.

To our knowledge, there have been eight reports on the efficacy of BCAA granules in patients being treated for HCC; the HCC treatment in these reports was surgical operation (2 reports), RFA (3 reports), TACE (1 report), and molecular target-based therapy (2 reports). In terms of study design, both cohort studies (5 reports) and RCTs (3 reports) were available (Table 1)^[41-48].

Early recovery of protein metabolism after hepatectomy can be achieved by administering BCAA granules^[41]. Ichikawa *et al*^[42] also reported that BCAA granules were effective in inhibiting early relapse after hepatectomy.

Reduction in the cumulative relapse rate and improvement in survival rate were observed after long-term oral administration of BCAA granules to patients who had received RFA^[43-45]. Nishikawa *et al*^[43] performed a retrospective study of 256 patients who had received RFA and had serum albumin levels of 3.5 g/dL or less. They reported improvements in overall survival (OS) and recurrence-free survival after oral administration of BCAA granules. The study also reported an improvement in OS in patients with HCC who suffered

from obesity (\geq BMI 25 kg/m²) and diabetes. Yoshiji *et al*^[44] performed a RCT involving 93 patients who had received RFA and reported improvement of insulin resistance after oral administration of BCAA granules. They also found a decrease in levels of the plasma soluble form of vascular endothelial growth factor receptor 2 (VEGFR2) and a reduction in the cumulative relapse rate after RFA in liver cancer patients who had insulin resistance (\geq homeostasis model assessment for insulin resistance of 2.5). Thus, BCAA can be considered to inhibit recurrence of HCC and to improve survival rates through improved insulin resistance and an anti-angiogenic effect. This may be the same mechanism by which BCAA inhibits hepatocarcinogenesis in liver cirrhotic patients suffering from obesity.

For unresectable HCC, it is common to perform TACE repeatedly, but it is necessary to pay attention to the liver function after TACE. In this respect, it has been reported that administration of BCAA granules prior to TACE inhibited reduction of serum albumin levels measured three and six months after TACE, and helped maintain residual liver function in patients with Child-Pugh A/B^[46].

In molecular target-based therapy using sorafenib for treatment of unresectable HCC, it is important to maintain residual liver function, as any reduction could lead to discontinuation of treatment and a poor prognosis. In patients with Child-Pugh A (but not in patients with Child-Pugh B), administration of BCAA granules when sorafenib is used inhibits reduction of serum albumin levels. The dosing period of sorafenib and the survival period are also prolonged^[47,48].

These observations suggest that BCAA is effective in inhibiting hepatocarcinogenesis, maintaining residual liver function after HCC treatment, and preventing recurrence of HCC in patients with chronic liver disease.

Table 2 Cohort studies (2 reports) and randomized controlled trial (3 reports)

Ref.	Group	Patient number	Therapy for HCC	Male/Female	Age (yr)	Child-Pugh A/B/C	Maximum tumor size (mm)	Study design
Okabayashi <i>et al</i> ^[56] 2008	LES-BCAA	40	surgery	29/11	65.7 ± 8.6	33/7/0	ND	cohort
	control	72		55/17	68.3 ± 8.1	62/10/0	ND	
Kuroda <i>et al</i> ^[57] 2010	LES-BCAA	20	RFA	13/7	65.6 ± 7.0	8/11/1	20.2 (median)	cohort
	control	15		9/6	66.0 ± 8.1	6/8/1	19.8 (median)	
Moriyama <i>et al</i> ^[58] 2012	LES-BCAA	10	RFA	8/2	73.5 ± 8.5	9/1/0	20.0 ± 10.7	RCT
	Morning-BCAA	10		8/2	66.9 ± 9.7	7/3/0	24.3 ± 7.7	
Takeshita <i>et al</i> ^[59] 2009	LES-BCAA	28	TACE	19/9	69.1 ± 8.231	6.107 ± 1.315 (score)	ND	RCT
	control	28		21/7	70.6 ± 9.745	5.53 ± 0.516 (score)	ND	
Harima <i>et al</i> ^[60] 2010	LES-BCAA	13	HAIC	11/2	64.5 ± 9.5	6/7/0	77.7 ± 50.5	RCT
	control	10		8/2	66.4 ± 12.8	6/4/0	88.0 ± 39.7	

LES-BCAA: Late evening snack using branched-chain amino acid; Morning-BCAA: Morning BCAA administration; RFA: Radiofrequency ablation; TACE: Trans-catheter arterial chemoembolization; HAIC: Hepatic arterial infusion chemotherapy; ND: Not done; RCT: Randomized control trial.

