─Original─

Impact of Branched-Chain Amino Acid-Enriched Nutrient on liver Cirrhosis with Hepatocellular Carcinoma Undergoing Transcatheter Arterial Chemoembolization in Barcelona Clinic Liver Cancer Stage B: A Prospective Study

Shunichi Shiozawa, Takebumi Usui, Kotaro Kuhara, Akira Tsuchiya, Tatsuomi Miyauchi, Teppei Kono, Shinichi Asaka, Kentaro Yamaguchi, Hajime Yokomizo, Takeshi Shimakawa, Kazuhiko Yoshimatsu, Takao Katsube and Yoshihiko Naritaka

Department of Surgery, Tokyo Women's Medical University Medical Center East, Tokyo, Japan

Background: In decompensated liver cirrhosis, hypoalbuminemia still persists even after they have been treated with branched-chain amino acid (BCAA) granules. We prospectively evaluated whether BCAA enriched nutrient switched from BCAA granules would increase the serum albumin level, and consequently extend the survival time after hepatocellular carcinoma (HCC) treatment.

Methods: This study included 77 patients treated for liver cirrhosis with HCC. After the nutritional assessment, all patients initially received BCAA granules. In patients with unchanged or decreased serum albumin levels, BCAA granules were discontinued and BCAA enriched nutrient was started. Transcatheter arterial chemembolization (TACE) for HCC were performed in those with an improved Child-Pugh score.

Results: TACE were performed following the aggressive intervention with BCAA nutritional education in 54 of 77 (70.1%) patients. Finally, survival time was significantly extended in the TACE group (P< 0.0001).

Conclusion: Timely aggressive nutritional intervention in Barcelona Clinic Liver Cancer stage B HCC, namely, early partial replacement with BCAA enriched nutrient may consequently improve the treatment outcome of HCC. (J Nippon Med Sch 2016; 83: 248−256)

Key words: liver cirrhosis, hepatocellular carcinoma, transcatheter arterial chemoembolization, branched-chain amino acid, Child-Pugh score

Introduction

Hepatocellular carcinoma (HCC) is one of the high incidence cancer in the world[1], and its rate has also increased over the last decade. Curative treatment approaches including surgical hepatectomy, liver transplant and local treatment of radiofrequency ablation (RFA) are indicated for 30% to 60% of all HCC[1,2]. Transcatheter arterial chemoembolization (TACE) will be used in other patients with a specific severity of liver damage, specifically, Barcelona Clinic Liver Cancer (BCLC) stage B (intermediate stage) HCC[3-5]. Since patients with intermediate-stage HCC have varying tumor backgrounds and liver damage

severity, the prognostic impact of TACE on HCC may also vary among patients.

After TACE was found to be involved in HCC prognosis in recent years[6,7], Bolondi et al.[8] advocated segmentalizing the intermediate stage for a clear definition of the indication of TACE to improve the situation described earlier. The Child-Pugh score is used as an important factor to indicate the liver damage severity in the BCLC staging. The serum albumin level, one of the basic constituents of the Child-Pugh scoring system, will affect the treatment of HCC because it may be increased by aggressive nutrition therapy. Now branched-chain amino acid

Table 1   Patient baseline demographics and clinical characteristics

Characteristics	No.	%
Age/year, mean (range)	73 (40–84)	
Male	55	71.4
Etiology		
hepatitis B infection	24	31.2
hepatitis C infection	56	72.7
other	4	5.2
Child-Pugh score		
A 5	1	1.3
6	2	2.6
B 7	34	44.2
8	30	40.0
9	10	13.0
Eastern Cooperative Oncology Group performance status		
0	59	76.6
1	12	15.6
2	6	7.8
Symptoms		
ascites	29	37.7
edema	41	53.2
fatigability	35	45.5
muscle clamp	19	24.7
sleep disturbance	14	18.2
Baseline laboratory values		
albumin	3.1±0.4	
total bilirubin	1.5±1.9	
branched-chain amino acid to tyrosine ratio	4.3±1.2	
serum ammonia	26.5±24.9	

(BCAA) is increasingly being used for the treatment of cirrhosis in general when the patient's nutritional status does not improve with appropriate nutritional education[9]. Two types of BCAA products available in Japan, BCAA granules and BCAA enriched nutrient, are often used according to the patient's dietary intake and presence or absence of encephalopathy[10]. In some patients with no encephalopathy and adequate dietary intake, however, hypoalbuminemia still persists even after they have been treated with BCAA granules. They are a group of patients with BCLC stage B HCC not benefiting from TACE. This study focused on the group of patients with persistently low serum albumin levels even after long-term treatment with BCAA granules and prospectively evaluated whether BCAA enriched nutrient switched from BCAA granules would increase the serum albumin level, improve the nutritional status and the general condition, and consequently extend the survival time as part of the HCC treatment.

