# Guideline on the use of new anticancer drugs for the treatment of Hepatocellular Carcinoma 2010 update

**Guideline on the Use of New Anticancer Drugs for the Treatment of Hepatocellular Carcinoma 2010 update**

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**Abstract:**

The '*Guideline on the Use of New Anticancer Drugs for the Treatment of Hepatocellular Carcinoma*' was prepared by the Study Group on New Liver Cancer Therapies established by the '*Research Project on Emergency Measures to Overcome Hepatitis*' under the auspices of the Health and Labour Sciences Research Grant. The Guideline brings together data collected by the Study Group on the use and incidence of adverse events in 264 patients with advanced HCC treated using sorafenib and in 535 patients with advanced HCC treated using miriplatin at 16 participating institutions up until 22 December 2010, as well as referring to the published studies, academic presentations, and reports from the private sector. The aim of this Guideline is to facilitate understanding and current thinking regarding the proper usage of new anticancer drugs towards actual use in therapy. In terms of the format, the Guideline presents 'clinical questions' on issues pertaining to medical care, makes 'recommendations' on diagnosis and treatment in response to each of these clinical questions, and provides a rationale for these recommendations in the form of 'scientific statements'.

## Introduction

The molecular-targeted agent sorafenib has been found to significantly prolong survival in patient with hepatocellular carcinoma (HCC).[1, 2)] In May 2009, sorafenib was approved in Japan for unresectable HCC. Furthermore, miriplatin was approved in Japan for the treatment of HCC in January 2010, and clinical trials are also currently underway on a number of other promising new anticancer agents. Treatment of HCC is thus undergoing a period of major transition, but the role of these anticancer drugs and conventional therapies remains unclear, leading to concerns about the risk of serious AEs (SAEs).

The Study Group on New Liver Cancer Therapies (the Study Group) was formed as part of the 'Research Project on Emergency Measures to Overcome Hepatitis' sponsored by the Health and Labour Sciences Research Grant, with the overall purpose of formulating a guideline to facilitate understanding on the practical usage of new anticancer drugs.

The Study Group collected information on the use of new anticancer drugs, sorafenib and miriplatin at 16 affiliated institutions and compiled current opinions regarding the proper use of these drugs based on published studies, academic conference papers and reports from the private sector. These results have now been compiled in the form of a guideline.

However, it takes notice that this guideline is provisional and has been prepared to expedite the provision of proper information because information on these new anticancer drugs is constantly being updated.

## I. Study methods, subjects and participating institutions

### A. Basic statistics

The Study Group's 'New Liver Cancer Therapies' (NLCT) study was based on data from patients with advanced HCC treated using sorafenib or miriplatin up until 22 December 2010 at the participating institutions. Clinical data were recorded by each institution in case report files (CRFs) created by the Study Group. Of the patients enrolled in this study, 264 were treated with sorafenib and 535 were treated with miriplatin. Any input variables that were unclear were excluded from the analyzed data. After analyzing collecting data on the use of these drugs, the Study Group compiled current opinions on proper use based on published papers, academic conference papers and reports from the private sector. The Study Group proposed a series of ‘clinical questions’ (CQ) on issues pertaining to practical medical care and summarized the current evidence in response to each of these CQ in the form of 'scientific statements', as well as making ‘recommendations’.

**<Participating institutions>**

The 16 institutions that participated in this study were: Kinki University; Chiba University; Yamaguchi University; Kurume University; Kyorin University; Showa University; Ehime University; Okayama University; Kyoundo Hospital; Tohoku University; Osaka University; Gifu University; Hyogo College of Medicine; Toranomon Hospital; Saitama Medical University; and Kanazawa University.

## II. Results

### II-1 Sorafenib therapy

#### II-1-1. Indications

***CQ1-1***

For whom patients with HCC is sorafenib therapy indicated?

***Recommendation***

Sorafenib therapy is indicated in HCC patients with good performance status (PS) and Child-Pugh class A for whom surgical resection, local ablation therapy (LAT), and transcatheter arterial chemoembolization (TACE) are not possible or not indicated.

The safety and efficacy of sorafenib has not been established in Child-Pugh class B/C patients.

Furthermore, the usefulness of sorafenib as adjuvant chemotherapy after resection, LAT, or TACE of HCC has not been demonstrated.

