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Review Article

Efficacy of Branched-Chain Amino Acid Supplementation in the Nutritional Strategy for Patients with Liver Cirrhosis

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Abstract

Liver cirrhosis often has Protein-Energy Malnutrition (PEM). Administration of Branched Chain Amino Acids (BCAA) in nutritional intervention could improve of PEM for patients with cirrhosis. Moreover, administration of BCAA significantly inhibited liver carcinogenesis, and is an important strategy for improving prognosis of hepatocellular carcinoma (HCC). Hence, BCAA / Tyrosine Ratio (BTR) predict serum albumin level changes, so the timing of administration of BCAA can also be predicted.

Therapeutic intervention of BCAA using BTR as a prognostic marker contributes to liver cirrhosis and hepatocellular carcinoma patients liver reserve improvement and is expected to contribute to survival.

Introduction

The liver is the main organ of "metabolism/nutrition", and in liver cirrhosis various "metabolic/nutritional" disorders occur. That is, many patients with cirrhosis complicated Protein-Energy Malnutrition (PEM), especially in the decompensated state [1]. In order to improve the prognosis of patients with cirrhosis, it is extremely important to improve PEM. In this article, clinical significance of administration of Branched Chain Amino Acids (BCAA) in nutritional intervention for improvement of PEM for patients with cirrhosis will be outlined, including clinical results of our department including hepatocellular carcinoma treatment.

BCAA therapy for liver cirrhosis

Branched Chain Amino Acids (BCAA) generically refer to three types of valine, leucine, and isoleucine, of which essential amino acids have a structure in which the carbon skeleton of the amino acid is not linear but branched. BCAA has the effect of promoting protein synthesis and inhibiting muscle protein collapse, and in particular, leucine plays a central role. Improvement of PEM in patients with liver cirrhosis, improvement of low protein nutritional status, improvement of Fischer ratio described below is important for maintenance of hepatic function reserve and prevention of progression to liver failure, and BCAA supplementation that promotes albumin synthesis has been used for long term administration.

It is reported by multicenter, randomized study that oral supplementation with a BCAA preparation that can be administered for a long period improves event-free survival, serum albumin concentration, and Quality of Life (QOL) in patients with decompensated cirrhosis with an adequate daily food intake [2]. Furthermore, according to a sub-analysis of this study, it was revealed that the risk factors of hepatocellular carcinogenesis are high in males, alphafetoprotein (AFP) level of 20ng/mL or higher, lower serum albumin levels, diabetes mellitus and higher Body Mass Index (BMI), and patients with liver cirrhosis showing obesity with BMI≧25. It was also reported that administration of BCAA significantly inhibited liver carcinogenesis, suggesting the usefulness of BCAA as a preventive measure for hepatocellular carcinoma [3].

Significance of BCAA therapy for treatment of hepatocellular carcinoma

Although the BCAA administration is expected to contribute to the improvement of the prognosis also from the above report, what is the clinical significance in cases of hepatocellular carcinoma, which is the greatest complication of liver cirrhosis?

Radio Frequency Ablation (RFA) for hepatocellular carcinoma is now the standard method for local treatment of hepatic malignancy. However, although RFA is considered to be a relatively less invasive treatment, it is important to consider the influence on hepatic function reserve. On the other hand, in the hepatocellular carcinoma treatment strategy, we must always be conscious of recurrence. The intrahepatic recurrence rate was 17.8% and 44.2%, respectively, 1 and 2 years after RFA in cases where RFA was selected for initial

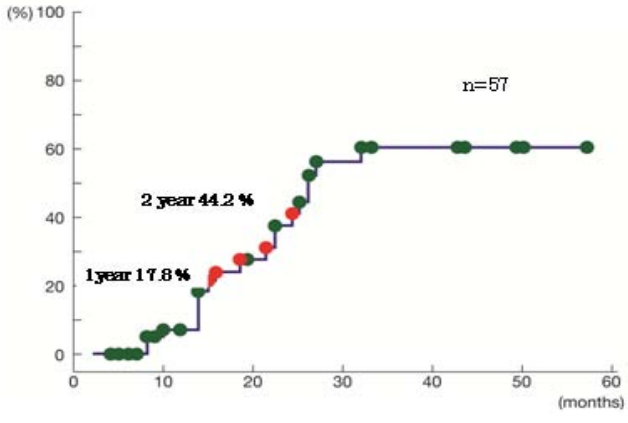

Figure 1: Intrahepatic tumor recurrence rate after RFA.

