(ii) Multiple new lesions observed on at least two consecutive occasions in CT assessment of therapeutic response immediately after (>1 month) TACE;
(2) Appearance of vascular invasion;
(3) Appearance of distant metastasis;
(4) Tumor markers.
(i) Continued increase in tumor markers with transient decrease only immediately after TACE procedure.

In the present NLCT study, as many as 91% of patients underwent prior treatment, in whom 29% received hepatic arterial infusion chemotherapy (HAIC). Comparison of the characteristics of the remaining NLCT study patients with those of previous clinical trials[1,2,4–6] is presented in Table 1.

An adverse event (AE) report on all-patient special drug use surveillance (SDUS) conducted in Japan[7] contains analysis and reporting of AEs for 777 patients for whom CRFs were collected up until 19 December 2009.

That report compared the clinical characteristics for 51 of these 777 patients who died within 30 days of treatment ("early death group") and the 382 patients who survived for ≥61 days ("control survival group"). The data indicate that the prevalence of Eastern Cooperative Oncology Group (ECOG) PS grades ≥2 tended to be high among patients in the "early death group" at 5.9% compared with those in the "control survival group" at 0.5%, suggesting the need to carefully follow the course of patients with poor PS. In the NLCT study, 98% of patients had a PS score of 0–1.

In terms of hepatic function, two randomized, placebo-controlled trials demonstrating the usefulness of sorafenib were conducted on Child–Pugh class A patients.[1,2]

Meanwhile, in the NLCT study, 81% of evaluable patients were Child–Pugh class A, and 94% had a Child–Pugh score of ≤7. Comparison of treatment results of Child–Pugh class A and B patients did not reveal any difference in tumor control rates (46% vs. 50%; $P = 0.52$), but overall survival (OS) was inferior in Child–Pugh class B patients (median OS: 11.5 months vs. 5.2 months; $P < 0.01$).

In a Phase I trial conducted in Japan, no clear increase in toxicity was observed in Child–Pugh class B patients compared with Child–Pugh class A patients.[8] On the other hand, the aforementioned SDUS found that hepatic functional reserve was poor in the "early death group" compared to the "control survival group".[4]

A Phase II study of sorafenib therapy in HCC patients including those with Child–Pugh class B is currently underway in Japan (UMIN [University Hospital Medical Information Network] 000002972). Another study currently being conducted worldwide is the Global Investigation of therapeutic decisions in HCC and of its treatment with sorafenib (GIDEON); a large-scale prospective study on actual sorafenib therapy of patients with unresectable HCC. The GIDEON study is recruiting 3000 patients from over 400 sites in more than 40 countries in the Asia-Pacific region, Europe, USA, Latin America, and Japan.[9] The study's first interim analysis has been released and the findings of 511 recruited patients including those in Child–Pugh class B have been examined. No significant difference in grade 3 or 4 AEs was found to exist between Child–Pugh class A and B patients, at 31% and 38%, respectively.[10] Future GIDEON study analyses are expected to provide crucial information concerning the safety of sorafenib for Child–Pugh class B patients.

A Phase III study of post-TACE adjuvant sorafenib chemotherapy versus placebo conducted in Japan and South Korea failed to demonstrate the usefulness of sorafenib administration.[11] In addition, a Phase III placebo-controlled trial of adjuvant sorafenib chemotherapy following radical treatment (either surgical resection or LAT) of HCC (STORM Trial) is currently underway.[12]

The NLCT study did not include any patients treated with sorafenib as adjuvant chemotherapy.

Method of administration

CQ1-2 What is the optimal dosage regimen for sorafenib therapy?

Recommendation The standard dosage regimen for sorafenib therapy is 400 mg administered twice daily (800 mg/day).

The safety and efficacy of sorafenib therapy in combination with other anti-neoplastic agents or TACE have not been established.

Scientific statement In the two aforementioned randomized, placebo-controlled trials demonstrating the usefulness of sorafenib, a single 400 mg dose of sorafenib was administered twice daily (800 mg/day),[1,2] and usefulness was not observed at a reduced dosage. A high-fat diet reportedly lowers the plasma concentration of sorafenib so administration should be avoided from 1 h before to 2 h after meals.