Patients and Methods

Study Population

This study included 77 patients treated at our hospital for liver cirrhosis (LC) and HCC for which neither RFA nor TACE was indicated between January 2005 and December 2013. The baseline clinical characteristics of the patients are shown in **Table 1**. None of the patients had ever been treated for HCC or taken oral BCAA. All the patients had Eastern Cooperative Oncology Group (ECOG) performance status[11] ≤2, HCC of Child-Pugh class A or B, and baseline BCLC stage B HCC. HCC was comprehensively diagnosed based on dynamic computed tomography, dynamic magnetic reasonance imaging, and tumor markers (AFP, PIVKA-II) blood tests[12].

Study Design and Protocol

The nutritional assessment in all patients consisted of a one-week diary of diet intake and estimation of total daily caloric intake and protein/fat/carbohydrate ratio. Dieticians prescribed a diet limiting the total daily calorie intake to 30 to 35 kcal/kg/day and protein intake to 1.5

Table 2 Contents of branched-chain amino acid-containing medicines

	Granules (Livact)	Enriched nutrient (Aminoleban EN)
Calories (kcal)	4.15 g/16	50 g/210
Branched-chain amino acid (g)	4.0	6.1
L-isoleucine (mg)	952	1,922
L-leucine (mg)	1,904	2,037
L-valine (mg)	1,144	1,602
Aromatic amino acid (g)	-	0.21
Fischer ratio	-	38
Protein (g)	-	13.5
Carbohydrate (g)	-	31.1
Fat (g)	-	3.5
Vitamins§	-	+
Minerals¶	-	+

§Vitamins include retinol palmitate, ergocalciferol, bisbentiamine, riboflavin, pyridoxine HCL, cyanocobalamin, folic acid, sodium L-ascorbate, tocopherol acetate, phytonadione, calcium pentothenate, nicotinamide and biotin

¶Minerals include trace amounts of magnesium sulphate, calcium glycerophosphate, potassium iodine, potassium chloride, sodium dihydrogen phosphate, sodium ferrous citrate, cupric sulphate, zinc sulphate and manganese sulphate

g/kg/day to the patients based on the estimation. The ingredients and composition of 2 types of BCAA products used in this study are shown in **Table 2**. All patients initially received BCAA granules (LIVACT 4.74 g; L-isoleucine, L-leucine and L-valine granules; Ajinomoto Pharma Co., Ltd, Tokyo, Japan) 3 times a day after meals[13]. TACE was performed for the treatment of HCC in patients with increased serum albumin levels and improved Child-Pugh score at 3 months. In patients with unchanged or decreased serum albumin levels, BCAA granules were discontinued with their consent and BCAA enriched nutrient (Aminoleban EN powder mix; Otsuka Pharmaceutical Co., Ltd, Tokyo, Japan) was started twice a day after breakfast and before bedtime as a late evening snack for another 3 months[14]. The protein and calorie intake from meals was reduced to about 50 g/day and about 1,500 to 1,700 kcal/day, respectively, while the patients were receiving BCAA enriched nutrient. Patients with lactose intolerance were excluded since BCAA enriched nutrient is a semi-digested nutrient containing casein. The Child-Pugh score and the change of symptoms were evaluated in patients receiving BCAA enriched nutrient at 3 months[15], and TACE was performed for the treatment of HCC in those with an improved Child-Pugh score. The efficacy of TACE was evaluated by dynamic computed tomography at about 1 month. TACE was performed every 3 to 4 months in patients with inadequate response to the first TACE or enlarged tumor as long as the severity of liver damage was acceptable. The study protocol specified an eleven-year observation period from January 2005 to December 2015. The study treatment was administered to only patients who had given written informed consent. This study conformed to the Declaration of Helsinki and was approved by the institutional ethical review board of our hospital.

