6 T-Bil elevation;
7 Amylase elevation;
8 Electrolyte abnormality (hyponatremia, hypokalemia, hypocalcemia, hypophosphatemia);
9 Hypoalbuminemia.

Scientific statement The incidence of sorafenib-related AEs was 80% in the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) trial and 81.9% in the Asia-Pacific trial. Frequently occurring AEs were HFSR, rash/desquamation, diarrhea, anorexia, hypertension, fatigue, alopecia, and nausea.[1,2]

Sorafenib-related AE incidence in the NLCT study was 87%, of which 36% were ≥grade 3 AEs. While incidences of HFSR, diarrhea and alopecia in the NLCT study were similar to those of the Asia-Pacific trial[2] and SDUS,[6] incidences of rash/desquamation, anorexia, hypertension and fatigue were slightly higher in the present study (Table 2).

Evaluation of changes in clinical laboratory data was achieved by examining the CRFs to find the largest variations during sorafenib therapy, as well as the test date on which variations occurred. Consequently, the frequency of abnormal values in the NLCT study differed from those of the SHARP trial[1] and SDUS[6] (Table 3).

Changes in laboratory values were seen in 96% of the sorafenib group, with 64% showing an AE ≥ grade 3. Incidence of diminished blood cell counts was high compared with previous studies, with thrombocytopenia, leukopenia, neutropenia, and anemia seen in 56%, 43%, 37%, and 34% of the sorafenib group, respectively.

Hepatic impairment was also frequent, with elevated AST and ALT occurring in ≥50% of sorafenib-treated patients (70% and 55%, respectively), of whom a further 25% and 15% had AST and ALT readings ≥grade 3, indicating levels exceeding 200 IU/L after commencement of treatment. Similar results were observed for ALP and γ-GTP. Elevated T-Bil was seen in 53% of the sorafenib group, of whom 11% had readings that were ≥grade 3, which is more than three times the upper limit of normal (ULN).

Increased amylase was seen in 49% of the sorafenib group, of whom 12% had levels ≥grade 3, which is more than twice the ULN. In terms of electrolyte abnormalities, hyponatremia and hypokalemia were observed in 50% and 25% of the sorafenib group, respectively. Hypocalcemia and hypophosphatemia were also seen in ≥50% of the sorafenib group, but the valid response rate was low for these variables.

Hypoalbuminemia was seen in 48% of the sorafenib group, of whom only 5% had readings <2.0 g/dL.

No significant difference was seen in AE incidences for Child–Pugh class A and B patients, at 88% and 83%, respectively ($P = 0.53$). The incidence of AEs ≥grade 3 was also insignificant between Child–Pugh class A and B patients (35% vs. 39%, $P = 0.76$).

Similar comparisons for sorafenib group patients with Child–Pugh class A scoring 5 and 6 also did not reveal any significant differences in either total incidence of AEs at 89% and 88%, respectively ($P > 0.99$), or in the incidence of AEs ≥ grade 3, at 35% each ($P > 0.99$).

Incidence of abnormal laboratory data also did not vary significantly among Child–Pugh class A and B patients, at 96% and 95%, respectively ($P > 0.99$). Similarly, no significant difference was observed in the incidence of abnormal laboratory data ≥grade 3, at 63% and

Table 2 Incidence of drug-related adverse events with sorafenib therapy

AE	NLCT Study ($n = 264$)		SDUS[6] ($n = 777$)		SHARP Trial[1,6] ($n = 267$)		Asia-Pacific Trial[2] ($n = 149$)	
	Total (%)	G3/4 (%)	Total (%)	SAEs (%)	Total (%)	G3/4 (%)	Total (%)	G3/4 (%)
HFSR	44	10	47.9	2.8	21.2	7.7	45.0	10.7
Rash/desquamation	31	5	20.7	3.1	15.8	1.08	21.1	0.7
Diarrhea	32	5	21.9	1.4	39.1	8.4	25.5	6.0
Anorexia	27	4	13.8	1.9	13.8	0.3	12.8	0
Hypertension	26	8	19.2	0.6	5.1	1.7	18.8	2.0
Fatigue	24	2	4.6	0.6	–	–	20.1	3.4
Alopecia	15	0	11.4	–	13.8	–	24.8	–
Nausea	10	1	4.0	0.3	11.1	0.3	11.4	0.7

Common Terminology Criteria for Adverse Events (CTC-AE) v3.0
HFSR, hand-foot skin reaction; NLCT, New Liver Cancer Therapies; SDUS, special drug use surveillance; SHARP, sorafenib hepatocellular carcinoma assessment randomized protocol.

Table 3 Abnormal clinical laboratory values with sorafenib therapy

Clinical laboratory data	NLCT Study ($n = 264$)		SDUS[6] ($n = 777$)		SHARP Trial[1,6] ($n = 297$)	
	AE incidence					
	Total (%)	G3/4 (%)	Total (%)	SAEs (%)	Total (%)	G3/4 (%)
Leukopenia	43	8	1.9	0.3	0.3	0.3
Neutropenia	37	6	0.9	0.2	–	–
Anemia	34	11	0.8	0.2	4.4	1.3
Thrombocytopenia	56	12	8.5	0.9	1.7	0.7
PT-INR	25	2	–	–	–	–
Elevated AST	70	25	1.4	–	1.7	1.7
Elevated ALT	55	15	0.9	0.2	0.7	0.7
Elevated ALP	35	5	0.3	–	–	–
Elevated γ-GTP	36	19	0.2	–	–	–
Elevated T.Bil	53	11	2.6	0.2	0.7	–
Elevated amylase	49	12	4.2	–	–	–
Elevated lipase	78	37	3.7	–	1.3	–
Elevated Cre	23	2	–	–	–	–
Hyponatremia	50	14	–	–	–	–
Hypokalemia	25	6	–	–	–	–
Hypocalcemia	55	1	–	–	–	–
Hypophosphatemia	66	29	3.6	0.5	34.9	10.5
Hypoalbuminemia	48	5	1.1	–	–	–

Common Terminology Criteria for Adverse Events (CTC-AE) v3.0.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ-GTP, γ-glutamyltransferase; NLCT, New Liver Cancer Therapies; SAEs, severe adverse events; SDUS, special drug use surveillance; SHARP, sorafenib hepatocellular carcinoma assessment randomized protocol; T-Bil, total bilirubin.

66% of class A and B patients, respectively. Performing the same comparisons for sorafenib group patients with Child–Pugh class A scoring 5 and 6 also failed to reveal any significant differences either in total incidence of abnormal laboratory values (97% and 95%, respectively; $P > 0.80$) or in the incidence of abnormal laboratory data ≥ grade 3 (58% and 68%, respectively; $P > 0.26$), despite a higher percentage for patients with Child–Pugh score 6.

AE management

CQ1-5 What measures should be taken in management to sorafenib-related AEs?

Recommendation Preventative measures and careful monitoring of the patient are required for frequently occurring AEs such as HFSR, hypertension, and hepatic impairment.

Patients undergoing sorafenib therapy often experience AEs soon after beginning of treatment. Careful monitoring of the patient by carrying out blood test and medical examinations etc. at least once a week for 4 weeks after initiating therapy is therefore preferable.

Scientific statement The NLCT study investigated measures taken in management to sorafenib-related AEs (Table 4). Management to HFSR was common, with topical application of emollients performed most frequently (69%), and followed by topical application of steroids (38%) and consultation to a dermatologist

Table 4 Incidence of drug-related adverse events with sorafenib therapy

Response to AE	Valid responses %	Prevention for AE %
Consultation to dermatologist	89	24
Steroid ointment	89	38
Emollient	91	69
Hypotensive drug dose increased	90	21
Intestinal drug	90	19
Anti-diarrheal drug	89	16
Antiemetic drug	89	5

AE, adverse event.

(24%). An increased dose of hypotensive drugs was prescribed in 21% of patients, while diarrhea was treated with antiflatulent and anti-diarrheal drugs in 19% and 16% of patients, respectively. Antiemetic agents were administered in 5% of patients.

Most AEs observed in the NLCT study, including abnormal laboratory values, occurred early at up to 8 weeks after initiating sorafenib therapy. For this reason, careful, early monitoring of the patient is essential. Bayer Yakuhin's "Nexavar Proper Use Guidelines"[7] recommends that a battery of tests be performed regularly or as required during sorafenib therapy (Table 5). Educating patients to withhold taking the drug and consult their doctors immediately if they begin to feel unwell early in the treatment is another important way to prevent AEs from becoming severe.

Serious adverse events (SAEs) should generally be handled by immediately withholding administration or reducing the dose, and reinstitution of treatment or dose increase can be considered if the patient recovers.

Provided below is a summary of management to prevent and respond to major sorafenib AEs.

- Hand-foot skin reaction (HFSR)

Prevention: HFSR occurs most frequently in areas affected by hyperkeratosis and induration. Risk factors for HSFR include physical stimulation of the skin such as compression, heat or friction, so the patient's hands and feet should always be inspected before treatment. Any thickening of the stratum corneum should be removed and the patient instructed to cover and bathe the affected areas to prevent physical stimulation. An emollient containing urea or salicylic acid should be applied to the hands from 1–2 weeks before commencing therapy.[7]

Management: Minor, painless skin changes such as erythema can be treated with steroid ointment without reducing or discontinuing sorafenib therapy. If further deterioration such as formation of blisters occurs, the dosage should be reduced. If the condition interferes with the patient's activities of daily living due to ulcers, cracking or pain etc., the therapy should be withheld and the patient consulted to a dermatologist as necessary. If the condition improves after withholding the sorafenib, therapy can be resumed at a reduced dose, and can subsequently be increased on the basis of the AE condition.

- Hepatic impairment, hepatic failure and hepatic encephalopathy

Prevention: Sorafenib therapy should be avoided in patients with severe liver impairment; particularly those with AST and ALT levels exceeding 200 IU/L.