Reduced dose regimen due to AEs was conducted in the abovementioned studies as follows:
Step-down dose (step 1): 400 mg once a day
Step-down dose (step 2): 400 mg every another day

Table 1 Characteristics of patients receiving sorafenib therapy

	NLCT Study ($n = 264$) %	SDUS[4,6] ($n = 777$) %	SHARP Trial[1] ($n = 299$) %	Asia-Pacific Trial[2] ($n = 150$) %	Sorafenib phase II[5] ($n = 137$) %
Age (years)					
Median	70		64.9 ± 11.2	51	69
Range	33–87		(mean ± SD)	23–86	28–86
Gender					
Male	79		87	84.7	71
PS					
0	83	69.5	54	25.3	50
1	15	26.5	38	69.3	50
Child–Pugh class					
A	81	88.2	95	97.3	72
B	19	9.9	5	2.7	28
HBs antigen					
Positive	20	24.6	19	70.7	17
HCV antibody					
Positive	62	52.2	29	10.7	48
Prior treatment					
Yes	91	91.2	49		
Resection	31		19		
LAT	47		15		
TACE	78		29		
HAIC	29				
Advanced vascular invasion					
Yes	18		36	36.0	
Extrapulmonary lesion(s)					
Yes	51	54.4	53	68.7	–
Lymph node(s)	22	15.4	30	52	–
Lung(s)	26	30.6	22	30.7	–
Maximum tumor size (mm)	34				
Range	7–170				
≥30 mm	59				
Stage	†	‡	§	§	‡
I	1	1.2			0
II	9	4.8			3
III	30	20.7	B: 18	B: NE	31
IV A	17	23	C: 82	C: 95.3	66
IV B	43	47.6			
T-Bil (mg/dL)					
Median	0.8		0.7		
Range	0–7.7		0.1–16.4		
Alb (g/dL)					
Median	3.5		3.9		
Range	1.7–4.8		2.7–5.3		
AFP (ng/mL)					
Median	218		44.3		
Range	0.8–252150		0–2080000		
≥10	84			77.3	76

†Japanese Classification of Liver Cancer.
‡UICC classification.
§BCLC classification.
AFP, α fetoprotein; Alb, albumin; HAIC, hepatic arterial infusion chemotherapy; HBs, Hepatitis B surface antigen; HCV, hepatitis C virus; LAT, local ablation therapy; NLCT, New Liver Cancer Therapies; PS, performance status; SD, standard deviation; SDUS, special drug use surveillance; SHARP, sorafenib hepatocellular carcinoma assessment randomized protocol; TACE, transcatheter arterial chemoembolization; T-Bil, total bilirubin.

In the NLCT study, 77% of patients received the standard dosage regimen of 400 mg twice daily, while 21% were started on a reduced dose.

Comparison of the group started on the standard dose of 800 mg/day and the group started on a reduced dose did not reveal any significant differences in either duration of treatment (117 days vs. 81 days; $P = 0.05$) or number of dosing days (107 days vs. 78 days; $P = 0.10$). Furthermore, dosage was subsequently increased in 22% of the reduced initial dose group. Daily dosage intensity (DI) was 615 mg in the standard-dose group and 387 mg in the reduced-dose group.

It is conceivable to start sorafenib therapy at a reduced dose according to the condition of the patient or prevention of AEs. Because efficacy at reduced doses has not been demonstrated, as long as no AEs are encountered in the course of treatment, consideration should be given to increasing the dose to the standard dosage regimen.

With regard to sorafenib combination therapies, Phase I and Phase II studies on systemic chemotherapy in combination with sorafenib therapy have been published for radiotherapy,[13,14] doxorubicin,[15] tegafur/uracil,[16] and octreotide.[17] Several Japanese clinical trials are also being conducted on combination therapy, specifically low-dose cisplatin/fluorouracil HAIC (UMIN000004315), cisplatin HAIC (UMIN000001496), and S-1 chemotherapy (UMIN000002418, UMIN000002590). Therapies combining sorafenib with other anti-neoplastic agents are therefore still in the research stage, and their efficacy is yet to be demonstrated.