Procedure of TACE

The application of TACE to HCC in this study is patient's Child-Pugh score 5 to 7 with total bilirubin level <2.0 mg/dL and besides nothing of ascites. As previously reported[16,17], a 4-Fr catheter was inserted into the left radial artery, and super selective embolization was performed on the tumor with staining on hepatic arteriography concurrently using a microcatheter in the TACE procedure. Miriplatin (miriplatin hydrate, Sumitomo Dainippon Pharma Co., Ltd, Osaka, Japan) 40 to 80 mg/body and iodized oil (Lipiodol; Lipiodol Ultrafluide, Laboratoire Guerbet, Aulnay-sous-Bois, France) were mixed at an equal ratio and injected during the embolization according to the diameter and number of tumors. Porous gelatin granules (Gelpart; Nippon Kayaku Co., Ltd, Tokyo, Japan) were used as the embolization material. Tu-
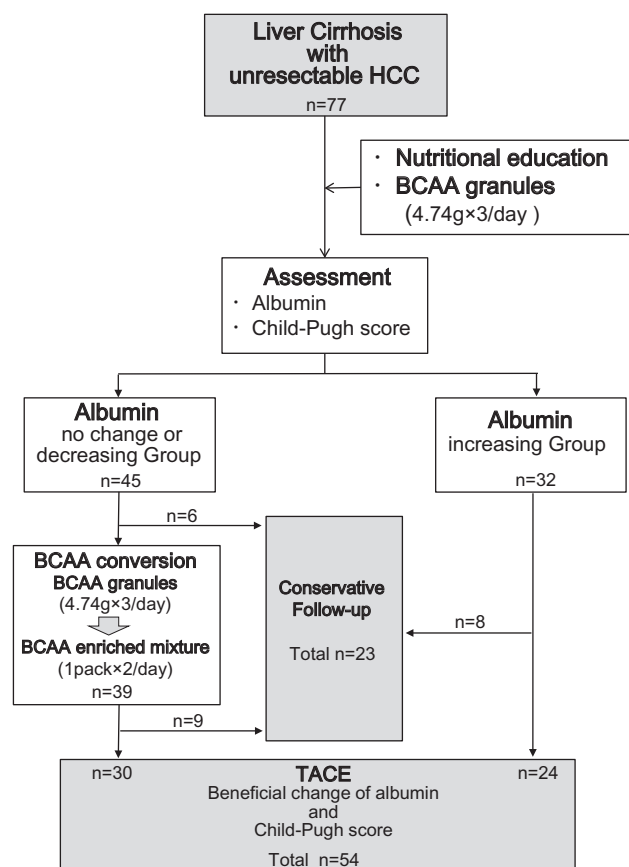
Fig. 1 Therapeutic consequences

mors and tumor vessels filled with the drug were confirmed on the fluoroscopic monitor to complete the procedure.

Clinical Endpoint

The serum albumin level and branched-chain amino acid to tyrosine ratio (BTR) were measured before and after starting BCAA granules and after switching to BCAA enriched nutrient every month. In patients who switched to BCAA enriched nutrient, the change of symptoms was evaluated using the Short Form-8 (SF-8)[18] every month. Overall survival was compared between patients who had undergone TACE and those with untreated BCLC stage B HCC to evaluate whether TACE affected the prognosis of HCC.

Statistical Analysis

Changes in the serum albumin level and BTR were analyzed using analysis of variance. The Kaplan-Meier method was used for the comparison of the survival rate between the patient groups, followed by a log-rank test. A statistical significance level of $P<0.05$ and the standard statistical software (JMP Pro version 8.02 software for Windows, SAS institute, Cary, NC, USA) were used for all the analyses.

Results

Changes of Nutrition Balance

The total calorie and protein intake from meals (30 to 35 kcal/kg/day and 1.5 g/kg/day, respectively) were determined based on the average body size of Japanese cirrhosis patients. According to the dieticians' assessment, however, the mean total calorie and protein intake in 77 patients were below the required level: 1,880 kcal and 72 g, respectively. Fat and carbohydrate accounted for 90% of the total calorie intake, suggesting unbalanced diet and low-protein/poor nutritional condition of the patients. The intervention by dieticians with the nutritional education and the use of BCAA granules increased the total daily calorie intake to 2,040 kcal ($P=0.0243$) and the protein intake to 75 g ($P=0.0621$). The proportion of fat and carbohydrate in the total calorie intake decreased to about 85%. The total daily calorie intake and protein intake significantly increased to 2,200 kcal ($P=0.082$) and 85 g ($P=0.0226$), respectively, in patients who switched from BCAA granules to BCAA enriched nutrient.

Therapeutic Consequences

The intervention with nutritional education and the use of BCAA granules increased the serum albumin level in 32 of 77 (41.6%) patients. Of those with an unchanged serum albumin level (n=45; 58.4%), BCAA granules were switched to BCAA enriched nutrient in 39 (86.7%) patients with their consent. Six patients did not give consent to the treatment switch and continued to receive BCAA granules. The Child-Pugh score improved in 30 of 39 (76.9%) patients at 3 months of using BCAA enriched nutrient. TACE was performed in all 30 patients. Thus, TACE was performed for the treatment of HCC following the aggressive intervention with nutritional education and BCAA in 54 of 77 (70.1%) patients. The mean number of TACE procedures performed was 3.1 (range, 1 to 6). Twenty-three patients who did not undergo TACE were followed without treatment for HCC. Only a subjective symptom assessment was made in these patients (**Fig. 1**).