Management: The patient should be carefully monitored by performing medical examinations and hepatic function tests once weekly for the first month of treatment, once fortnightly for the next 3 months, and once monthly thereafter. Reducing, withholding, or discontinuing sorafenib therapy should be considered if the patient exhibits symptoms of hepatic failure including hepatic encephalopathy and ascites or a sudden increase in AST and ALT levels. Immediate suspension of therapy and careful in- or outpatient monitoring is recommended if the patient's AST and ALT levels increase beyond 200 IU/L or if T-Bil exceeds 3.0 mg/dL.[7] Treatment can be resumed after the patient recovers and increased on the basis of the AE condition.

- Diarrhea

Prevention: Patients should refrain from eating foods and beverages that contain a lot of spices, fat, or caffeine. Laxatives and dietary fiber supplements should also be avoided.

Management: If frequency of defecation increases to 3 times/day, intestinal drugs such as bifidobacterium powders and albumin tannate, and anti-diarrheal drugs such as loperamide and cholestyramine should be administered.[18] In addition, the patient should be instructed to drink fluids to prevent dehydration. Reducing, withholding, or discontinuing sorafenib therapy should be considered if the frequency of defecation increases to ≥4 times/day and the patient exhibits symptoms of dehydration. Dehydration symptoms should be managed systemically with fluid replacement, etc. Treatment can be resumed after the patient recovers and subsequently increased on the basis of the AE conditions.

- **Hypertension**

Prevention: If hypertension is observed prior to sorafenib therapy, systolic blood pressure (SBP) and diastolic blood pressure (DBP) should be controlled to ≤140 mmHg and ≤90 mmHg, respectively.

Management: Patients should be instructed to measure home blood pressure during the early treatment period. If elevated blood pressure (BP) is observed, hypotensive drugs should be administered or the dosage increased. Calcium antagonists and angiotensin receptor blockers (ARBs) are commonly used as hypotensive agents. A single drug is typically administered to begin with, and other types of hypotensive drugs may be co-administered if the reduction in BP is insufficient. Regardless of therapy, administration of sorafenib should be withheld if SBP is ≥180 mmHg or DBP is ≥110 mmHg. Treatment can be resumed after the patient recovers and then increased on the basis of the AE conditions.

Table 5 Clinical laboratory tests recommended in proper use guidelines for sorafenib therapy[7]

Test/Test variable	Cautionary AEs etc.	Subjects	Frequency/Duration											
			Baseline	1 week	2 weeks	3 weeks	4 weeks	6 weeks	8 weeks	10 weeks	12 weeks	16 weeks	20 weeks	– Post-therapy
Hepatic function	Hepatic impairment	All patients	○	○	○	○	○	○	○	○	○	○	○	○
Pancreatic function	Increased pancreatic function, pancreatitis	All patients	○		○		○		○		○	○	○	○
Blood count	Neutropenia, thrombocytopenia, etc.	All patients	○		○		○		○		○	○	○	○
Serum phosphate	Hypophosphatemia	All patients	○		○		○		○		○	○	○	○
Blood pressure	Hypertension, hypertensive crisis, reversible leukoencephalopathy	All patients	At hospital visit (simple HBP measurement once weekly [daily if possible])											
Abdominal imaging	GI perforation, pancreatitis	Patients complaining of abdominal pain	As appropriate											
Coagulation parameters	Hemorrhage	Patients on concomitant vitamin K antagonists	As appropriate											
Thyroid function (thyroid hormone, thyroid-stimulating hormone, etc.)	Reduced thyroid function	Patients with specific symptoms suggestive of reduced thyroid function	As appropriate											
Thoracic imaging (Chest x-ray, chest CT, KL-6)	Interstitial pneumonia	Patients with symptoms suggestive of interstitial pneumonia	As appropriate											

AEs, adverse events; CT, computed tomography; GI, gastrointestinal; HBP, home blood pressure.

- **Amylase elevation**

Management: Increases in amylase are usually transient and gradually subside even when sorafenib therapy is continued. However, some cases of pancreatitis has previously been reported in patients treated with sorafenib, so if the patient has abdominal pain or other symptoms suggestive of pancreatitis, or elevated amylase levels are sustained, sorafenib therapy should be withheld and imaging procedures such as dynamic CT performed to determine whether pancreatitis is present.[7]

- **Interstitial pneumonia**

Management: Interstitial pneumonia should be suspected and sorafenib therapy discontinued immediately in patients exhibiting clinical symptoms such as dyspnea, dry cough and fever, and lung crepitation or reduced SpO_2 (percutaneous oxygen saturation) on physical examination. In addition, diagnosis and proper treatment should be carried out based on prompt diagnostic imaging such as chest X-ray or high-resolution chest CT (HRCT) and blood tests such as KL-6 after consulting with a respiratory specialist.[7]

Evaluation of therapeutic response

CQ1-6 How and when should therapeutic response of sorafenib be evaluated?

Recommendation The antitumor effects of sorafenib therapy are normally evaluated by diagnostic imaging with dynamic CT or dynamic magnetic resonance imaging (MRI) and subsequent measurement of tumor size based on a single cycle of 4–6 weeks of sorafenib administration.

Changes in intra-tumoral blood flow are often seen following sorafenib therapy, so evaluation can also be performed by measuring the area of tumor staining in addition to tumor size.

α-fetoprotein (AFP) and PIVKA-II (DCP) (protein induced by vitamin K absence or abnormality, des-γ-carboxyprothrombin) tumor markers are also typically evaluated in conjunction with tumor images at cycles of 4–6 weeks.

Elevated PIVKA-II (DCP) concentrations during sorafenib therapy may not always be due to disease progression. Consideration should also be given to evaluation of tumors in patients for whom treatment was interrupted due to AEs.

Scientific statement In the two randomized, placebo-controlled trials demonstrating the usefulness of sorafenib therapy,[1,2] therapeutic response to sorafenib was evaluated every 6 weeks on the basis of diagnostic imaging.

In the NLCT study, median overall survival (OS) was 10.8 months, 6-month survival rate was 65%, 1-year survival rate was 45%, and median progression-free survival (PFS) was 2.1 months (Fig. 1). Comparison of efficacy evaluation findings with those of previous clinical trials[1,2,5] are presented in Table 6.

Reductions in intra-tumoral blood flow are often observed with sorafenib therapy, so instead of simply evaluating tumor size based on the conventional Response Evaluation Criteria in Solid Tumors (RECIST), the use of therapeutic response criteria for evaluating intra-tumoral necrotic regions such as modified RECIST[19] or the Response Evaluation Criteria in Cancer of the Liver (RECICL)[20] has recently been advocated.[21,22] Even if the size of the tumor has slightly increased, therapy may be deemed effective and subsequently continued if the area of reduced intra-tumoral blood flow has increased.

Previous studies have reported that PIVKA-II (DCP) expression is induced in hypoxic HCC cells following sorafenib therapy[23] and that elevated PIVKA-II (DCP) concentrations may act as surrogate markers for HCC tissue ischemia.[24] However, elevated PIVKA-II levels are also seen in disease progression, so care should be taken during assessment of therapeutic response.

According to the NLCT study data, therapeutic response was not evaluated in 20% of sorafenib group patients. However, short-term administration of sorafenib was found to inhibit tumors in some patients on whom therapy was interrupted due to AEs, suggesting that regular tumor assessment should also be considered for patients with interrupted treatment.

Continuation of therapy

CQ1-7 How long should sorafenib therapy be continued?

Recommendation Sorafenib therapy should preferably be maintained until clear disease progression is determined on evaluation of therapeutic response.

If clear disease progression is not identified in diagnostic imaging, therapy may be continued after considering the risks and benefits.

No data are currently available on the efficacy/safety of continued sorafenib administration after disease progression has been confirmed.

Scientific statement In the NLCT study, 31% of patients in the sorafenib group underwent some form of additional treatment after completion of the therapy. Specifically, 12% underwent TACE, 8% underwent systemic chemotherapy, 7% underwent HAIC, 4% underwent radiotherapy, and 2% underwent hepatectomy/LAT.

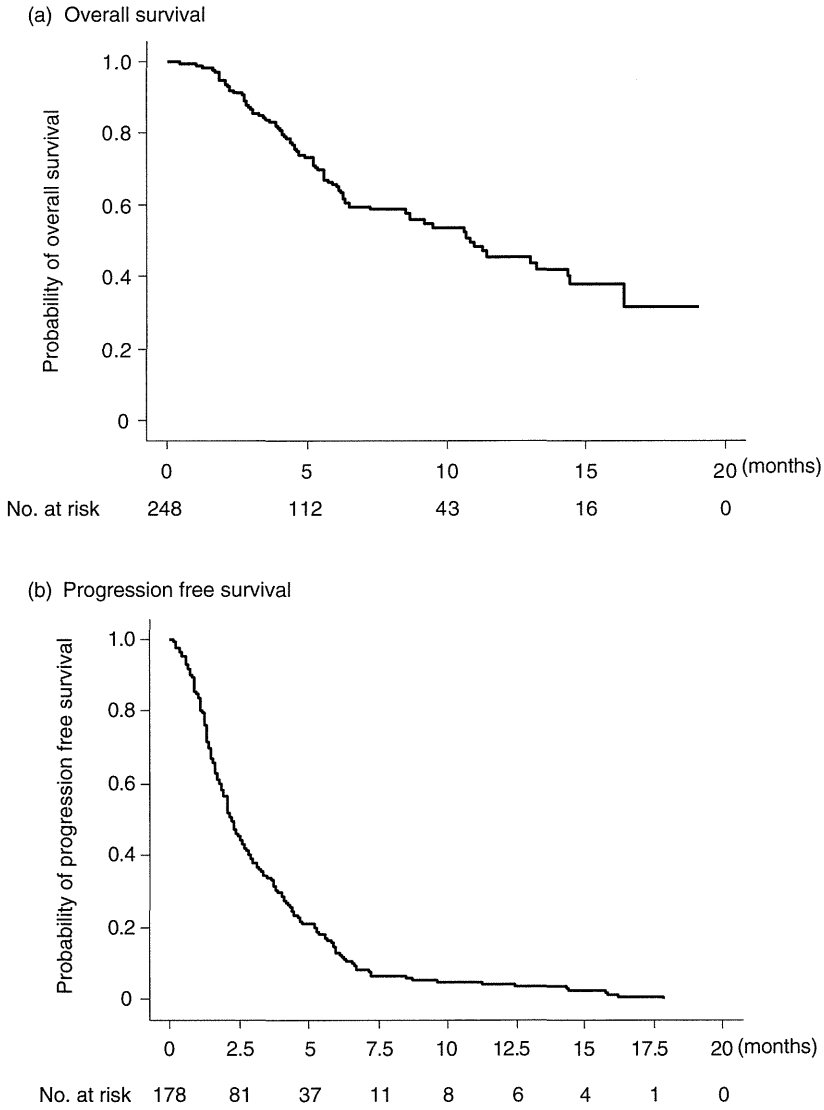

Figure 1 Therapeutic efficacy of sorafenib. (a) Overall survival. (b) Progression free survival.