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Table 1: Risk factors of intrahepatic tumor recurrence in patients with primary HCC by multivariate analysis using the Cox proportional hazard model.

Factor	P value	Hazard Ratio
Child A/B,C	0.039	4.233
Etiology	0.142	2.152
TAE	0.446	0.579

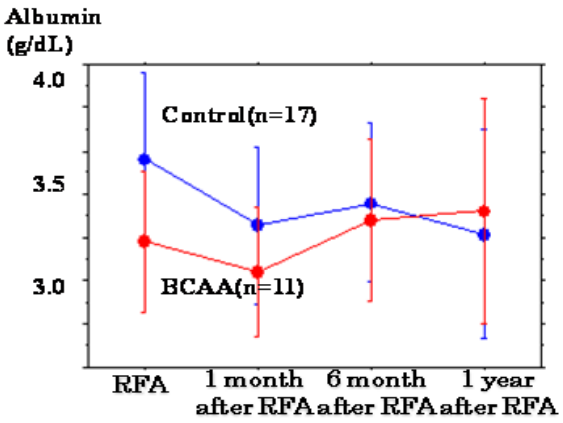

Figure 2: Changes in serum albumin levels after RFA in patients (Child B) treated with BCAA and control.

treatment in cases of hepatocellular carcinoma of the first less than 30 mm in our department (Figure 1) [4]. Multivariate analysis showed that the Child-Pugh grading is the most important factor related to intrahepatic distant recurrence following by RFA. (Table 1). Twenty-eight patients with the Child-Pugh B/C grade who received RFA therapy were divided into two groups: 11 who received a BCAA-enriched nutrient mixture, and17 who did not [4]. Although a tendency toward recovery was noted 6 months after RFA, serum albumin levels tended to decrease one year after RFA to levels lower than its pre-RFA baseline. In comparison to the afore mentioned results of the control group, patients with Child-Pugh B who were administered BCAA formulation after hepatocellular carcinoma RFA showed improvement tendency as suggested by the maintenance of albumin value and hepatic functional reserve [4] (Figure 2). This fact suggests that treatment options for hepatocellular carcinoma recurrence are increased by administration of BCAA formulation, and as a result, improvement of survival of hepatocellular carcinoma is expected to be expected. As our results, Nishiguchi et al. reported that BCAA treatment may improve overall survival and recurrence free survival after RFA in patients with HCV-related HCC ≤ 3 cm in diameter with up to 3 nodules and a serum albumin level before RFA of 3.5 g/dL [5]. In randomized study, BCAA may be beneficial for cirrhotic patients after RFA to relieve mental stress and reduce the risks for intrahepatic recurrence and complications [6]. As this background, supplementation with BCAA granules improves energy metabolism including non-protein Respiratory Quotient (npRQ) in addition to the liver function after RFA [7]. Furthermore, it is notable that BCAA supplementation as a Late-Evening Snack (LES) significantly and rapidly improves liver functioning and Child Pugh score in cirrhotic patients who have undergone RFA for HCC [8]. Hence, Transcatheter Arterial Chemo Embolization (TACE) is the standard therapy for Barcelona Clinic Liver Cancer (BCLC) classification intermediate stage B HCC. For TACE, a BCAA supplement taken orally as LES prevents suppression of liver function by TACE in patients with cirrhosis complicated with HCC during the 2-week period after TACE [9].

As above, BCAA administration is an important strategy for improving prognosis of HCC.

When should BCAA be administered?

In liver cirrhosis, fluctuation of plasma free amino acid concentration was observed, a marked decrease in Branched Chain Amino Acids (BCAA; valine, leucine, isoleucine) and an increase in Aromatic Amino Acids (AAA; tyrosine, phenylalanine, methionine) etc. were observed and BCAA / AAA molar concentration ratio (Fischer ratio) or branched chain amino acid / tyrosine molar ratio (BCAA / tyrosine ratio; BTR) decreases with the severity of the lesion. Fisher ratios have been used for a long time as plasma free amino acid analysis [10], but BTR is more simplified. Azuma and colleagues pointed out that the BCAA / Tyr ratio by the enzyme method could be an indicator of hepatic injury as a substitute for the Fischer ratio, and then reflect the progress of chronic liver disease [11].