Changes of Serum Albumin and BTR

From baseline to 3 months after switching to BCAA enriched nutrient (n=39), the serum albumin level slightly increased during the treatment with BCAA granules ($P=0.0682$) and significantly increased after switching to BCAA enriched nutrient ($P=0.0004$). The change in BTR was comparable to the serum albumin level, which significantly increased after switching to BCAA enriched nutrient ($P<0.0001$; **Fig. 2a**). On the other hand, there were no remarkable change of serum albumin level (P=
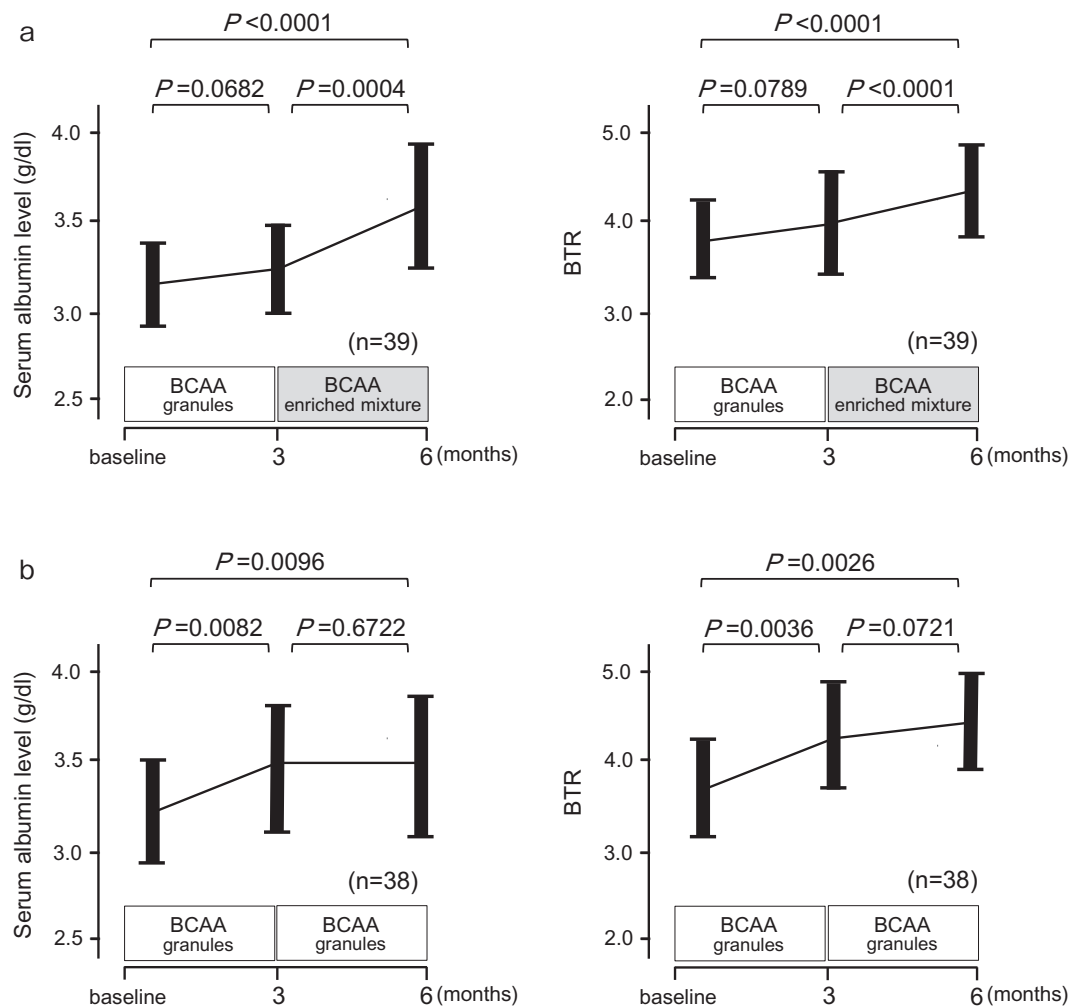
Fig. 2 Changes of Albumin level and branched-chain amino acid to tyrosine ratio (BTR): Sequential changes in serum albumin level and BTR at three months using branched-chain amino acid (BCAA) granules and after 3 months switched BCAA enriched nutrient. Albumin level and BTR were significantly increased in parallel from baseline after switching BCAA enriched nutrient (P<0.0001) (2a). There were 38 patients with increased serum albumin level and BTR after 3 months using BCAA granules, but further improvements were not observed significantly (P=0.6722, P=0.0721) (2b).

0.6722) and BTR (P=0.0721) after 3 months or later in albumin increasing group (n=38; **Fig. 2b**).

Changes of Child-Pugh Score

Figure 3 illustrates the result of Child-Pugh score after switching BCAA enriched nutrient from BCAA granules group (n=39) and BCAA granules continuing group (n=38). In patients with unchanged serum albumin level, Child-Pugh score improved at 3 months of using BCAA enriched nutrient. Besides, over 80 percent of them were assessed liver damages as Child-Pugh score 5 to 7 (P=0.0020). The patients who continued to receive BCAA granules were not remarkable change of Child-Pugh score over the last 3 months period (**Fig. 3**).