Progressive disease (PD) was confirmed in 165 patients in the sorafenib group during the study's observation period, of whom a further 23 patients (14%) underwent continued oral administration of sorafenib for ≥1 month after PD confirmation. Comparison of these 23 patients with those in whom therapy was discontinued did not reveal any significant differences in OS, and no data are currently available regarding the efficacy/safety of continued sorafenib administration after confirmation of PD.

Predictors of therapeutic efficacy

CQ1-8 What are the predictors of therapeutic efficacy for sorafenib therapy?

Recommendation Clear predictors of therapeutic efficacy for sorafenib have yet to be established, but the number of intrahepatic lesions and pretreatment levels of tumor markers (AFP, PIVKA-II [DCP]) may be predictors of efficacy.

Scientific statement A study of biomarkers in patients treated with sorafenib has suggested the efficacy of sorafenib is associated with low serum HGF and high c-KIT levels at baseline.[25] Efficacy of sorafenib has also been linked to high levels of ERK expression in tumor tissue.[25,26] However, these reported associations cannot yet be described as established predictors of efficacy, and biomarkers are currently being sought in some prospective clinical trials using sorafenib.

Table 6 Summary of efficacy measures for sorafenib therapy

	NLCT Study ($n = 250$)	SHARP Trial[1] ($n = 299$)	Asia-Pacific Trial[2] ($n = 150$)	Sorafenib phase II[5] ($n = 137$)
OS (months)				
Median	11.0	10.7	6.5	9.2
1-year SR (%)	45	44	–	59
6-month SR (%)	65	–	53	–
PFS (months)	†			
Median	2.1	5.5	3.5	4.2/5.5
Antitumor effect (%)	‡			
Complete remission	0	0	0	0
Partial remission	4	2	5	2
Stable	45	71	46	34
Tumor control rate	49	43	53	–

†Patients who died without confirmation of disease progression were excluded.
‡Patients not evaluated for therapeutic response were excluded.
NLCT, New Liver Cancer Therapies; OS, overall survival; PFS, progression-free survival; SHARP, sorafenib hepatocellular carcinoma assessment randomized protocol.

The current results indicate that early AFP response is a useful surrogate marker to predict treatment response and prognosis in patients with advanced HCC who receive anti-angiogenic therapy.[27]

In an attempt to identify predictors of therapeutic efficacy for sorafenib, the NLCT study examined baseline patient characteristics (age, sex, BMI [body mass index], ECOG-PS [Eastern Cooperative Oncology Group – performance status], hepatic functional reserve, prior treatment, cause of hepatic impairment, clinical laboratory values) and tumor factors (presence or absence of intrahepatic/extrahepatic lesions, maximum tumor size, vascular invasion, stage), and consequently found that tumor control rates tended to be higher in patients with <5 intrahepatic lesions compared to those with ≥5 lesions (54% vs. 40%, respectively; $P = 0.058$). In addition, the tumor control rate was significantly higher in patients with a baseline AFP value <10 ng/mL compared with those with values ≥10 ng/mL (68% vs. 43%, respectively; $P = 0.021$). The tumor control rate also tended to be higher in patients with baseline PIVKA-II (DCP) value <40 mAU/mL than in those with a value of ≥40 mAU/mL (60% vs. 42%, respectively; $P = 0.051$) (Table 7).

Hepatic arterial infusion with miriplatin

Indications

CQ2-1 Is miriplatin a platinum preparation that can be used on renal disorder patients?

Recommendation Renal disorder patients can be treated using miriplatin as long as they are capable of undergoing angiography (serum Cre [creatinine] level <2.0 mg/dL) and as long as administration is performed carefully so as to avoid elevation in serum Cre levels after treatment.

Scientific statement Miriplatin remains in the tumor together with Lipiodol, where it slowly releases platinum compounds. This agent is thus believed to gradually increase serum platinum concentration with minimal adverse effect on renal function.

In a randomized phase II trial comparing miriplatin and zinostatin stimalamer (SMANCS) in patients with normal serum Cre levels, renal dysfunction indicated by serum Cre level >1.5 mg/dL was observed in only 2.4% of patients in the miriplatin treatment group (Table 8).[28]

In the NLCT study, median serum Cre prior to miriplatin therapy was 0.8 mg/dL (range, 0.4–10.5 mg/dL), of which patients with a serum Cre level >1.0 mg/dL accounted for 17.7%. Median serum Cre after treatment was 0.8 mg/dL (range, 0.1–12.6 mg/dL), which was unchanged from baseline, and 94.7% of patients experienced an increase of ≤0.5 mg/dL (Table 9). Only 1.8% of patients exhibited renal dysfunction ≥grade 3 as indicated by serum Cre level >3 mg/dL.

Analysis of patients with baseline serum Cre <2.0 mg/dL shows that just 2.5% of patients increased serum Cre >0.5 mg/dL, and no more than 0.6% of patients experienced renal dysfunction ≥grade 3 (Table 9).

In addition, no serious renal dysfunction was observed after miriplatin administration in patients with serum Cre levels around 2.0 mg/dL.

Table 7 Factor analysis of tumor control with sorafenib therapy

	n	Tumor control rate (%)	*P**
Age (years)			
≥65	137	49	0.75
<65	56	46	
Gender			
Male	147	50	0.72
Female	43	47	
ECOG-PS			
0	163	50	0.24
1–3	29	38	
Child–Pugh score			
5	65	48	0.82
6	70	44	
7	23	48	
≥8	10	60	
Child–Pugh class			
A	135	46	0.52
B–C	33	56	
Prior treatment			
Yes	173	48	0.87
None	18	50	
HBs antigens			
Positive	36	50	0.91
Negative	149	49	
HCV antibodies			
Positive	112	50	0.66
Negative	77	47	
Intrahepatic lesions			
Yes	174	47	0.26
None	18	61	
Intrahepatic nodules			
≥5	95	40	0.058
<5	83	54	
Advanced vascular invasion			
Yes	36	50	0.68
None	141	46	
Extrapulmonary lesion(s)			
Yes	105	47	0.64
None	88	50	
Maximum tumor size (mm)			
≥30	108	47	0.79
<30	67	49	
Stage (Japanese Classification of Lung Cancer)			
I–II	15	53	0.41
III	53	57	
IV A	31	39	
IV B	84	46	
Initial dose			
Normal dose	153	48	0.91
Reduction	39	49	
Baseline AFP			
≥10	151	43	0.021
<10	25	68	
Baseline PIVKA-II			
≥40	132	42	0.051
<40	40	60	

*Fisher's exact test.
AFP, α fetoprotein; ECOG-PS, Eastern Cooperative Oncology Group Performance status; HBs, Hepatitis B surface antigen; HCV, hepatitis C virus.

Based on these findings, the Study Group considers that miriplatin therapy can be administered without instigating renal dysfunction in patients with serum Cre <2.0 mg/dL who are capable of undergoing angiography.

However, transcatheter arterial infusion (TAI)/TACE with miriplatin simultaneously uses an iodinated contrast medium with drugs that can cause renal dysfunction such as anti-inflammatory analgesics to treat postoperative fever. Sufficient consideration should therefore be given to the risk of drug-induced renal dysfunction, and monitoring of urine volume and fluid replacement should be implemented as necessary.

CQ2-2 Can miriplatin be used safely in patients with Child–Pugh class B?

Recommendation Miriplatin can be used to treat these patients without causing serious complications.

Furthermore, no demonstrable difference in the antitumor effects of miriplatin has been observed between Child–Pugh class A and B patients.

Scientific statement The NLCT study included 281 Child–Pugh class A and 144 Child–Pugh class B patients. In Child–Pugh class B patients, the only SAEs ≥grade 3 were fever and anorexia, at incidences of 0.7% each, with no cases of ascites or hepatic failure ≥grade 3 (Table 10). In a study of TAI with miriplatin, in 17 Child–Pugh class B patients, no significant differences were seen in pre- or posttreatment 15-min retention rates of indocyanine green (ICG_{15}), and no SAEs or increased ascites or hepatic failure necessitating additional therapy or prolonged hospitalization were observed.[30]

Although the retrospective analysis of the NLCT study coupled with differences in characteristics of Child–Pugh class A and B patient effectively precludes simple comparisons of these patients, no significant differences in respective AE incidences were seen, apart from a higher frequency of fever and thrombocytopenia ≥grade 3 among Child–Pugh class B patients (Tables 10 and 11).

In terms of evaluation of antitumor effects according to the RECICL proposed by the Liver Cancer Study Group of Japan, the present study did not reveal any significant differences in therapeutic responses of Child–Pugh class A and B patients (Table 12), while 50% of Child–Pugh class B patients in the aforementioned study of TACE with miriplatin achieved a treatment effect (TE) of "TE3" or "TE4", in which tumor was controlled.[30]

CQ2-3 Is miriplatin effective against cisplatin-resistant HCCs?