In terms of sorafenib combined with LAT, a Phase III placebo-controlled trial of adjuvant sorafenib chemotherapy following radical treatment (surgical resection or LAT) of HCC (STORM Trial) is presently underway.[12] Meanwhile, sorafenib combined with TACE has been investigated in a Phase III study of post-TACE adjuvant sorafenib chemotherapy versus placebo conducted in Japan and South Korea, but the study failed to demonstrate the usefulness of sorafenib administration.[11] Another Phase II trial on TACE in combination with sorafenib is presently being carried out in Japan (TACTICS; UMIN 000004316).

Discontinuation criteria

CQ1-3 How and when should sorafenib therapy be discontinued?

Recommendation Administration of sorafenib should be discontinued immediately in the event of SAEs.

Discontinuation should also be considered when disease progression is confirmed by radiological imaging or on the basis of patient symptoms.

Scientific statement In the two randomized, placebo-controlled trials demonstrating the usefulness of sorafenib therapy, administration was discontinued upon confirmation of radiologic or symptomatic progression or in the event of SAEs.[1,2]

In the NLCT study, sorafenib therapy was discontinued in 185 patients with 63% due to disease progression and 22% due to AEs. Moreover, 60% of discontinued patients did not undergo post-treatment.

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

Adverse events

CQ1-4 What are the adverse events associated with sorafenib therapy?

Recommendation Some form of AE has appeared in almost all patients treated with sorafenib.

These AEs vary, and have even included serious adverse events (SAEs) resulting in death. Familiarity with these AEs is therefore essential, to carefully monitor patient progress while taking the necessary precautions, and to respond rapidly when an AE occurs.

The following AEs are known to occur frequently in patients treated with sorafenib.

1 Hand-foot skin reaction (HFSR);
2 Rash/desquamation;
3 Diarrhea;
4 Anorexia;
5 Hypertension;
6 Fatigue;
7 Alopecia;
8 Nausea.

While infrequent, life-threatening SAEs include hepatic failure, interstitial pneumonia, and gastrointestinal hemorrhage.

In addition, the following blood test abnormalities are known to occur frequently in patients treated with sorafenib.

1 Leukopenia;
2 Neutropenia;
3 Anemia;
4 Thrombocytopenia;
5 Hepatic impairment (elevated AST [aspartate aminotransferase], ALT [alanine aminotransferase], ALP [alkaline phosphatase], γ-GTP [γ-glutamyltransferase], T-Bil [total bilirubin]);

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.