Changes of Symptom

Change of symptoms after using BCAA was evaluated based on SF-8. Although not significant, only edema tented to improve, decreasing from 53.2% to 39.0% after using BCAA granules (P=0.0754). After switching to BCAA enriched nutrient, ascites (P=0.001), edema (P< 0.0001), and muscle cramp in lower limbs (P=0.0007) were significantly improved. General fatigue and sleep disturbance did not improve with either of the BCAA products (**Table 3**).

Overall Survival Analysis

Overall survival was compared between 54 patients who underwent TACE for HCC and 23 patients who were followed without treatment. The 1- and 3-year sur-
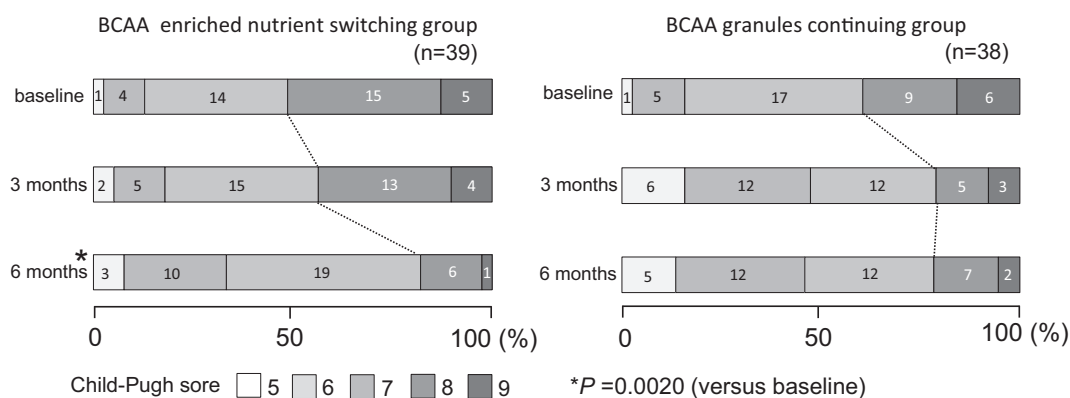
Fig. 3 Changes of Child-Pugh score: Finally, patients in Child-Pugh scores of 5 to 7 accounted for more than 80% of branched-chain amino acid enriched nutrient switching group (n=39) after 6 months (P=0.0020). But there were no significant changes throughout the course of branched-chain amino acidTa granules continuing group (n=38) (P=0.1387), and was no remarkable distribution of Child-Pugh score over the last three-month period.

Table 3   Changes in symptoms after using branched-chain amino acid products

(n=77)

Symptom	Patient baseline number	Branched-chain amino acid granules 3 months after	Branched-chain amino acid switching 3 months after	p-value
Ascites	29 (37.7%)	25 (32.5%)	9 (11.7%)*	0.0010
Edema	41 (53.2)	30 (39.0)	12 (15.6)**	<0.0001
Fatigability	35 (45.5)	31 (40.3)	25 (32.5)	0.2521
Muscle clamp	19 (24.7)	18 (23.4)	3 (3.9)***	0.0007
Sleep disturbance	14 (18.2)	13 (16.9)	9 (11.7)	0.5011

*p=0.0002 **p<0.0001 ***p=0.0002 (versus baseline)

vival rates were 97% and 56% in the TACE group, respectively. In the no treatment group, the 1-year survival rate was relatively good (92%) but the 3-year survival rate was low (12%). The survival time was significantly extended in the TACE group (P<0.0001) (**Fig. 4a**). This trend was almost similar in BCAA enriched mixture switching group (P=0.0004) (**Fig. 4b**) and in BCAA granules continuing group (P=0.0001) (**Fig. 4c**). In undergoing TACE group, the 1- and 3-year survival rate was 100% and 61% in the BCAA mixture switching patients, on the other hand 95% and 44% in BCAA granules continuing patients (P=0.0294).

Discussion

After being developed in Japan[19], TACE was shown to be effective in 2 randomized controlled trials[6,20]. The procedure is now defined as an essential treatment for HCC together with hepatectomy and RFA in the BCLC staging system[21]. In practice, the curative treatment including hepatectomy and RFA is indicated only for 30% to 60% of

HCC. Many of the remaining cases will be candidates for TACE. The reasonable indication of TACE is BCLC stage B (intermediate stage) HCC, specifically, performance status 0, Child-Pugh class A or B, and 4 or more tumors or multiple tumors of which at least one is >3 cm³. Although TACE has been shown to extend the survival time compared with the supportive therapy[22], TACE may affect the prognosis differently in patients with varying tumor background and liver damage severity defined as BCLC stage B HCC. In Europe, BCLC stage B is now further segmentalized based on the Child-Pugh score and the up-to-7 criteria to determine the optimal treatment according to the sub-classes[8]. This study focused on patients whose Child-Pugh score improved with BCAA supplementation to define a patient group with BCLC stage B HCC that would benefit from TACE and evaluate whether BCAA would favorably affect the treatment outcome of concurrent HCC.