Table 8 Abnormal clinical laboratory values with miriplatin therapy

	NLCT Study ($n = 535$)		Phase III Trial[29] ($n = 16$)		Randomized Phase II Trial[28] ($n = 83$)	
	Total (%)	G3/4 (%)	Total (%)	G3/4 (%)	Total (%)	G3/4 (%)
Leukopenia	38.2	5.1	51	0	41.0	1.2
Neutropenia	20.1	5.1	63	19	53.0	8.4
Eosinophilia	14.6	–	100	0	84.3	0
Monocytosis	–	–	–	–	57.8	0
Lymphocytopoenia	–	–	51	0	79.5	0
Thrombocytopenia	32.1	9.3	44	0	50.6	1.2
Increased AST	49.9	12.4	56	44	62.7	26.5
Increased ALT	78.4	26.6	44	19	59	24.1
Increased bilirubin	31.6	3.2	31	19	57.8	12.0
Increased γGTP	16.1	2.0	–	–	49.4	0
Increased ALP	12.3	0.2	44	0	30.1	1.2
Elevated Cre	11.5	1.8	25	0	–	2.4†

CTC-AE v3.0 Japan Society of Clinical Oncology Adverse Drug Reaction Criteria.
†Increased Cre data includes G2 patients.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ-GTP, γ-glutamyltransferase.

Table 9 Incidence of drug-related adverse events with miriplatin therapy (Renal dysfunction)

Elevated Cre	all ($n = 513$)	Baseline Cre <2.0 mg/dL	Baseline Cre ≥2.0 mg/dL
≤0.5 mg/dL	94.7%	97.5%	13.3%
0.6–1.0 mg/dL	2.4%	1.7%	20.0%
1.1–2.0 mg/dL	1.2%	0.2%	33.3%
2.1–3.0 mg/dL	0.6%	0.0%	20.0%
>3.0 mg/dL	1.0%	0.6%	13.3%

Recommendation The clinical usefulness of miriplatin against cisplatin-resistant HCC is not currently known.

Scientific statement Miriplatin is classified as a third-generation platinum drug and a basic research on the drug suggested potential activity in cisplatin-resistant HCCs because cisplatin-resistant HCC cell lines did not show cross-resistance to miriplatin.[31]

A Japanese Phase I trial combining miriplatin and TAI using Lipiodol (Lip-TAI) on HCC refractory to cisplatin/Lip-TAI has reported a treatment success rate of 18.2%.[32]

Table 10 Comparison of adverse events with miriplatin therapy according to Child–Pugh classification

	All ($n = 535$)		Child–Pugh class A ($n = 281$)		Child–Pugh class B ($n = 144$)	
	Total (%)	G3/4 (%)	Total (%)	G3/4 (%)	Total (%)	G3/4 (%)
Fever	81.3	0.2	75.5	0	86.1	0.7*
Biphasic fever	2.8	–	2.5	–	5.1	–
Anorexia	29.7	0.2	31.7	0	34.0	0.7
Administration site pain	21.2	0	25.6	0	15.3	0
Nausea	18.8	0	21.4	0	12.5	0*
Vomiting	13.5	0	11.6	0	6.1	0
Fatigue	9.3	0	12.2	0	10.3	0
Diarrhea	2.0	0	1.8	0	1.0	0
Ascites	1.2	0	0	0	3.0	0
Hepatic failure	0.3	0.3	0.3	0.3	0	0

CTC-AE v3.0.
*$P < 0.05$ (A vs. B).

Table 11 Comparison of clinical laboratory value anomalies with miriplatin therapy according to Child–Pugh classification

	All ($n = 535$)		Child–Pugh class A ($n = 281$)		Child–Pugh class B ($n = 144$)	
	Total (%)	G3/4 (%)	Total (%)	G3/4 (%)	Total (%)	G3/4 (%)
Leukopenia	38.2	5.1	18.2	3.3	25.2	5.8
Neutropenia	20.1	5.1	17.3	3.6	23.4	5.8
Eosinophilia	14.6	–	17.9	–	11.5	–
Thrombocytopenia	32.1	9.3	30.9	5.8	30.2	13.7*(G3)
Increased AST	49.9	12.4	45.2	13.5	50.7	19.4
Increased ALT	78.4	26.6	81.0	28.8	70.3	28.3*
Increased bilirubin	31.6	3.2	26.1	0	46.0	5.8*
Increased γGTP	16.1	2.0	15.8	2.6	14.5	0
Increased ALP	12.3	0.2	12.7	0	10.1	0.7
Elevated Cre	11.5	1.8	11.6	2.2	10.8	1.4

CTC-AE v3.0.
*$P < 0.05$ (A vs. B).
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ-GTP, γ-glutamyltransferase.

However, the study was conducted on a small patient population, so the usefulness of this therapy is yet to be established and future studies are awaited.

Furthermore, no data are currently available regarding the efficacy of miriplatin therapy in patients who are unresponsive to TAI/HAIC using cisplatin.

Method of administration

CQ2-4 What are the effects and AEs of combining embolic materials with miriplatin?

Recommendation Combination therapy of embolic materials and miriplatin is expected to improve antitumor effects compared with miriplatin alone, but there is currently insufficient evidence to support this.

Adverse events associated with combination therapy of embolic materials and miriplatin may not differ noticeably from those of conventional TACE therapy using epirubicin.

Scientific statement Compared with stand-alone therapy, the combination of embolic materials in the hepatic arterial catheterization treatment is generally considered to deliver enhanced antitumor effects based on its blood flow blockage effect,[33] so treatment combined with embolic materials are mostly selected for the treatment of HCC. However, Phase I and II trials using miriplatin have opted not to use embolic materials in combination with miriplatin.[29,32]

Meanwhile, two studies on miriplatin used in combination with embolic materials on a small number of patients have reported high rates of treatment success, with TE3 and TE4 scores obtained in 60.0–77.7% of patients.[30,34]

Table 12 Summary of efficacy measures with miriplatin therapy

	NLCT Study			Phase II Trial[29] ($n = 16$)	Randomized Phase II Trial[28] ($n = 83$)
	All ($n = 535$)	Child–Pugh class A ($n = 281$)	Child–Pugh class B ($n = 144$)		
Anti-neoplastic effect (%)					
TE4	22.8	25.3	23.6	56	26.5
TE3	24.3	26.7	20.8	6	25.3
TE2	26.0	26.0	29.9	19	22.9
TE1	16.6	12.5	17.4	19	20.5
Not evaluated	10.3	9.6	8.3	0	4.8
TE3 + TE4	47.1	52.0	44.4	61	51.8

Response Evaluation Criteria in Cancer of the Liver' (RECICL).

Table 13 Independent factors contributing to effective (TE3/4) achievement with miriplatin therapy

Factor	Category	Risk ratio	95% CI	*P*-value
Embolic material	None	1		<0.001
	Yes	3.66	2.13–6.29	
No. tumors	Single	1		0.017
	2–3	1.01		
	4–9	0.66		
	≥10	0.3	0.13–0.67	
Past history of TAE	None	1		0.018
	Yes	0.48	0.26–0.88	

Cox proportional hazards model.
CI, confidence interval; TAE, transcather arterial embolization.

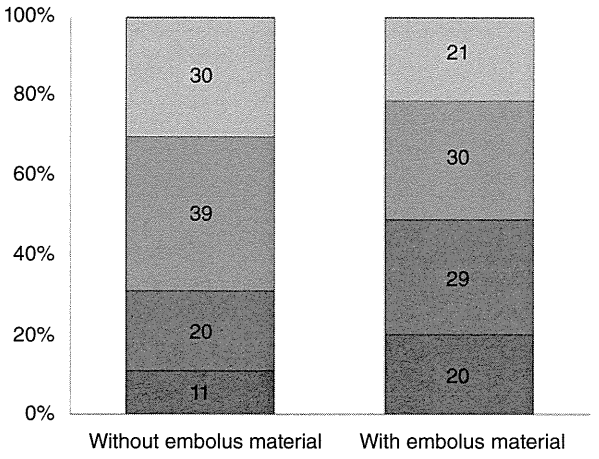

Figure 2 Therapeutic efficacy of miriplatin with or without embolus material.

In the NLCT study, embolic material was used in combination with miriplatin on 473 patients (88.4%). Simple comparison of patients undergoing miriplatin/embolic material combination therapy and those who underwent miriplatin alone therapy was not possible due to the retrospective nature of this study, as well as the different patient characteristics of the respective treatment groups. However, antitumor effects were higher in the miriplatin/embolic material therapy group than in the miriplatin therapy group, at 49% and 31%, respectively (Fig. 2). Analysis of independent factors contributing to the achievement of TE3/4 scores in TAI/TACE therapy using miriplatin showed that the use of embolic material had a higher risk ratio of 3.66 ($P < 0.001$) (Table 13).

A Phase III trial of TACE using miriplatin is currently underway, and the results will likely be useful in investigating the efficacy of using miriplatin in combination with embolic materials.

In the NLCT study, patients who underwent combination therapy with embolic material showed a high incidence of fever, suspected to be due to post-embolization syndrome. Although high incidences of hematological AEs neutropenia and elevated AST were seen, no significant differences were identified in the incidences of most AEs, and no serious complications such as hepatic failure or ascites were observed (Tables 14 and 15).

Table 14 Comparison of adverse events with or without embolic material during miriplatin therapy

	All ($n = 535$)		TACE patients ($n = 425$)		TAI patients ($n = 54$)	
	Total (%)	G3/4 (%)	Total (%)	G3/4 (%)	Total (%)	G3/4 (%)
Fever	81.3	0.2	84.4	0.2	56.1	0*
Biphasic fever	2.8	–	3.0	–	0	–
Anorexia	29.7	0.2	30.4	0.2	22.4	0
Administration site pain	21.2	0	22.2	0	13.8	0
Nausea	18.8	0	20.1	0	4.0	0
Vomiting	13.5	0	14.2	0	0	0
Fatigue	9.3	0	9.2	0	–	–
Diarrhea	2.0	0	2.1	0	0	0
Ascites	1.2	0	0.9	0	5.6	0
Hepatic failure	0.3	0.3	0.3	0.3	0	0

CTC-AE v3.0.
*$P < 0.05$ (TACE vs. TAI).
TACE, transcatheter arterial chemoembolization; TAI, transcatheter arterial infusion.