Early administration of BCAA granules is expected to be useful for patients, with or without HCC, whose plasma BCAA levels have decreased. However, many of the findings above are based on reports from retrospective studies. Further evaluation of data from RCTs will be required in the future to corroborate these results.

LES

Patients with liver cirrhosis enter a nocturnal starvation state, LES is recommended in the guidelines of both the ASPEN and ESPEN^[16,17]. LES with BCAA nutrients improves serum albumin and energy metabolism more than LES with ordinary food; LES with BCAA nutrients is therefore typical^[49]. Therefore, BCAA nutrients has been used in a LES. We have reported previously that LES with BCAA nutrients improve energy malnutrition, amino acid imbalance, and glucose intolerance in liver cirrhotic patients^[50-52]. However, at present, there are no guidelines for nutrition care in the treatment of HCC^[53-55].

To our knowledge, there are as few as five reports on the effects of LES with BCAA nutrients on liver cirrhotic patients with HCC; the HCC treatment in the studies included surgical resection (1 report), RFA (2 reports), TACE (1 report), and HAIC (1 report). The study designs included cohort studies (2 reports) and RCTs (3 reports) (Table 2)^[56-60].

LES with BCAA nutrients prior to surgical resection was shown to significantly improve postoperative liver function, significantly reduce postoperative complications, and significantly shorten hospitalization^[56]. In patients treated with RFA, LES with BCAA nutrients improved liver function^[57,58], nutritional status, and quality of life (QOL)^[57]. Takeshita *et al*^[59] reported that LES with BCAA nutrients for two weeks caused a reduction in decreased liver function in patients treated with TACE.

We measured energy metabolism using indirect calorimetry (Figure 1) in liver cirrhosis patients without HCC and in liver cirrhosis patients with HCC at different stages as classified by the Liver Cancer Study Group of

Japan criteria. In the Child-Pugh A score, the non-protein respiratory quotient (npRQ) significantly decreased in patients with advanced HCC at stage IV^[60]. In the Child-Pugh B score, nutritional status was generally poor, and npRQ decreased in all patient groups; there were no significant differences between the groups (unpublished data). Therefore, in patients with advanced HCC, LES with BCAA nutrients may be necessary depending on the Child-Pugh A score. In fact, LES with BCAA nutrients (LES group) improved the energy metabolism in advanced HCC patients undergoing HAIC compared with ordinary food (control group)^[60]. In the 75-g oral glucose tolerance test (75-g OGTT), the area under the concentration curve for glucose (AUC glucose) showed an improvement in the LES group ($P = 0.055$). No significant difference in survival was identified between the groups ($P = 0.667$). However, the survival time of the patients whose therapeutic effect of HAIC was stable disease (SD) or progressive disease (PD) tended to be longer in the LES group ($P = 0.156$) than in the control group. For patients with SD or PD, a significant improvement in npRQ was observed in the LES group, whereas significant reductions in cholinesterase and natural killer cell activity were observed in the control group^[61].

Thus, we consider that nutritional therapy tailored to tumor stage and residual liver capacity is required for HCC patients. However, further investigations are necessary because the previous reports examined only a small number of HCC patients.

CHEMOPREVENTION OF HCC RECURRENCE

In HCC patients, the recurrence rate is approximately 50% even after radical treatment^[62,63]. Notably, it is approximately 70% in patients with HCV-related HCC^[64]. Therefore, various studies on the inhibition of recurrence after radical treatment have been conducted. However, prevention of recurrence should be addressed based on the causative diseases of