A variety of dysfunctions are generally involved in decompensated LC, likely leading to complications such as
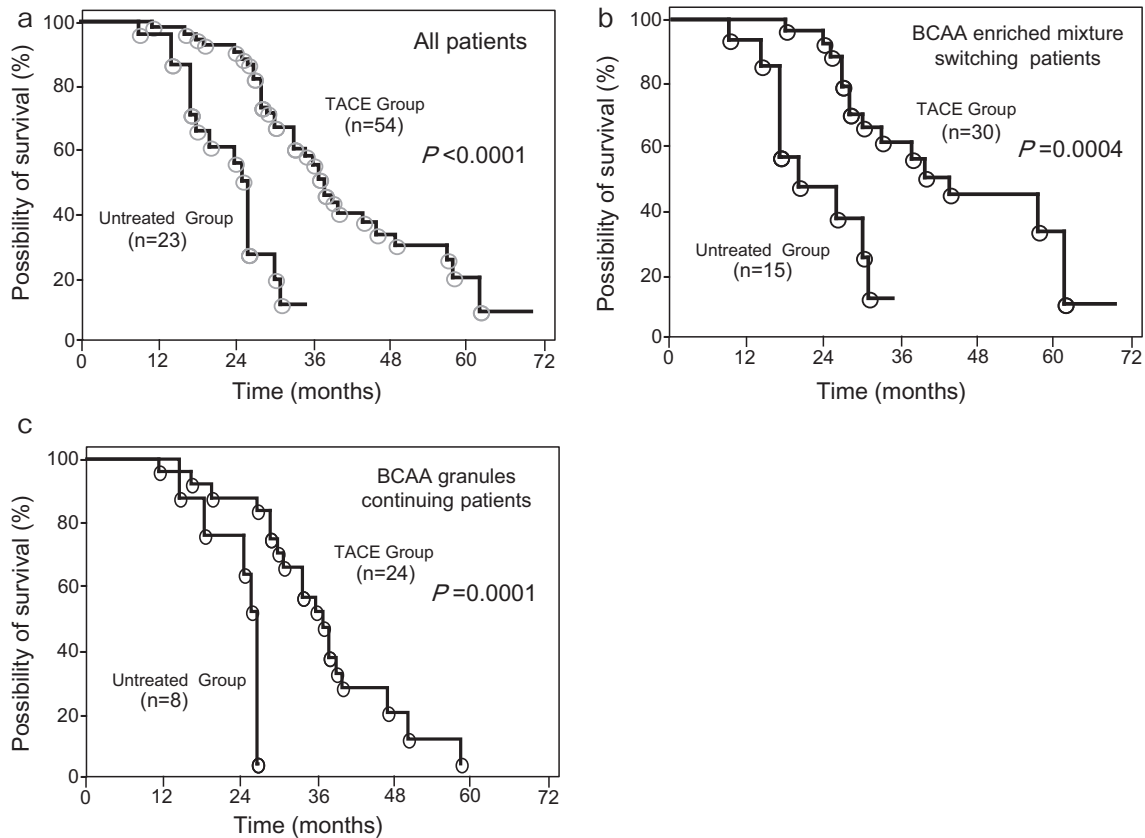
Fig. 4 Overall survival analysis: Kaplan-Meire curves for transcatheter arterial chemoembolization (TACE) group (n=54) and untreated group (n=23). The survival time was significantly extended in the TACE group (*P*<0.0001) (a). The survival time in branched-chain amino acid enriched mixture switching and undergoing TACE group was significantly longer than that in untreated group (*P*=0.0004) (b). It showed a similar trend in branched-chain amino acid granules continuing patients (*P*=0.0001) (c).

malnutrition, ascites, edema, and hepatic encephalopathy. Nutrition therapy is the core of the LC treatment since the complications greatly affect the life prognosis and quality of life[23]. However, nutrition therapy solely relying on the unsupervised diet of the patient or nutritional education provided by dieticians are effective only to a certain extent. This study found the aggressive nutritional intervention with BCAA was mandatory. Decompensated LC is defined as protein-energy malnutrition[24]. Patients can receive high Fischer ratio protein without changing the total amount of calorie/protein intake by partially replacing their diet with BCAA enriched nutrient. The serum albumin level and BTR significantly increased, and ascites, edema, and muscle cramp decreased with the improved nutritional condition. About 77% of the patients became eligible to undergo TACE with an improved Child-Pugh score after the aggressive intervention with BCAA enriched nutrient. This study showed the survival time of HCC patients was significantly extended for the first time. Among patients with BCLC

stage B HCC with varying tumor background and liver damage severity, those with an improved Child-Pugh score after an aggressive nutritional intervention may likely benefit from TACE. BCAA granules should be switched to BCAA enriched nutrient in patients unresponsive to the former even if they have no encephalopathy.