Table 15 Comparison of abnormal clinical laboratory values with or without embolic material during miriplatin therapy

	All ($n = 535$)		TACE patients ($n = 425$)		TAI patients ($n = 54$)	
	Total (%)	G3/4 (%)	Total (%)	G3/4 (%)	Total (%)	G3/4 (%)
Leukopenia	38.2	5.1	22.8	5.5	20.4	1.9
Neutropenia	20.1	5.1	21.4	5.5	3.7	0*
Eosinophilia	14.6	–	14.8	–	11.8	–
Thrombocytopenia	32.1	9.3	33.2	10.4	24.1	0
Increased AST	49.9	12.4	52.8	19.3	25.9	8.6*
Increased ALT	78.4	26.6	78	24.5	81.5	44.4*
Increased bilirubin	31.6	3.2	32.1	3.3	27.8	0
Increased γ-GTP	16.1	2.0	16.1	1.8	14.8	3.7
Increased ALP	12.3	0.2	12.6	0.2	9.3	0
Elevated Cre	11.5	1.8	10.7	1.8	18.5	1.9

CTC-AE v3.0.
*$P < 0.05$ (TACE vs. TAI).
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ-GTP, γ-glutamyltransferase; TACE, transcatheter arterial chemoembolization; TAI, transcatheter arterial infusion.

Similarly, a small pilot study (Phase II clinical trial) on miriplatin combined with an embolic material found some mild complications, but none of a serious nature.[34] Another study on the small number of patients did not reveal any serious complications.[30]

CQ2-5 Is standard hydration required prior to administration of miriplatin?

Recommendation Standard hydration is not required except in the case of renal failure.

Scientific statement Sufficient hydration before and after administration of cisplatin (IA-call, Nippon Kayaku, Tokyo, Japan) used in HAIC is necessary to prevent nephrotoxicity.

Miriplatin is highly soluble in Lipiodol and remains in tumor with Lipiodol, where it continuously releases platinum compounds.[35] So only a small amount enters systemic circulation expecting to reduce systemic AEs, including renal dysfunction.

As stated in CQ1, the effect of miriplatin on renal function is considered to be mild. Two of the aforementioned Phase II trials did not perform pretreatment hydration to prevent renal impairment.[28,30] In the NLCT study, patients with advanced renal insufficiency were excluded and no serious renal impairment occurred in patients treated with miriplatin without prior hydration.

Adverse events

CQ2-6 What are the adverse events associated with miriplatin therapy?

Recommendation Post-embolization syndrome characterized mainly by fever is often seen, and biphasic fever is relatively infrequent. Incidences of nausea and vomiting are also low compared with other platinum agents. Complications such as ascites, liver abscess, biloma, and dyspnea have incidences of about 1%.

Scientific statement In the NLCT study, post-embolization syndrome was observed in ≥90% of patients treated with miriplatin. However, the incidence of biphasic fever, which is said to be a characteristic AE associated with miriplatin, was low at 2.8% (Tables 16, 17).

Incidences of nausea and vomiting were low compared with other platinum agents, at 18.8% and 13.5%, respectively.

Hematological AEs were leukopenia at 38.2%, thrombocytopenia at 32.1%, and neutropenia at 20.1%. Incidence of eosinophilia, which is also reported as a characteristic AE of miriplatin, was relatively low at 14.6% (Table 8).[28,29]

Abnormal hepatic function was frequent, with elevated AST and ALT occurring in 49.9% and 78.4% of patients, respectively, of whom a further 12.4% and 26.6% had respective AST and ALT values ≥grade 3. Elevated T-Bil was seen in 31.6% of patients, of whom 3.2% had value ≥grade 3, more than three times the upper limits of normal (ULN).

CQ2-7 What is the extent of deterioration in hepatic function caused by TAI/TACE using miriplatin?

Table 16 Incidence of drug-related adverse events with miriplatin therapy (1)

	NLCT Study ($n = 535$)		Phase II Trial[29] ($n = 16$)		Randomized Phase II Trial[28] ($n = 83$)	
	Total (%)	G3/4 (%)	Total (%)	G3/4 (%)	Total (%)	G3/4 (%)
Fever	81.3	0.2	94	0	96.4	3.6
Biphasic fever	2.8	–	–	–	–	–
Anorexia	29.7	–	–	–	–	–
Abdominal pain	21.2	0	50	0	–	–
Nausea	18.8	0	25	0	–	–
Vomiting	13.5	0	–	–	55.4	1.2
Fatigue	9.3	0	–	–	39.8	0
Chills	–	0	–	–	39.8	0
Administration site pain	21.2	0	50	0	43.4	0
Diarrhea	2.0	0	31	0	–	–
Ascites	1.2	0	–	–	–	–
Hepatic failure	0.3	0.3	–	–	–	–
Vascular injury	–	–	–	–	0	0

CTC-AE v3.0 Japan Society of Clinical Oncology Adverse Drug Reaction Criteria

Recommendation Typically, no deterioration is seen in postoperative ICG_{15}, but prothrobmin time (PT) ratio (%) may display a transient decline.

Scientific statement Hepatic impairment after miriplatin administration has been reported to peak within 2 weeks in 46% of patients, at 3–5 weeks in 23% of patients, and at 9–11 weeks in 31% of patients.[29]

The NLCT study also found that in evaluable patients, ICG_{15} values had not deteriorated at 1–2 weeks after therapy and that PT ratio (%) exhibited a transient decline, but subsequently recovered in the majority of patients.

Child–Pugh class B patients did not find any significant differences in pre- or post-treatment ICG_{15}, and did not find any SAEs or increased ascites or hepatic failure necessitating additional therapy and prolonged hospitalization.[32]

However, the safety of miriplatin used in combination with embolic materials has yet to be established, and a Phase III study on concomitant use of miriplatin and embolizing agents is currently underway.[34]

Table 17 Incidence of drug-related adverse events with miriplatin therapy (2)

	Incidence (%)
Ascites	1.2
Liver abscess	0.6
Biloma	0.3
Dyspnea	0.3

CQ2-8 Does vascular injury occur after intra-arterial administration of miriplatin?

Recommendation Vascular injuries such as hepatic artery occlusion, arterial stenosis and arterioportal shunts, and hepatic lobar atrophy caused by vascular damage are rare.

Scientific statement No reports have described vascular injuries from non-hematological toxicity in previous Japanese Phase I and II trials on miriplatin therapy.[29,32] Likewise, no vascular injuries have been reported in the NLCT study (Table 16). In TAI without the use of embolic materials, the aforementioned randomized phase II trial comparing miriplatin and zinostatin stimalamer (SMANCS) found that vascular injuries occurred in 48.4% of the SMANCS treatment group ($n = 31$), but that no vascular injuries occurred in the miriplatin treatment group ($n = 73$).[28] In a limiting study performing follow-up angiography on nine patients at 2–6 months after treatment, no arterial stenoses, arterial occlusions, or arterioportal shunts were observed.[30]

Evaluation of therapeutic response

CQ2-9 After how many weeks should therapeutic response to miriplatin be evaluated?

Recommendation Non-specific accumulation of Lipiodol appears on dynamic CT at 1 week after administration of miriplatin, so evaluation of therapeutic response should preferably be performed at 4–8 weeks after administration.

Scientific statement Evaluation of therapeutic response performed at 1 day or 1 week after starting miriplatin therapy may result in overestimation of response due to the appearance of non-specific Lipiodol deposits. Evaluation of therapeutic response using dynamic CT at 4–8 weeks after therapy is therefore preferable, to allow these non-specific deposits to disappear. In the above-mentioned Phase I clinical trial, therapeutic response to miriplatin was evaluated with dynamic CT at 1 week, 5 weeks, and 3 months after therapy,[32] while the Phase II trial evaluated the antitumor effects of miriplatin using dynamic CT every 3 months.[29]