***Scientific statement***

Two randomized, placebo-controlled trials demonstrating the usefulness of sorafenib were conducted on patients in whom surgical resection, LAT and TACE were not indicated or who were unresponsive to TACE.[1, 2)]

The Japan Society of Hepatology provides the following definitions for impossible and refractory cases to TACE.[3)]

Definition of “Impossible cases to TACE”

1. Deterioration of treated vessel resulting in inability to select catheter for insertion into the nutrient vessel
2. Deterioration in hepatic function to Child-Pugh class C due to repeated treatment
3. Patients with tumor thrombus in main trunk or first branch of portal vein
4. Patients with large arterio-portal shunts

Definition of “Refractory cases to TACE”

1) Intrahepatic lesion(s)

(i) Poor Lipiodol® deposits (≤50%) observed on at least 2 consecutive occasions in CT assessment of therapeutic response immediately after (>1 month) correctly performing TACE

(ii) Multiple new lesions observed on at least 2 consecutive occasions in CT assessment of therapeutic response immediately after (>1month) TACE

2) Appearance of vascular invasion

3) Appearance of distant metastasis

4) Tumor markers

Continued increase in tumor markers with transient decrease only immediately after TACE procedure

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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 to 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, 2 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 to Child-Pugh class A patients.[6] 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 hepatocellular carcinoma 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 3,000 patients from over 400 sites in more than 40 countries in the Asia-Pacific region, Europe, USA, Latin America, and Japan.[8] 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.[9] 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.[10] 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.[11]

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

### II-1-2 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 hour before to 2 hours after meals.

Reduced dose regimen due to AEs was conducted in the above-mentioned studies as follows:

| | |
|---|---|
| Step-down dose (step 1): | 400 mg once a day |
| Step-down dose (step 2): | 400mg every another day |

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,[12, 13)]doxorubicin,[14)]tegafur/uracil,[15)] and octreotide.[16)] 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.[11] 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.[10]Another Phase II trial on TACE in combination with sorafenib is presently being carried out in Japan (TACTICS; UMIN 000004316).

### II-1-3 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.

### II-1-4 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 occur.

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

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- 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.

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1. Leukopenia
2. Neutropenia
3. Anemia
4. Thrombocytopenia
5. Hepatic impairment (elevated AST/ALT/ALP/γ-GTP)
6. T-Bil elevation

7. Amylase elevation
8. Electrolyte abnormality (hyponatremia, hypokalemia, hypocalcemia, hypophosphatemia)
9. Hypoalbuminemia

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AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, γ-GTP; gamma-glutamyltransferase, T-Bil: total bilirubin

***Scientific statement***

The incidence of sorafenib-related AEs was 80% in the 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,[17)] 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[17)] (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 to

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 3 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 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.

### II-1-5. 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 (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.

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[17].

**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.

- **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)]

### II-1-6. 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 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.

AFP (alpha-fetoprotein) and PIVKA-II (DCP) (protein induced by vitamin K absence or abnormality, des-gamma-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.

### II-1-7. Continuation of therapy

***CQ1-7***

How long sorafenib therapy should 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.

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.

**II-1-8. 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 searching in some prospective clinical trials using sorafenib.

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 to 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).

## II-2 Hepatic arterial infusion with miriplatin

### II-2-1. 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 11). 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 11).

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

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 post-operative 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 12). In a study of TAI with miriplatin**,** in 17 Child-Pugh class B patients, no significant differences were seen in pre- or post-treatment 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.[29)]

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 12, 13).

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 14), 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 controled.[29)]

***CQ2-3***

Is miriplatin effective against cisplatin-resistant HCCs?

***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.[30)]

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%.[31)] 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.

### II-2-2. 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 comparing to miriplatin alone, but there is currently insufficient evidence to support this.

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

***Scientific statement***

Compared to 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,[32)]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.[31, 33)]

Meanwhile, two studies on miriplatin used in combination with embolic material s

on small number of patients have reported high rates of treatment success, with TE3 and TE4 scores obtained in 60.0-77.7% of patients.[29, 34)]

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 15).

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 16, 17).

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 small number of patients did not reveal any serious complications.[29)]

***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 impact of miriplatin on renal function is considered to be mild. Two of the aforementioned Phase II trials did not perform pre-treatment hydration to prevent renal impairment.[28, 29]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.

**II-2-3. 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 to 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% (Table 9).

Incidences of nausea and vomiting were low compared to 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, 33, 34)]

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 3 times the Upper limits of normal (ULN).

***CQ2-7***

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

***Recommendation***

Typically, no deterioration is seen in post-operative $ICG_{15}$, 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.[33)]

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.[31)]

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)]

***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.[31, 33)] Likewise, no vascular injuries have been reported in the NLCT study (Table 9). 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 9 patients at 2-6 months after treatment, no arterial stenoses, arterial occlusions, or arterioportal shunts were observed.[29)]

**II-2-4. 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,[27] while the Phase II trial evaluated the antitumor effects of miriplatin using dynamic CT every 3 months.[33]

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**Table 1:** Characteristics of patients receiving sorafenib therapy

| | NLCT Study (n=264) | SDUS[4] (n=777) | SHARP Trial[1,16] (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 | *1 | *2 | *3 | *3 | *2 |
| 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 |