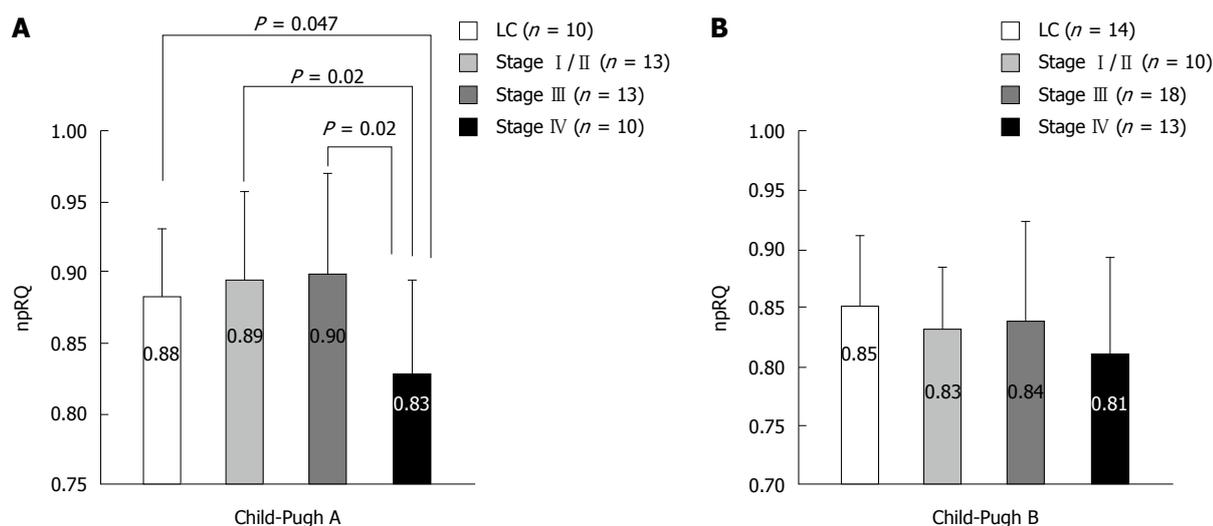


Figure 1 Non-protein respiratory quotient values in cirrhotic patients without hepatocellular carcinoma and with hepatocellular carcinoma at different stages as classified by the Liver Cancer Study Group of Japan criteria. In patients with Child-Pugh A score, no significant difference in npRQ was seen among three groups [liver cancer study (LC) group, hepatocellular carcinoma (HCC) stage I / II group, and HCC stage III group]; however, the npRQ was significantly lower in the HCC stage IV group than in the LC, HCC stage I / II, or HCC stage III groups (LC group vs HCC stage IV group, $P = 0.047$; HCC stage I / II vs HCC stage IV group, $P = 0.02$; HCC stage III group vs HCC stage IV group, $P = 0.02$). In Child-Pugh B patients, no significant difference in npRQ was seen among the four groups.

HCC. This chapter describes this issue with respect to antiviral treatment for viral (*e.g.*, HBV and HCV) hepatitis and other cancer inhibitors.

Hepatitis virus-related HCC

For HBV- and/or HCV-related HCC, it has been suggested that antiviral treatment for inhibition of HCC recurrence is best administered after radical treatment rather than before. The efficacy of IFNs as antiviral treatments in viral-related HCC has been reported in six meta-analyses^[65-70]. However, these meta-analyses had limitations. In the meta-analyses of Zhang *et al.*^[65] and Breitenstein *et al.*^[70], HBV and HCV patients were examined together and only IFN- α was evaluated. In the study of Miao *et al.*^[68], HBV patients and HCV patients were also examined together and various IFNs were assessed. In the study by Singal *et al.*^[66], only HCV patients were examined, a cohort study was also included, and various IFNs (IFN- α , α -2b, PEGylated IFN, and IFN- β) were evaluated. In the study by Shen *et al.*^[67], both HBV and HCV patients were examined together, a cohort study was also included, and various IFNs were evaluated. In the study by Miyake *et al.*^[69], only patients with HCV-related HCC were examined and tumor factors were limited. In any case, as an overall conclusion, it was reported that IFN- α may inhibit postoperative recurrence within the Milan criteria (a generally accepted set of criteria used to assess suitability of patients with cirrhosis and hepatocellular carcinoma for liver transplantation.). Sustained virological response was particularly associated with inhibition of recurrence.

HBV-related HCC

Lee *et al.*^[71] reported that scores calculated from age,

sex, alanine aminotransferase, HBe antigen, content of HBV-DNA, and HBV genotype were informative as predictors of cancer associated with HBV. There are many reports on the cancer inhibition effect of IFN and nucleic acid analogs administered to patients with HBV-related chronic liver disease^[69,72]. Hosaka *et al.*^[73] also conducted a propensity score matching analysis after classifying patients with HBV-related chronic liver disease into an entecavir (a deoxyguanosine analog)-therapy group and a non-therapy group. They reported that the 5-year cancer incidence rate was significantly reduced (3.7% vs 13.7%; HR = 0.37, $P = 0.030$) in the therapy group. Sohn *et al.*^[74] reported that higher amounts of HBV-DNA were associated with higher risk of early recurrence and that a higher amount of HBs antigen was associated with higher risk of late recurrence. These data strongly support the value of antiviral therapy after HCC treatment, and meta-analyses have shown that the use of nucleic acid analogs after HCC treatment can help inhibit HCC recurrence and improve prognosis^[75,76]. Although results from an RCT suggested that IFN can inhibit HCC, no firm conclusion was reached, and further investigation will be required^[76]. Recently, Lee *et al.*^[77] reported on the beneficial effect of a nucleic acid analog on inhibition of HCC recurrence after radical treatment with RFA.