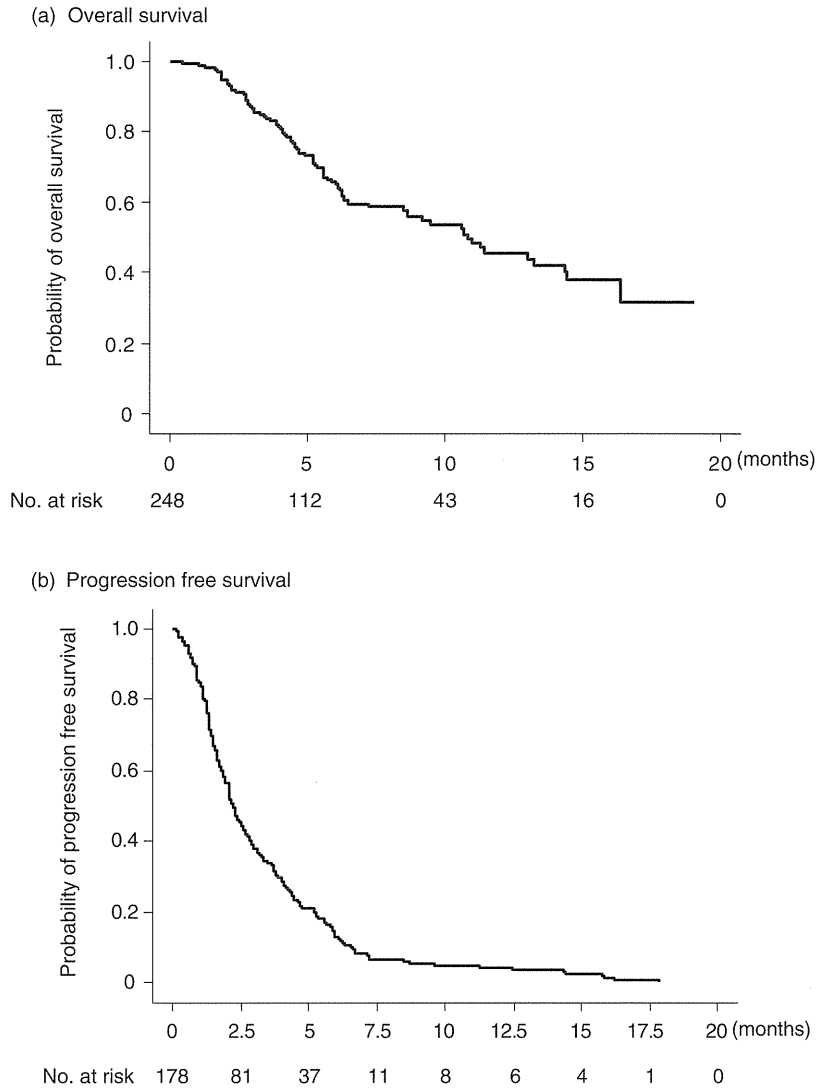

Figure 1 Therapeutic efficacy of sorafenib. (a) Overall survival. (b) Progression free survival.

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.

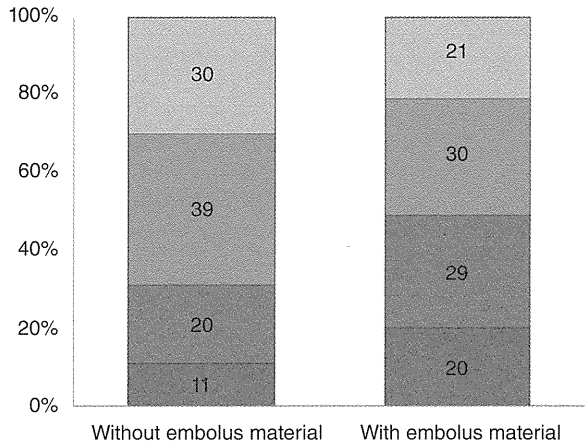

Figure 2 Therapeutic efficacy of miriplatin with or without embolus material.

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]

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Original Article

Cost-effectiveness analysis on the surveillance for hepatocellular carcinoma in liver cirrhosis patients using contrast-enhanced ultrasonography

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Aim: Sonazoid is a new contrast agent for ultrasonography (US). Contrast-enhanced ultrasonography (CEUS) using Sonazoid enables Kupffer imaging, which improves the sensitivity of hepatocellular carcinoma (HCC) detection. However, there are no studies on the cost-effectiveness of HCC surveillance using Sonazoid.

Methods: We constructed a Markov model simulating the natural history of HCV-related liver cirrhosis (LC) patients, and compared three strategies (no surveillance, US surveillance and CEUS surveillance). The transition probability and cost data were obtained from published data. The simulation and analysis were performed using TreeAge pro 2009 software.

Results: When compared to the no surveillance group, the US and CEUS surveillance groups increased the life expectancy by 1.67 and 1.99 quality-adjusted life-years (QALY), respectively, and the incremental cost effectiveness ratio (ICER) were 17 296 $US/QALY and 18 384 $US/QALY, respectively. These results were both less than the commonly-accepted threshold of $US 50 000/QALY. Even if the CEUS surveillance group was compared with the US surveillance group, the ICER was $US 24 250 and thus cost-effective. Sensitivity analysis showed that the annual incidence of HCC and CEUS sensitivity were two critical parameters. However, when the annual incidence of HCC is more than 2% and/or the CEUS sensitivity is more than 80%, the ICER was also cost-effective.