REFERENCES

1 Llovet JM, Ricci S, Mazzaferro V *et al.* Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008; **359**: 378–90.
2 Cheng AL, Kang YK, Chen Z *et al.* Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2009; **10**: 25–34.
3 Kudo M. *Chapter 3 Treatment Strategy for HCC Cases Refractory for TACE (Japanese) Hepatocelluar Carcinoma Practice Manual*, 2nd edn. Tokyo: Igaku-syoin, 2010; 118–21.
4 Nexavar® adverse reaction reports liver injury and interstitial pulmonary disease (Japanese). 2010. Bayer Heathcare May.
5 Abou-Alfa GK, Schwartz L, Ricci S *et al.* Phase II study of sorafenib in patients with advanced hepatocellular carcinoma. *J Clin Oncol* 2006; **24**: 4293–300.
6 Nexavar® special post marketing surveillance report for unresectable hepatocelluar carcinoma (Japanese). 2010. Bayer Heathcare September.
7 Akaza H, Okita K *et al.* Guideline for proper use of Nexavar® 2nd edition (Japanese). 2010. Bayer Heathcare May
8 Furuse J, Ishii H, Nakachi K *et al.* Phase I study of sorafenib in Japanese patients with hepatocellular carcinoma. *Cancer Sci* 2008; **99**: 159–65.
9 Lencioni R, Marrero J, Venook A *et al.* Design and rationale for the non-interventional Global Investigation of Therapeutic DEcisions in Hepatocellular Carcinoma and Of its Treatment with Sorafenib (GIDEON) study. *Int J Clin Pract* 2010; **64**: 1034–41.
10 Marrero J. Sorafenib treatment and safety profile in Child-Pugh B patients characterized in first interim results of Global Investigation of therapeutic DEcisions in hepatocellular carcinoma and Of its treatment with sorafeNib (GIDEON) study 61st Annual meeting of the American Association for the Study of Liver Diseases. 2010. 1721, poster presentation.
11 Okita K. Phase III study of sorafenib in patients in Japan and South Korea with advanced hepatocellular carcinoma treated after transarterial chemoembolization. 2010. Gastrointestinal Cancers Symposium 2010.
12 Printz C. Clinical trials of note. Sorafenib as adjuvant treatment in the prevention of disease recurrence in patients with hepatocellular carcinoma (HCC) (STORM). *Cancer* 2009; **115**: 4646.
13 Zhao JD, Liu J, Ren ZG *et al.* Maintenance of Sorafenib following combined therapy of three-dimensional conformal radiation therapy/intensity-modulated radiation therapy and transcatheter arterial chemoembolization in patients with locally advanced hepatocellular carcinoma: a phase I/II study. *Radiat Oncol* 2010; **5**: 12.
14 Hsieh CH, Jeng KS, Lin CC *et al.* Combination of sorafenib and intensity modulated radiotherapy for unresectable hepatocellular carcinoma. *Clin Drug Investig* 2009; **29**: 65–71.
15 Abou-Alfa GK, Johnson P, Knox JJ *et al.* Doxorubicin plus sorafenib vs doxorubicin alone in patients with advanced hepatocellular carcinoma: a randomized trial. *JAMA* 2010; **304**: 2154–60.
16 Hsu CH, Shen YC, Lin ZZ *et al.* Phase II study of combining sorafenib with metronomic tegafur/uracil for advanced hepatocellular carcinoma. *J Hepatol* 2010; **53**: 126–31.
17 Prete SD, Montella L, Caraglia M *et al.* Sorafenib plus octreotide is an effective and safe treatment in advanced hepatocellular carcinoma: multicenter phase II So.LAR. study. *Cancer Chemother Pharmacol* 2010; **66**: 837–44.
18 Bhojani N, Jeldres C, Patard JJ *et al.* Toxicities associated with the administration of sorafenib, sunitinib, and temsirolimus and their management in patients with metastatic renal cell carcinoma. *Eur Urol* 2008; **53**: 917–30.
19 Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Semin Liver Dis* 2010; **30**: 52–60.
20 Kudo M, Kubo S, Takayasu K *et al.* Response Evaluation Criteria in Cancer of the Liver (RECICL) proposed by the Liver Cancer Study Group of Japan (2009 Revised Version). *Hepatol Res* 2010; **40**: 686–92.
21 Spira D, Fenchel M, Lauer UM *et al.* Comparison of different tumor response criteria in patients with hepatocellular carcinoma after systemic therapy with the multikinase inhibitor sorafenib. *Acad Radiol* 2011; **18**: 89–96.
22 Horger M, Lauer UM, Schraml C *et al.* Early MRI response monitoring of patients with advanced hepatocellular carcinoma under treatment with the multikinase inhibitor sorafenib. *BMC Cancer* 2009; **9**: 208.
23 Murata K, Suzuki H, Okano H *et al.* Hypoxia-induced des-gamma-carboxy prothrombin production in hepatocellular carcinoma. *Int J Oncol* 2010; **36**: 161–70.
24 Ueshima K, Kudo M. PIVKA-II is a predictive marker in the treatment response of sorafenib to hepatocellular carcinom. *Kanzo* 2010; **51**: 681.
25 Llovet JM. Biomarkers predicting outcome of patients with hepatocellular carcinoma: results from the randomized

phase III SHARP trial Presidential Plennary Session. *Hepatology* 2008; **48**: 372A, Abstract no. 149.
26 Zhang Z, Zhou X, Shen H *et al.* Phosphorylated ERK is a potential predictor of sensitivity to sorafenib when treating hepatocellular carcinoma: evidence from an *in vitro* study. *BMC Med* 2009; **7**: 41.
27 Shao YY, Lin ZZ, Hsu C *et al.* Early alpha-fetoprotein response predicts treatment efficacy of antiangiogenic systemic therapy in patients with advanced hepatocellular carcinoma. *Cancer* 2010; **116**: 4590–6.
28 Okusaka T, Kasugai H, Ishii H. A randomized phase II trial of intra-arterial chemotherapy using a novel lipophilic platinum derivative (SM-11355) in comparison with zinostatin sitmalamer in patients with hepatocellular carcinoma ASCO Annual Meeting 2009. 2009. #4583 Poster session.
29 Okusaka T, Okada S, Nakanishi T *et al.* Phase II trial of intra-arterial chemotherapy using a novel lipophilic platinum derivative (SM-11355) in patients with hepatocellular carcinoma. *Invest New Drugs* 2004; **22**: 169–76.
30 Imai N, Ikeda K, Seko Y. Transcatheter arterial chemotherapy with miriplatin for patients with hepatocellular carcinoma and Child-Pugh B liver cirrhosis. *Kanzo* 2010; **51**: 758–60.
31 Hanada M, Takasu H, Kitaura M. Acquired resistance to miriplatin in rat hepatoma AH109A/MP10 is associated with increased Bcl-2 expression, leading to defects in inducing apoptosis. *Oncol Rep* 2010; **24**: 1011–8.
32 Fujiyama S, Shibata J, Maeda S *et al.* Phase I clinical study of a novel lipophilic platinum complex (SM-11355) in patients with hepatocellular carcinoma refractory to cisplatin/lipiodol. *Br J Cancer* 2003; **89**: 1614–9.
33 Yamashita Y, Takahashi M, Fujimura N *et al.* Clinical evaluation of hepatic artery embolization: comparison between Gelfoam and Lipiodol with anticancer agent. *Radiat Med* 1987; **5**: 61–7.
34 Ikeda K, Okusaka T, Ikeda M *et al.* [Transcatheter arterial chemoembolization with a lipophilic platinum complex SM-11355(miriplatin hydrate) – safety and efficacy in combination with embolizing agents]. *Gan to Kagaku Ryoho* 2010; **37**: 271–5.
35 Maeda M, Uchida N, Sasaki T. Liposoluble platinum(II) complexes with antitumor activity.(Japanese) Japanese Journal of. *Cancer Res* 1986; **77**: 523–5.

Hepatology Research

Hepatology Research 2012; **42**: 621–626 doi: 10.1111/j.1872-034X.2012.00990.x

Special Report

Guidelines on nutritional management in Japanese patients with liver cirrhosis from the perspective of preventing hepatocellular carcinoma

Kazuyuki Suzuki,[1] Ryujin Endo,[1] Yutaka Kohgo,[3] Takaaki Ohtake,[3] Yoshiyuki Ueno,[4] Akinobu Kato,[2] Kazutomo Suzuki,[5] Ryo Shiraki,[6] Hisataka Moriwaki,[6] Daiki Habu,[7] Masaki Saito,[9] Shuhei Nishiguchi,[9] Kazuhiro Katayama,[8] Isao Sakaida[10] and for the Japanese Nutritional Study Group for Liver Cirrhosis 2008*

[1]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Iwate Medical University, [2]Morioka Municipal Hospital, Iwate, [3]Division of Gastroenterology and Hepatology/Oncology, Department of Medicine, Hokkaido Medical University, Hokkaido, [4]Division of Gastroenterology, Tohoku University Graduate School of Medicine, Miyagi, [5]Department of Gastroenterology and Hepatology, Koshigaya Hospital, Dokkyo Medical University, Saitama, [6]Department of Gastroenterology, Gifu University Graduate School of Medicine, Gifu, [7]Department of Food and Human Health Science, Graduate School of Human Life Science, Osaka City University, [8]Department of Hepatobiliary and Pancreatic Oncology, Osaka Medical Center for Cancer and Cardiovascular diseases, Osaka, [9]Division of Hepatobiliary and Pancreatic Disease, Department of Internal Medicine, Hyogo College of Medicine, Hyogo, and [10]Department of Gastroenterology and Hepatology, Yamaguchi University Graduate School of Medicine, Yamaguchi, Japan

Aim: The Japanese Nutritional Study Group for Liver Cirrhosis (JNUS) was assembled in 2008 with the support of a Health Labor Sciences Research Grant from the Ministry of Health, Labor and Welfare of Japan. The goal of the study group was to propose new nutritional guidelines for Japanese patients with liver cirrhosis (LC), with the aim of preventing hepatocellular carcinoma.

Methods: Between 2008 and 2010, the member investigators of JNUS conducted various clinical and experimental studies on nutrition on LC. These included anthropometric studies, a questionnaire study on daily nutrient intake, clinical trials, experimental studies using animal models, re-evaluation of previous publications and patient education. Over this 3-year period, the group members regularly discussed the nutritional issues related to LC, and a proposal was finally produced.

Results: Based on the results of JNUS projects and discussions among the members, general recommendations were made on how Japanese patients with LC should be managed nutritionally. These recommendations were proposed with a specific regard to the prevention of hepatocarcinogenesis.

Conclusion: The new JNUS guidelines on nutritional management for Japanese patients with LC will be useful for the actual nutritional management of patients with LC. The JNUS members hope that these guidelines will form the basis for future discussions and provide some direction in nutritional studies in the field of hepatology.

Key words: hepatocellular carcinoma, liver cirrhosis, malnutrition, nutrition, protein-energy malnutrition

Correspondence: Dr Kazuyuki Suzuki, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Iwate Medical University School of Medicine, 19-1 Uchimaru, Morioka, Iwate 020-8505, Japan. Email: kasuzuki@iwate-med.ac.jp

**Collaborators in the JNUS group*: Naohiro Kawamura (The Third Department of Internal Medicine, Kyorin University), Koichi Shiraishi (Division of Gastroenterology, Department of Internal Medicine, Tokai University), Masahiko Kato (School of Life Science, Sugiyama Jogakuin University), Motoh Iwasa (Department of Gastroenterology and Hepatology, Mie University), Kazuho Imanaka (Department of Hepatobiliary and Pancreatic Oncology, Osaka Medical Center for Cancer and Cardiovascular Disease), Toshinori Ito (Department of Medicine, Osaka Koseinenkin Hospital), Makoto Kuboki (Department of Gastroenterology, Hepatology and Nutrition, Kurashiki Medical Center), Yoshio Tokumoto (Department of Gastroenterology and Metabology, Ehime University) and Takumi Kawaguchi (Department of Digestive Disease Information and Research, Kurume University).

Received 26 December 2011; revised 13 February 2012; accepted 16 February 2012.