Thus, it is suggested that viral control after radical treatment is important for inhibiting HCC recurrence in patients with HBV-related HCC.

HCV-related HCC

The effect of IFN on cancer inhibition in patients with HCV-related chronic liver disease has been reported in many previous studies^[78-80]. Miyake *et al.*^[81] reported in

a meta-analysis that IFN can decrease the carcinogenic risk. In addition, many studies have mentioned the value of IFN even after radical treatment for HCV-related HCC. In these studies, the effect of IFN on prognosis was reported; a trend in inhibiting recurrence was noted but the results did not reach statistical significance^[82,83]. However, several studies have reported that IFN- α after radical treatment for HCC inhibited later successive recurrences after a second recurrence^[64,84,85]. In addition, the effect of low dosages of IFN in long-term therapy on inhibition of recurrence has been reported. Thus, Kudo *et al.*^[86] reported that a small amount of IFN- α 2b inhibited the first, second, and third recurrence after radical treatment with RFA and contributed to survival (HR = 0.21)^[87]. It has also been reported that IFN- β inhibited recurrence after radical treatment for HCV-related HCC ($P = 0.0004$).

Several direct-acting antivirals (DAAs) have emerged recently as treatments for the safe elimination of viral infections, even in cirrhotic patients. Recently, Reig *et al.*^[88] administered DAAs to the patients after curative treatment of HCC and investigated subsequent recurrence rate. Although they reported high rate of recurrence after the viral elimination by DAAs, it is a small cohort retrospective study and the reliable opinion is not obtained. In addition, Pol S conducted a multicenter prospective study, and he concluded that there was no evidence that DAAs promote an HCC recurrence^[89]. It is still needed future analysis.

OTHER CANCER INHIBITORS

This section describes the current status and prospects of these three agents in the treatment of advanced HCC.

Sorafenib

Sorafenib is a standard therapeutic drug for advanced HCC that was developed as a C-Raf and B-Raf serine/threonine kinase activity inhibitor^[7]. It affects both the Raf/MEK/ERK signaling pathway, which influences cell proliferation, and VEGFR, which is associated with neovascularization. Sorafenib is also known to inhibit the tyrosine kinase activity of the platelet-derived growth factor receptor^[7].

In 2008, international cooperative group clinical trials involving patients with advanced HCC demonstrated that sorafenib offered a significant prolongation of OS when compared with placebo^[7]. To test the hypothesis that sorafenib could prevent HCC recurrence, a RCT targeting patients who had received HCC radical curative treatment (hepatectomy/RFA/PEI) was conducted^[88]. This trial (termed the STORM trial) comprised two groups: one that received sorafenib at 800 mg/d and the placebo group. Progression-free survival was set as the primary endpoint. However, sorafenib offered no significant prolongation effect. A major issue in the STORM trial was that long-term oral administration of sorafenib was not possible because of the high incidence

of adverse side effects associated with this treatment^[90].

Peretinoin

Peretinoin is an orally administered acyclic retinoid with a vitamin A-like structure that targets the retinoid nuclear receptor^[91]. It induces apoptosis and inhibits tumor growth in HCC cells^[91]. Recently, it has been reported that acyclic retinoids increase the expression of intra-nuclear transglutaminase-2 in JHH-7 cells and induce apoptosis in HCC^[92]. Muto *et al.*^[93] performed a small-scale RCT to determine the effect of peretinoin on inhibition of HCC recurrence after radical treatment (hepatectomy/PEI). They reported that pereretinoin inhibited the second recurrence (adjusted relative risk 0.31; 95%CI: 0.12-0.78)^[93]. Based on these results, Okita *et al.*^[94,95] performed a randomized double-blind placebo-controlled study in patients after radical treatment for HCV-related HCC (operation/RFA). Recurrence was significantly inhibited in the peretinoin (600 mg/d) group ($P = 0.023$; multiplicity-adjusted $P = 0.048$)^[94,95]. A double-blind, placebo-controlled, multicenter, randomized, parallel intergroup trial is currently under way (NCT01640808) to verify these findings.