The significance of metabolic syndrome has been emphasized in recent years in Japan and worldwide. Obesity is a risk factor for progression of LC[25]. A recent study found more than 50% of LC patients were in the state of protein-energy malnutrition but about 30% of them had an estimated BMI of ≥25[24]. A multicenter randomized controlled study in patients with decompensated LC identified obesity as a risk factor for HCC[26]. Supplementation with BCAA enriched nutrient containing balanced vitamin/mineral/sugar/fat is quite beneficial for LC patients compared with BCAA granules since the nutrients are easily depleted. However, accurate "partial replacement" should be ensured to avoid excess in total daily

calorie intake when giving BCAA enriched nutrient (210 kcal/pack) twice a day, including late evening snack.

This study had the following limitations. First, the total calorie intake from meals and BCAA were self-reported by patients and may not have been accurate. We need more patient's support for BCAA treatment adherence to be successful[27]. Second, this study was prospectively designed but unfortunately failed to stratify the patients with BCLC stage B HCC because of the small sample size of 77 from a single institution. We concluded that BCAA-rich formula was beneficial, it can't deny the possibility that "carry-over" effect of BCAA granules might be present in BCAA-rich formula period. But randomization at 3 months in unchanged albumin group was not appropriate approach in terms of disadvantage to improvement in liver damages.

Third, TACE was performed in the aforementioned procedure in this study. The treatment outcome may have been better if the other procedure reported in a recent study[28] had been used.

In conclusion, the serum albumin level is expected to be low especially when decompensated LC is diagnosed based on mild edema. Therefore, the amino-acid balance should always be evaluated based on the Fischer ratio or BTR in patients with decompensated LC for timely aggressive nutritional intervention. Early partial replacement with BCAA enriched nutrient, to ensure high Fischer ratio protein in the patient's diet may consequently improve the treatment outcome of HCC.

Conflict of Interest: The authors declare no conflict of interest.

References

1. Llovet JM, Burroughs A, Bruix J: Hepatocellular carcinoma. Lancet 2003; 362: 1907−1917.
2. El-Serag HB, Rudolph KL: Hepatocellular carcinoma epidemiology and molecular carcinogenesis. Gastroenterology 2007; 132: 2557−2576.
3. de Lope CR, Tremosini S, Forner A, Reig M, Bruix J: Management of HCC. J Hepatol 2012; 56 (Supple 1): S75−S87.
4. Dufour JF, Bargellini I, De Maria N, De Simone P, Goulis I, Marinho RT: Intermediate hepatocellular carcinoma: current treatments and future perspectives. Ann Oncol 2013; 24 (Supple 2): ii24−ii29.
5. Yamakado K, Miyama S, Hirota S, Mizunuma K, Nakamura K, Inaba Y, Yamamoto S, Matsuo K, Nishida N, Aramaki T, Anai H, Kora S, Oikawa S, Watanabe K, Yasumoto T, Furuichi K, Yamaguchi M: Prognosis of patients with intermediate-stage hepatocellular carcinomas based on the Child-Pugh score: subclassifying the intermediate stage (Barcelona Clinic Liver Cancer stage B). Jpn J Radiol 2014; 32: 644−649.
6. Lo CM, Ngan H, Tso WK, Liuel L, Lam CM, Poon RT, Fans T, Wong J: Randomized controlled trial of transarterial lipidol chemoembolization for unresectable hepatocellular carcinoma. Hepatology 2002; 35: 1164−1171.
7. Camma C, Schepis F, Orlando A, Albanese M, Shehied L, Trevisawi F, Andreone P, Craxi A, Cottone M: Transarterial chemoembolization for unresectable hepatocellular carcinoma: meta-analysis of randomized controlled trials. Radiology 2002; 224: 47−54.
8. Bolondie L, Burroughs A, Dufour JF, Galle PR, Mazzaferro V, Piscaglia F, Raoul JL, Sangro B: Heterogeneity of patients with intermediate (BCLB B) hepatocellular carcinoma: proposal for a subclassification to facilitate treatment decisions. Semin Liver Dis 2012; 32: 348−359.
9. Ishihara T, Iwasa M, Tanaka H, Kaito M, Ikoma J, Shibata T, Takei Y: Effect of branched-chain amino acids in patients receiving intervention for hepatocellular carcinoma. World J Gastroentrol 2014; 20: 2673−2680.
10. Sato S, Watanabe A, Muto Y, Suzuki K, Kato A, Moriwaki H, Kato M, Nakamura T: LIV-EN Study Group: Clinical comparison of branched-chain amino acid (L-leucine, L-isoleucine, L-valine) granules and oral nutrition for hepatic insufficiency in patients with decompensated liver cirrhosis (LIV-EN study). Hepatol Res 2005; 31: 232−240.
11. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP: Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5: 649−655.
12. Ichikawa T, Kumazaki T: Clinical usefulness of computed tomography arteriography and computed tomography during arterial portography for the diagnosis of early and early advanced hepatocellular carcinoma. J Nippon Med Sch 2000; 67: 105−109.
13. Muto Y, Sato S, Watanabe A, Moriwaki H, Suzuki K, Kato A, Kato M, Nakamura T, Higuchi K, Nishiguchi S, Kumada H: Long-Term Survival Group: Effects of oral branched-chain amino acid granules on event-free survival in patients with liver cirrhosis. Clin Gastroenterol Hepatol 2005; 3: 705−713.
14. Poon RTP, Yu WC, Fan ST, Wong J: Long-term oral branched chain amino acids in patients undergoing chemoembolization for hepatocellular carcinoma: a randomized trial. Aliment Pharmacol Ther 2004; 19: 779−788.
15. Tsuda Y, Fukui H, Sujishi T, Ohama H, Tsuchimoto Y, Asai A, Fukunishi S, Higuchi K: Is administrating branched-chain amino acid-enriched nutrition achieved symptom-free in malnourished cirrhotic patients? J Clin Biochem Nutr 2014; 54: 51−54.
16. Shiozawa S, Tsuchiya A, Endo S, Kato H, Katsube T, Kumazawa K, Naritaka Y, Ogawa K: Transradial approach for transcatheter arterial chemoembolization in patients with hepatocellular carcinoma: comparison with conventional transfemoral approach. J Clin Gastroenterol 2003; 37: 412−417.
17. Shiozawa S, Usui T, Kuhara K, Tsuchiya A, Miyauchi T, Yamaguchi K, Yokomizo H, Shimakawa T, Yoshimatsu K, Katsube T, Naritaka Y: Does interventional radiological treatment (transcatheter arterial chemoembolizaion/transradial infusion) improve the prognosis of patients with unresectable and recurrent hepatocellular carcinomas? Gan To Kagaku Ryoho 2013; 40: 1819−1821.
18. Turner-Bowker DM, Bayliss MS, Ware JE Jr, Kosinski M: Use fullness of the SF-8 Health Survey for comparing the impact of migraine and other conditions. Qual Life Res 2003; 12: 1003−1012.
19. Yamada R, Sato M, Kawabata M, Nakatsuka H, Naka-