INTRODUCTION

THE LIVER IS a major organ in nutritional metabolism. Therefore, metabolic abnormalities in nutritional elements are generally observed in the progression of chronic liver disease (CLD). Malnutrition, which is characterized by protein-energy malnutrition (PEM), is known as an essential complication in patients with liver cirrhosis (LC) and is closely associated with LC prognosis.[1–7] On the other hand, the major cause of CLD in Japan is infection by hepatitis B virus (HBV) and hepatitis C virus (HCV) and approximately 34 000 patients with CLD die annually due to hepatocellular carcinoma (HCC).[8–11] Importantly, 90% of HCC cases are associated with LC.[12,13] Therefore, standard therapeutic guidelines on the use of antiviral agents for CLD patients with HBV and HCV infection have been established to prevent the occurrence of HCC.[14,15] However, because the number of elderly CLD patients is increasing, patients are often unable to tolerate full antiviral therapy. CLD caused by non-alcoholic steatohepatitis (NASH), which is associated with overweight status, has also been increasing.[16–18] These findings indicate that total nutritional management, including both diet and nutritional supplements, is required in order to prevent the progression of CLD and onset of HCC.[19–22]

Japanese dietitians were consulted in preparing the guidelines of both the Japan Society of Metabolism and Clinical Nutrition (2003)[23] and the European Society of Parenteral and Enteral Nutrition (2006 and 2009).[24,25] In addition, nutritional recommendations for the treatment of LC in Japan were incorporated into guidelines in Japan in 2010.[26] However, specific and detailed guidelines for the nutritional management of patients with LC in Japan have been lacking.

From these perspectives, the Japanese Nutritional Study Group for Liver Cirrhosis (JNUS) was assembled between 2008 and 2010 in order to establish new nutritional guidelines for LC. The study group was supported by a Health Labor Sciences Research Grant from the Ministry of Health, Labor and Welfare of Japan (H20-Hepatitis-General-005). Here, we describe the guidelines on nutritional management of Japanese LC patients, with the aim of preventing HCC.

METHODS

THE JNUS GROUP performed the following projects: (i) investigation of clinical and anthropometric characteristics in Japanese patients with LC; (ii) evaluation of daily nutrient intake (total calories, and individual intake of protein, fat, carbohydrate, trace elements such as iron and zinc, and sodium) using a 3-day questionnaire in CLD patients; (iii) development of new biomarkers representing non-protein respiratory quotients (npRQ) measured by indirect calorimetry; (iv) development of a new analytical system to estimate iron status in the blood; (v) a prospective controlled trial to examine whether branched-chain amino acid (BCAA) granule supplementation prevents recurrence of HCC after primary HCC treatment; (vi) a prospective double-blind controlled study evaluating the effects of zinc supplementation on the ammonia metabolism in LC patients with hyperammonemia; (vii) a pilot study to evaluate the effects of late-evening snacks (LES) and a new treatment (α-glucosidase inhibitor) in LC patients with impaired glucose tolerance; (viii) an experimental study to estimate the effects of supplementation of BCAA granules on the development of HCC in a mouse model of NASH; (ix) education programs for nutritional management in both LC patients and the general Japanese population; and (x) re-evaluation of previous publications concerning nutritional therapies in LC patients. After repeated discussion of the results, we then proposed the new guidelines for nutritional management of Japanese LC patients with the aim of preventing HCC.

RESULTS

THE FOLLOWING FINDINGS were obtained: (i) approximately 30% of patients with LC are overweight (body mass index >25), with the incidence being higher in male LC patients due to NASH and alcohol; (ii) only 30% of LC patients have adequate dietary intake for both energy and protein; (iii) iron intake (mean value, 6.7 mg/day) does not differ among CLD patients; (iv) percent arm circumference, percent arm muscle circumference, and serum concentrations of free fatty acid, tumor necrosis factor (TNF)-α and soluble TNF receptors are significantly correlated with npRQ;[27–29] (v) serum non-transferrin-bound iron (NTBI) determined by a newly developed high-performance liquid chromatography system is elevated in LC patients,[30,31] although further study is necessary to clarify whether serum NTBI levels are associated with the development of HCC; (vi) plasma amino acid imbalance is closely associated with the numbers and functions of peripheral dendritic cells;[32] (vii) long-term zinc supplementation therapy in LC patients tends to decrease HCC occurrence; (viii) LES and administration of α-glucosidase inhibitor improve impaired glucose

Table 1 Recommendations for nutritional management of liver cirrhosis: part 1

I. Assessment before nutrition and diet therapy
(1) Evaluate clinical stage (compensated or decompensated liver cirrhosis) and the severity of liver damage (i.e. Child–Pugh classification) as well as presence of portal-systemic shunt.
(2) Perform SGA† and anthropometry.‡
(3) Evaluate impaired glucose tolerance, insulin resistance§ and postprandial hyperglycemia.
(4) Evaluate oxidative stress conditions.¶
(5) Examine dietary intake using a questionnaire.
(6) Perform indirect calorimetry†† and trace element measurement.

†Subjective global assessment (SGA) is an effective method in the screening of malnourished patients. It examines age, sex, height, bodyweight, changes in bodyweight, changes in food intake, the presence of gastrointestinal symptoms, intensity of activities of daily living (ADL), the condition of loss of subcutaneous fat and muscles, the presence of edema/ascites, hair condition, among other factors.
‡In addition to height, bodyweight and body mass index (BMI: bodyweight [kg]/height [m]^2), arm circumference (AC) and triceps skinfold thickness (TSF) are measured using an insert tape and adipometer. Moreover, arm muscle circumference (AMC) is calculated by AC – 3.14 × TSF. Data are evaluated using standard values for the physical measurements of a Japanese individual (Japanese Anthropometric Reference Data: JARD 2001).[39] This allows the calculation of basal energy expenditure, resting energy expenditure and protein (amino acid) requirements according to age, sex difference and physical measurements. More detailed body composition analysis methods have recently become available, and these are based on bioelectrical impedance analysis.
§Homeostatic Model of Assessment of Insulin Resistance (HOMA-IR = blood fasting insulin [μU/mL] × fasting blood glucose level [mg/dL] / 405) is used as an index for insulin resistance, with HOMA-IR ≥2.5 considered to indicate insulin resistance. However, this equation assumes that the fasting blood glucose levels are <140 mg/dL.
¶Although there are numerous biomarkers for evaluating oxidative stress, the measurement of serum ferritin levels should be used for the purpose of preventing hepatocellular carcinoma. In addition, the presence of anemia is examined using hemoglobin concentrations.
††Where indirect calorimeters are available, measurement of resting energy expenditure, non-protein respiratory quotient (npRQ) and oxidation rates for various nutrients (carbohydrate, fat, protein) after overnight fasting is useful in evaluating protein-energy malnutrition. Anthropometric values (%AC, %AMC) and the serum free fatty acid levels are useful indexes for npRQ during routine care; serum levels of tumor necrosis factor (TNF)-α and soluble TNF receptors and plasma ghrelin levels may also be used as references.

tolerance;[33–35] (ix) supplementation of BCAA granules and BCAA-enriched nutrients improve liver function and energy metabolism;[36,37] and (x) supplementation of BCAA granules inhibits carcinogenesis in a mouse model of NASH, possibly via improvement of insulin resistance.[38]

Based on these data and discussions among the members of JNUS, guidelines for nutritional management of Japanese LC patients were prepared and are shown in Tables 1 and 2. The guidelines consist of two parts. The first part (Table 1) describes essential nutritional assessments that should be performed before instituting nutritional and diet therapy. The second part (Table 2) describes the recommended dietary management for each nutrient, including energy, protein, fat, sodium chloride, iron and other nutrient requirements. Restriction of sodium chloride was decided based on the therapeutic guidelines for hypertension by the Japanese Society of Hypertension.[40] We also included supplemental descriptions in the tables in order to ensure that dietitians are able to perform nutritional assessment and therapy in accordance with these guidelines.

At this point, it is not clear whether supplementation with BCAA granules has any preventive effects on HCC recurrence after primary treatment for HCC, as the number of enrolled patients is small. A double-blind controlled study for zinc supplementation in LC patients with hyperammonemia is also still on-going. The final results of this study are expected to be available by the end of 2012.

DISCUSSION

IN ORDER TO establish new guidelines on nutritional management in LC patients, it is important to consider hepatocarcinogenesis. In this article, based on the results of JNUS projects between 2008 and 2010 and re-evaluation of previous publications concerning nutritional therapies in LC patients with or without HCC, we proposed new guidelines for nutritional management of Japanese LC patients, with the aim of preventing HCC.

We hope these guidelines will form a basis for future discussions on nutritional management of LC by specialists such as hepatologists and dietitians.

Table 2 Recommendations for the nutritional management of liver cirrhosis: part 2

II. Nutrition and diet therapy
(1) Energy requirements[a]
25–35 kcal/kg (ideal bodyweight) per day, based on *Standards for Dietary Intake* (2010 Edition, Recommended Dietary Allowance According to Intensity of Daily Activity).
If any abnormalities are seen in glucose tolerance, intake should be 25 kcal/kg (ideal bodyweight) per day.
(2) Required protein intake[b]
If there is no protein intolerance: 1.0–1.5 g/kg/day (including oral BCAA granules).[c]
If there is protein intolerance: 0.5–0.7 g/kg per day + BCAA-enriched enteral nutrient mixture.[d]
(3) Required fat intake:[e] lipid energy ratio 20–25%.
(4) Sodium chloride:[f] ≤6 g/day and <5 g/day if there are ascites and/or edema, respectively
(5) Iron:[g] ≤7 mg/day if serum ferritin levels are above the upper limit of the reference interval.
(6) Others: zinc supplementation,[h] adequate intake of vitamins and dietary fiber (e.g. vegetables, fruits).
(7) LES as a divided meal (4 times/day) (amounts to 200 kcal).[i]