Iron chelators

Iron is necessary for oxygen transport, energy production, and cell metabolism and growth^[96,97]. It is especially important in cells with active growth, including cancer cells^[98]. A clinical study on hepatocarcinogenesis and iron overload has been conducted; Kato *et al.*^[99] reported that reduction of iron levels through phlebotomy therapy might significantly inhibit hepatocarcinogenesis. Iron metabolism control may thus become a target for cancer inhibition. An antitumor effect of deferoxamine (DFO) in HCC patients has been reported^[100,101]. We have also reported on the antitumor effect of arterial DFO administration in patients with advanced HCC^[102]. In a fundamental experiment, we reported that DFO inhibited liver fibrosis and pre-neoplastic lesions in a rat model of hepato-carcinogenesis^[103]. Deferasirox (DFX) has also recently emerged as an orally administered iron chelator, and a strong antiproliferative effect associated with DFX has been reported *in vitro*. The effect of DFX on cancer inhibition in combination with losartan has also been reported in an *in vivo* study^[104]. By combining DFX and sorafenib, we confirmed not only a therapeutic effect against liver fibrosis and cancer but also a reduction in adverse side effects that were associated with treatment with sorafenib alone. As noted above, long-term administration of sorafenib alone was not possible in the STORM trial because of the high incidence of adverse side effects. In this respect, combined treatment of DFX and sorafenib may prove to be a new therapy to prevent recurrence of HCC.

BMCS

We have reported that infusion of BMCs decreased

livers fibrosis and improved liver function in mice^[105,106]. Based on these results, we initiated an autologous BMC infusion therapy for liver cirrhosis in 2003. The safety and efficacy of this therapy have been confirmed in clinical studies^[107-110]. Short-term results to date indicate no serious complications associated with reproduction therapy using BMCs. However, longer-term evaluation, particularly evaluation of the potential for hepatocarcinogenesis, is still required.

Ishikawa *et al.*^[111] generated a rodent model of chemical carcinogenesis by injecting mice with diethylnitrosamine and phenobarbital. They then infused BMCs into these mice. No tumorigenesis associated with the BMC infusion was observed, and the authors reported that the potential for carcinogenesis was low. We examined the influence of BMC infusion on hepatocarcinogenesis using a highly oncogenic cirrhotic murine model. The influence of BMCs on hepatocarcinogenesis was evaluated histologically. The number of liver tumors was smaller and liver fibrosis was inhibited in mice treated with repeated doses of BMCs^[112]. This confirmed that BMC infusion contributed to inhibition of hepatocarcinogenesis. Most of the BMCs that engrafted into the damaged liver expressed superoxide dismutase 3, which is an antioxidant protein^[112]. It is therefore considered that BMCs inhibit hepatocarcinogenesis by regulating redox homeostasis.

Although it is known that bone marrow-derived mesenchymal stem cells (MSCs) migrate to tumor tissues, their role is mostly unclear. As MSCs secrete a variety of growth factors, there is concern about their effects on tumor progression^[113]. In previous studies, it has been reported that growth, invasion, and metastasis of lung cancer and neovascularization are promoted by MSC secretion of factors such as IL-6, VEGF, and IGF-1^[114]; that tumor cells cause epithelial-mesenchymal transition^[115]; and that tumors are activated as MSCs are differentiated into carcinoma-associated fibroblasts comprising the tumor microenvironment^[116].

Conversely, it has also been reported that MSCs inhibit tumor proliferation by controlling WNT signaling and PARP cleavage of tumor cells, thus promoting apoptosis^[117,118]. Furthermore, in a clinical study, carcinogenesis was not observed in follow-up at 11 years and five months after cultured MSC was used to reproduce cartilage^[119].

Thus, we consider that the potential for carcinogenesis associated with BMCs is low, and that these cells are likely play a minimal role in any newly occurring carcinogenesis. However, the potential for tumor formation through neovascularization or secretion by BMCs of various humoral factors also cannot be neglected. Therefore, it is important to generate further relevant data to determine whether or not tumorigenesis potentially associated with regenerative medicine using BMCs is a realistic concern, or whether BMCs can be developed as a safe and efficacious therapy.

CONCLUSION

We noted that BCAA and LES with BCAA, which address nutritional issues, were important for liver cirrhotic patients with HCC. We also emphasized that antiviral agents, including nucleic acid analogs and IFNs, were effective in the treatment of HCC. In addition, we described the potential of peretinoin, progress in the development of iron chelators, and the promise of BMCs to suppress hepato-carcinogenesis. We showed results on some positive trials supporting the prevention of HCC-recurrence and the preservation of liver function. Therefore, by generating further data and evidence, it is expected that new HCC strategies can be developed by combining the therapies above alongside treatments with anticancer drugs.

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