In clinical practice, among cases of cirrhosis in which serum albumin was kept at 3.6 g/ dL or more, there are many cases in which the amino acid imbalance has progressed as BTR is 4.0 or less (normally 6.0 to 8.0). Nishiguchi and colleagues studied and reported the clinical significance of long-term BCAA administration by stratifying into three groups by serum albumin and BTR. Class 1 was decompensated cirrhosis with serum albumin level less than 3.5mg/dl. Class 2 was compensated cirrhosis with serum albumin level over 3.6 mg/dl and molar ratio of BCAA to Tyrosine (BTR) less than 4. Class 3 was compensated cirrhosis with serum albumin level over 3.6 mg/dl and BTR over 4. In class 1 and class 2, the BCAA group exhibited significantly higher rates of maintaining serum albumin level than the control group for 2 years. In contrast, there was no significant difference between the BCAA group and control group in rate of maintaining serum albumin levels in class 3. Thus, even in cases where there is no hypoproteinemia in the early stage of cirrhosis, if there is amino acid imbalance, it is considered significant to administer BCAA preparation from the early stage [12].

Furthermore, changes in serum albumin levels can be predicted by measuring BTR, so the timing of administration of BCAA formulation can also be predicted. That is, when the nutritional

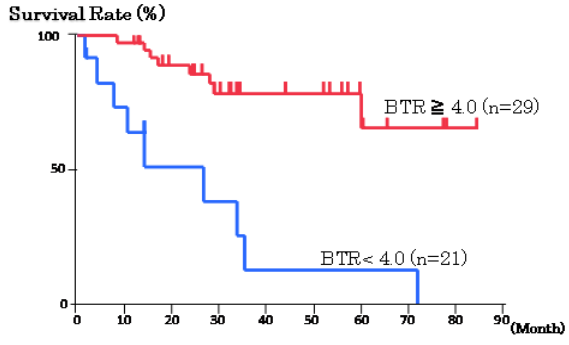

Figure 3: Cumulative survival of Stage I/II HCC patients according to BTR levels.

Table 2: Multivariate analysis of factors associated with intrahepatic distant recurrence of hepatocellular carcinoma.

Variables		Hazard ratio	95% confidence interval	*p* value
BTR	>4.0/≤4.0	0.27	0.11-0.66	0.0038
Albumin (g/dL)	>3.5/≤3.5	0.68	0.29-1.57	0.3668

Table 3: Multivariate analysis of factors associated with survival.

Variables		Hazard ratio	95% confidence interval	*p* value
BTR	>4.0/≤4.0	0.31	0.09-0.90	0.0314
Albumin (g/dL)	>3.5/≤3.5	0.29	0.07-0.92	0.0356

status is poor, since the BTR decreases before the decrease in serum albumin value, measurement of BTR is useful for early detection of a preliminary group of hypoalbuminemia [13]. Because of this time lag between serum albumin value and BTR, there is a need to separately monitor serum albumin and BTR when considering the prognostic factors of decompensated cirrhosis. The usefulness of administration of BCAA preparation has already been reported in large scale clinical trials for patients with decreased BTR and in this sense also the possibility that measurement of BTR becomes one of prognostic factors of decompensated cirrhosis patients. Treatment intervention of early BCAA granules in patients with lower BTR can contribute to the improvement of prognosis of decompensated cirrhosis. Moreover, treatment intervention of BCAA formulation in hepatocellular carcinoma treatment is expected to improve not only hepatic functional reserve but also Quality of Life (QOL).

We conducted a cohort study of 50 patients with stage I/II HCC. It was investigated whether BTR can serve as both a prognostic factor and a predictive factor for HCC recurrence. Overall survival rates were significantly higher in patients with high baseline BTR than in those with low BTR (Figure 3) [14]. Multivariate analysis showed that both BTR and serum albumin were prognostic factors, and that BTR was the best predictive factor for recurrence. BTR was a prognostic factor for early HCC and the most predictive factor for intrahepatic distant recurrence and contributing factors for survival (Table 2, 3).

Early BCAA treatment intervention based on BTR is a future task, and the effect of inhibiting carcinogenesis by BCAA preparation should also be demonstrated by large-scale research.

Conclusion

Measurement of BTR may determine the timing of application of BCAA formulation. Therapeutic intervention of BCAA formulation using BTR as a prognostic marker contributes to liver cirrhosis and hepatocellular carcinoma patients liver reserve improvement and is expected to contribute to survival.

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