Conclusions: Contrast-enhanced ultrasonography surveillance for HCC is a cost-effective strategy for LC patients and gains their longest additional life years, with similar degree of ICER in the US surveillance group. CEUS surveillance using Sonazoid is expected to be used not only in Japan, but also world-wide.

Key words: contrast-enhanced ultrasonography, cost-effective analysis, hepatocellular carcinoma, Sonazoid, surveillance

INTRODUCTION

HEPATOCELLULAR CARCINOMA (HCC) is the fifth most common neoplasm in the world.[1] Although many environmental factors, including aflatoxins and alcohol,[2,3] have been implicated in the development of HCC, hepatitis B virus and hepatitis C virus (HCV) are the most important factors associated with the progression from chronic hepatitis to cirrhosis, and eventually to HCC.[4] Surveillance for HCC is recommended in patients with chronic liver injury to detect small-sized HCCs, which can be efficiently treated.[5] Ultrasonography (US) is a major surveillance method, because it provides low cost, real-time and non-invasive detection. However, there are some problems associated with this surveillance approach. It is known that the annual incidence of HCC increases with the degree of fibrosis.[6] Unfortunately, an increase in fibrosis makes US surveillance substantially more difficult, because the

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intrahepatic echo patterns in US become rough with advanced fibrosis.

Recently, a novel intravenous contrast medium for US, "Sonazoid", has become available in Japan. This strategy of using US with Sonazoid dramatically improves the sensitivity in the diagnosis of hepatic malignancy.[7] Thus, contrast-enhanced ultrasonography (CEUS) using Sonazoid can effectively detect HCCs that are usually overlooked by B-mode, which is currently used for observation. Therefore, this new contrast medium would be desirable for use in HCC surveillance. However, it is almost five times more expensive than the conventional observational approach in Japan. Until now, the surveillance for HCC using this novel agent has not been evaluated with regard to its cost-effectiveness, and this is the focus of the current study.

METHODS

WE USED TREE Age Pro 2009 (Tree Age Software Inc., William-stown, MA, USA) software to construct a Markov model, and estimated the cost-effectiveness of a surveillance program for HCC. The transition probabilities used in the analysis are listed in Table 1. The age specific mortality rate was obtained

Table 1 Values used in the analyses

Variable	Base value	Range	References
Excess annual mortality			
Child A Cirrhosis	0.02	0.00–0.08	8–11
Child B/C Cirrhosis	0.13	0.07–0.40	
Large HCC	0.90	0.50–1.00	12–14
Annual transition rate			
Child A to Child B/C	0.04	0.02–0.08	8,10,15,16
Small HCC to Large HCC (Undetected)*	0.30	0.10–0.60	17–19
Small HCC to large HCC (TAE treated)*	0.10	0.02–0.20	20–22
Annual incidence of HCC			
Incidence of new HCC	0.07	0.01–0.08	6,8,23–27
Incidence of HCC after curative treatment	0.20	0.10–0.37	13,25,28
Probability of small HCC at diagnosis	0.90	0.66–1.00	23,29
Test characteristics			
US			
Sensitivity	0.70	0.40–0.80	30–32
Specificity	0.90	0.70–0.90	
CEUS			
Sensitivity	0.90	0.80–0.95	7
Specificity	0.95	0.80–0.95	
Cost data			20,23,31,33–37
US	61		
CEUS	248		
Confirmation test	862	170–1 100	
LC	587	300–1 200	38
Decompensated LC	6 422	6 422–23 000	38
Terminal care	5 556	5 000–42 000	38
Resection	19 390	12 000–40 000	39
RFA	10 333	35 000–11 000	39
TAE	7 778	35 000–12 000	
Health-related QOL			40
Child A	0.75	0.66–0.83	
Child B/C	0.66	0.46–0.86	
HCC	0.64	0.44–0.86	

*Per 6 months. The costs were $US/6 months, and the baseline cost has been adjusted to US dollars (Currency rate: $1.00 = ¥90.00). CEUS, contrast-enhanced ultrasonography; HCC, hepatocellular carcinoma; LC, liver cirrhosis; QOL, quality of life; RFA, radio-frequency ablation; TAE, transcatheter arterial embolization; US, ultrasonography.