[a]Resting energy expenditure is often accelerated in liver cirrhosis patients and protein-energy malnutrition (PEM) is observed in approximately 80–90% of patients. However, approximately 30% of patients are obese, with a body mass index (BMI) of ≥25. Moreover, in cases of hepatitis C, there is a high frequency of insulin resistance exhibited. It is important to determine the required amount of energy by taking into account such nutritional conditions.
[b]Required protein intake includes the protein content of branched-chain amino acid (BCAA) formulation (BCAA granules or BCAA-enriched nutrient mixture for chronic liver failure). The majority of patients with decompensated liver cirrhosis (LC) often have protein intolerance, which is determined by referring to the blood ammonia levels.
[c]Patients in the decompensated state, including cases with hyperammonemia, are judged as having protein intolerance. The administration of BCAA granules (e.g. Livact Granules) is essential for the patient with serum albumin <3.5 g/dL, Fischer's ratio <1.8 and/or BTR < 3.5, and is usually administrated by dividing the dosage of 3 packs/day (12 g) into 3 administrations, but there is also a method whereby 2 packs are administrated (before sleep). Prevention of hepatocellular carcinoma (HCC) is expected in male hepatitis C patients with BMI >25 due to long-term administration of this formula. Improvement of the amino acid imbalance is also useful in recovering decreased dendritic cell functions.
[d]When administrating BCAA-enriched enteral mixtures (e.g. Aminoleban EN and Hepan ED), the amount of energy and protein present in this nutrient should be included in the total intake of energy and protein for the day. BCAA-enriched enteral mixtures should be the first choice in patients with PEM, regardless of the presence of protein intolerance.
[e]Ideal ratio of fatty acid composition for the inhibition of HCC has not been clarified, but a decline in n-6 and n-3 polyunsaturated fatty acids has been observed in patients with LC.
[f]Even patients who are not physically observed to have edema/ascites have a tendency for water retention, so fundamentally salt should be restricted.
[g]Excess deposition of iron in the liver causes oxidative stress and promotes hepatocarcinogenesis; thus, unless severe anemia is observed, an iron-restricted diet should be standard. Moreover, although the standard value of serum ferritin level differs with sex, phlebotomy in small amounts should be considered for patients with values ≥150 ng/mL.
[h]Zinc supplementation improves hyperammonemia and may suppress the occurrence of HCC in patients with LC over long-term administration.
[i]Lifestyle and eating habits of patients should examine. Late-evening snack (LES) is also useful for managing the blood glucose level in patients with impaired glucose tolerance, and combined use with α-glucosidase inhibitor enhances this effect. Usually, snacks such as rice balls (*onigiri*) are provided, but with the recommendation of using enteral nutrients, food products rich in BCAA are also used.
Fischer's ratio: BCAA/tyrosine + phenylalanine.
BTR: molar ratio of BCAA and tyrosine.

ACKNOWLEDGMENTS

WE WOULD LIKE to thank the members of the JNUS and their collaborators in these projects. We would also like to thank Ms Koko Motodate for secretarial assistance. This research was supported by a Health Labor Sciences Research Grant from the Ministry of Health, Labor and Welfare of Japan (H20-Hepatitis-General-005).

REFERENCES

1 Caregaro L, Alberino F, Amodio P *et al.* Malnutrition in alcoholic and virus-related cirrhosis. *Am J Clin Nutr* 1996; **63**: 602–9.
2 Campillo B, Richardet JP, Scherman E, Bories PN. Evaluation of nutritional practice in hospitalized cirrhotic patients: results of a prospective study. *Nutrition* 2003; **19**: 515–21.

3 Cabré E, Gassull MA. Nutrition in liver disease. *Curr Opin Clin Nutr Metab Care* 2005; **8**: 545–51.
4 Riggio O, Angeloni S, Ciuffa L *et al.* Malnutrition is not related to alterations in energy balance in patients with stable liver cirrhosis. *Clin Nutr* 2003; **22**: 553–9.
5 Tajika M, Kato M, Mohri H *et al.* Prognostic value of energy metabolism in patients with viral liver cirrhosis. *Nutrition* 2002; **18**: 229–34.
6 Guglielmi FW, Panella C, Buda A *et al.* Nutritional state and energy balance in cirrhotic patients with or without hypermetabolism. Multicentre prospective study by the "Nutritional Problems in Gastroenterology" Section of the Italian Society of Gastroenterology (SIGE). *Dig Liver Dis* 2005; **37**: 681–8.
7 Tsiaousi ET, Hatzitolios AI, Trygonis SK, Savopoulos CG. Malnutrition in end stage liver disease: recommendations and nutritional support. *J Gastroenterol Hepatol* 2008; **23**: 527–33.
8 Shiratori Y, Shiina S, Imamura M *et al.* Characteristic difference of hepatocellular carcinoma between hepatitis B- and C- viral infection in Japan. *Hepatology* 1995; **22**: 1027–33.
9 Kiyosawa K, Umemura T, Ichijo T *et al.* Hepatocellular carcinoma: recent trends in Japan. *Gastroenterology* 2004; **127**: S17–26.
10 Michitaka K, Nishiguchi S, Aoyagi Y *et al.* Etiology of liver cirrhosis in Japan: a nationwide survey. *J Gastroenterol* 2010; **45**: 86–94.
11 Nagaoki Y, Hyogo H, Aikata H *et al.* Recent trend of clinical features in patients with hepatocellular carcinoma. *Hepatol Res* 2011; doi: 10.1111/j.1872-034X.2011.00929.x.
12 Ikai I, Arii S, Okazaki M *et al.* Report of the 17th nationwide follow-up survey of primary liver cancer in Japan. *Hepatol Res* 2007; **37**: 676–9.
13 Kudoh M, Arii S, Ikai I *et al.* The nationwide report registered every 2 years by the Liver cancer Study Group of Japan (in Japanese with English abstract). *Kanzo* 2007; **48**: 117–40.
14 Kumada H, Okanoue T, Onji M *et al.* Guidelines for the treatment of chronic hepatitis and cirrhosis due to hepatitis B virus infection for the fiscal year 2008 in Japan. *Hepatol Res* 2010; **40**: 1–7.
15 Kumada H, Okanoue T, Onji M *et al.* Guidelines for the treatment of chronic hepatitis and cirrhosis due to hepatitis C virus infection for the fiscal year 2008 in Japan. *Hepatol Res* 2010; **40**: 8–13.
16 Shimada M, Hashimoto E, Tasniai M *et al.* Hepatocellular carcinoma in patients with nonalcoholic steatohepatitis. *J Hepatol* 2002; **48**: S104–12.
17 Yoshiike N, Lwin H. Epidemiological aspects of obesity and NASH/NAFLD in Japan. *Hepatol Res* 2005; **33**: 77–82.
18 Hashimoto E, Yatsuji S, Tobari M *et al.* Hepatocellular carcinoma in patients with nonalcoholic steatohepatitis. *J Gastroenterol* 2009; **44** (Supple XIX): 89–95.
19 Marchesini G, Bianchi G, Merli M *et al.* Nutritional supplementation with branched-chain amino acids in advanced cirrhosis: a double-blind, randomized trial. *Gastroenterology* 2003; **124**: 1792–801.
20 Muto Y, Sato S, Watanabe A *et al.* Effects of oral branched chain amino acid granules on event-free survival in patients with liver cirrhosis. *Clin Gastroenterol Hepatol* 2005; **3**: 705–13.
21 Muto Y, Sato S, Watanabe A *et al.* Overweight and obesity increases the risk for liver cancer in patients with liver cirrhosis and long-term oral supplementation with branched-chain amino acid granules inhibits liver carcinogenesis in heavier patients with liver cirrhosis. *Hepatol Res* 2006; **35**: 204–14.
22 Kuroda H, Kasai K, Kakisaka K *et al.* Changes in liver function parameters after percutaneous radiofrequency ablation therapy in patients with hepatocellular carcinoma. *Hepatol Res* 2010; **40**: 550–54.
23 Watanabe A, Moriwaki H, Kato A, Teramoto F. Consensus of nutritional assessments and therapies in liver diseases. Eiyo-Hyoka to. *Chiryo* 2003; **20**: 181–96 (in Japanese).
24 Plauth M, Cabre E, Riggio O *et al.* ESPEN guidelines on enteral nutrition: liver disease. Clin. *Nutrition* 2006; **25**: 285–94.
25 Plauth M, Cabre E, Campillo O *et al.* ESPEN guidelines on parenteral nutrition: hepatology. *Clin Nutr* 2009; **28**: 436–44.
26 Imawari M, Fukui H, Moriwaki H *et al.* Nutritional therapy. In: the Japanese Society of Gastroenterology, ed. *Clinical Practice Guidelines for the Management of Liver Cirrhosis*, 1st edn. Tokyo: Nankodo, 2010; 22–33 (in Japanese).
27 Terakura Y, Shiraki M, Nishimura K *et al.* Indirect calorimetry and anthropometry to estimate energy metabolism in patients with liver cirrhosis. *J Nutr Sci Vitaminol (Tokyo)* 2010; **56**: 372–9.
28 Shiraki M, Terakura Y, Iwasa J *et al.* Elevated serum tumor necrosis factor-alpha and soluble tumor necrosis factor receptors correlate with aberrant energy metabolism in liver cirrhosis. *Nutrition* 2010; **26**: 269–75.
29 Suzuki K, Takikawa Y. Biomarkers of malnutrition in liver cirrhosis. In: Preedy VR, Lakshman R, Srirajaskanthan R *et al.*, eds. *Nutrition, Diet Therapy, and the Liver*. London: CRC Press, 2009; 203–15.
30 Kohgo Y, Ikuta K, Ohtake T, Torimoto Y, Kato J. Body iron metabolism and pathophysiology of iron overload. *Int J Hematol* 2008; **88**: 7–15.
31 Kohgo Y, Ohtake T, Ikuta K, Suzuki Y, Torimoto Y, Kato J. Dysregulation of systemic iron metabolism in alcoholic liver disease. *J Gastroenterol Hepatol* 2008; **23**: S78–81.
32 Kakazu E, Ueno Y, Kondo Y *et al.* Branched chain amino acids enhance the maturation and function of myeloid dendritic cells *ex vivo* in patients with advanced cirrhosis. *Hepatology* 2009; **50**: 1936–45.
33 Korenaga K, Korenaga M, Uchida K, Yamasaki T, Sakaida I. Effects of a late evening snack combined with alpha-glucosidase inhibitor on liver cirrhosis. *Hepatol Res* 2008; **38**: 1087–97.