mura K, Takashima S: Hepatic artery embolization in 120 patients with unresectable hepatoma. Radiology 1983; 148: 397−401.

20. Llovet JM, Real MI, Montana X, Planas R, Coll S, Aponte J, Ayuso C, Sala M, Muchart J, Sola R, Rodes J, Bruix J: Barcelona Liver Cancer Group: Arterial embolization or chemoembolization versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomized controlled trial. Lancet 2002; 359: 1734−1739.

21. Bruix J, Sherman M: Management of hepatocellular carcinoma. Hepatology 2005; 42: 1208−1236.

22. Camma C, Schepis F, Orlando A, Albanese M, Shahied L, Trevisani F, Andreone P, Craxi A, Cottone M: Transarterial chemoembolization for unresectable hepatocellular carcinoma: Meta-analysis of randomized controlled trials. Radiology 2002; 224: 47−54.

23. Plauth M, Cabré E, Riggio O, Assis-Camilo M, Pirlich M, Kondrup J, DGEM (German Society for Nutritional Medicine), Ferenci P, Holm E, Vom Dahl S, Müller MJ, Nolte W, ESPEN (European Society for Parenteral and Enteral Nutrition): ESPEN guidelines on enteral nutrition: Liver disease. Clin Nutr 2006; 25: 285−294.

24. Shiraki M, Nishiguchi S, Saito M, Fukuzawa Y, Mizuta T, Kaibori M, Hanai T, Nishimura K, Shimizu M, Tsurumi

H, Moriwaki H: Nutritional status and quality of life in current patients with liver cirrhosis in 2007-2011. Hepatol Res 2013; 43: 106−112.

25. Yu MW, Shih WL, Lin CL, Liu CJ, Jian JW, Tsai KS, Chen CJ: Body-mass index and progression of hepatitis B: a population-based cohort study in men. J Clin Oncol 2008; 26: 5576−5582.

26. Muto Y, Sato S, Watanabe A: Overweight and obesity increase the risk for liver cancer in patients with liver carcinogenesis in heavier patients with liver cirrhosis. Hepatol Res 2006; 35: 204−214.

27. Takaguchi K, Moriwaki H, Doyama H, Iida M, Yagura M, Shimada N, Kang M, Yamada H, Kumada H: Effects of branched-chain amino acid granules on serum albumin level and prognosis are dependent on treatment adherence in patients with liver cirrhosis. Hepatol Res 2013; 43: 459−466.

28. Nishikawa H, Kita R, Kimura T, Osaki Y: Transcatheter arterial embolic therapies for hepatocellular carcinoma: A literature review. Anticancer Res 2014; 34: 6877−6886.