*1 Japanese Classification of Liver Cancer; *2 UICC classification; *3 BCLC classification

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

| AE | NLCT Study (n=264) | | SDUS[16] (n=777) | | SHARP Trial[1,16] (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

**Table 3:** Abnormal clinical laboratory values with sorafenib therapy

| Clinical laboratory data | NLCT Study (n=264) | | SDUS[16] (n=777) | | SHARP Trial[1)16)] (n=297) | |
|---|---|---|---|---|---|---|
| | AE incidence | | | | | |
| | Total (%) | G3/4 (%) | Total (%) | SARs (%) | 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 γGTP | 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

**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 |

**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 W | 2 W | 3 W | 4 W | 6 W | 8 W | 10 W | 12 W | 16 W | 20 W | --- | 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 | | | | | | | | | | | | |

**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 (%) | § | | | |
| Total 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.

**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 | |
| Sex | | | | |
| | 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

**Table 8:** Abnormal clinical laboratory values with miriplatin therapy

| | NLCT Study (n=535) | | Phase III Trial[33] (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* |

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* Increased Cre data includes G2 patients

**Table 9:** Incidence of drug-related adverse events with miriplatin therapy (1)

| | NLCT Study (n=535) | | Phase II Trial[33] (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 |

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**Table 10:** Incidence of drug-related adverse events with miriplatin therapy (2)

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

**Table 11:** 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% |

**Table 12:** 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 13:** 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)

**Table 14:** Summary of efficacy measures with miriplatin therapy

| | NLCT Study | | | Phase II Trial[33] (n=16) | Randomized Phase II Trial28) (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 15:** Independent factors contributing to effective (TE3/4) achievement with miriplatin therapy

| Factor | Category | Risk ratio | 95% CI | P |
|---|---|---|---|---|
| Embolic material | None | 1 | | <0.001 |
| | Yes | 3.66 | 2.13-6.29 | |
| No. of 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

**Table 16:** 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)

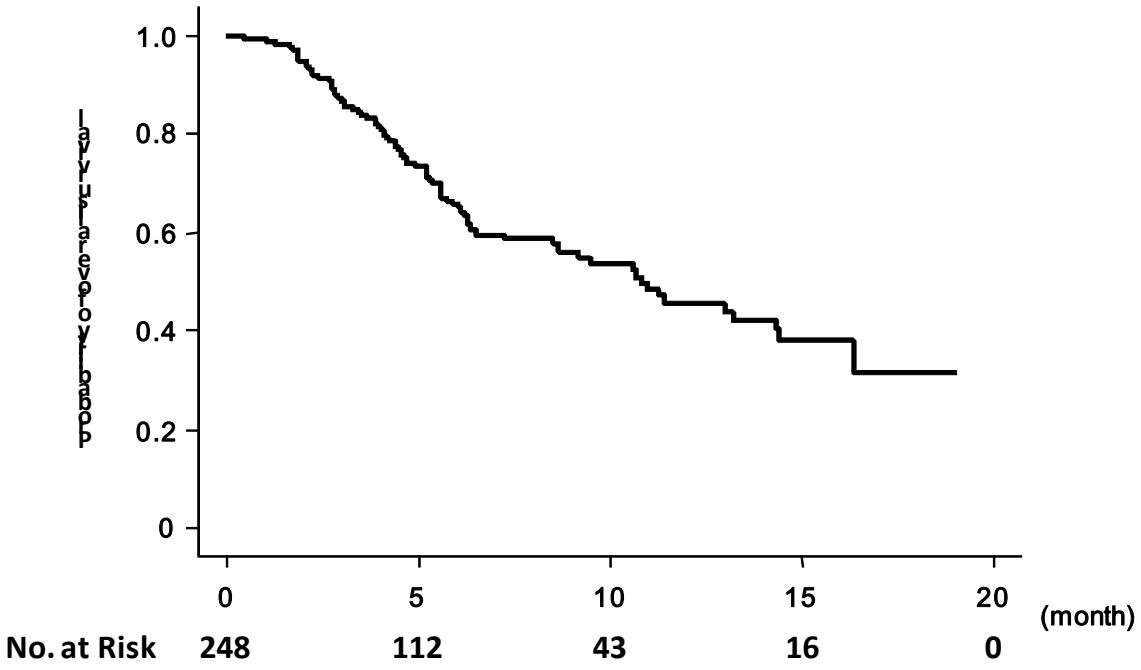
**Table 17.** Comparison of abnormal clinical laboratory values with or without embolic material during miriplatin therapy

| | 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 γGTP | 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)

**Figure 1:** Therapeutic efficacy of sorafenib

(A) Overall survival




(B) Progression Free Survival

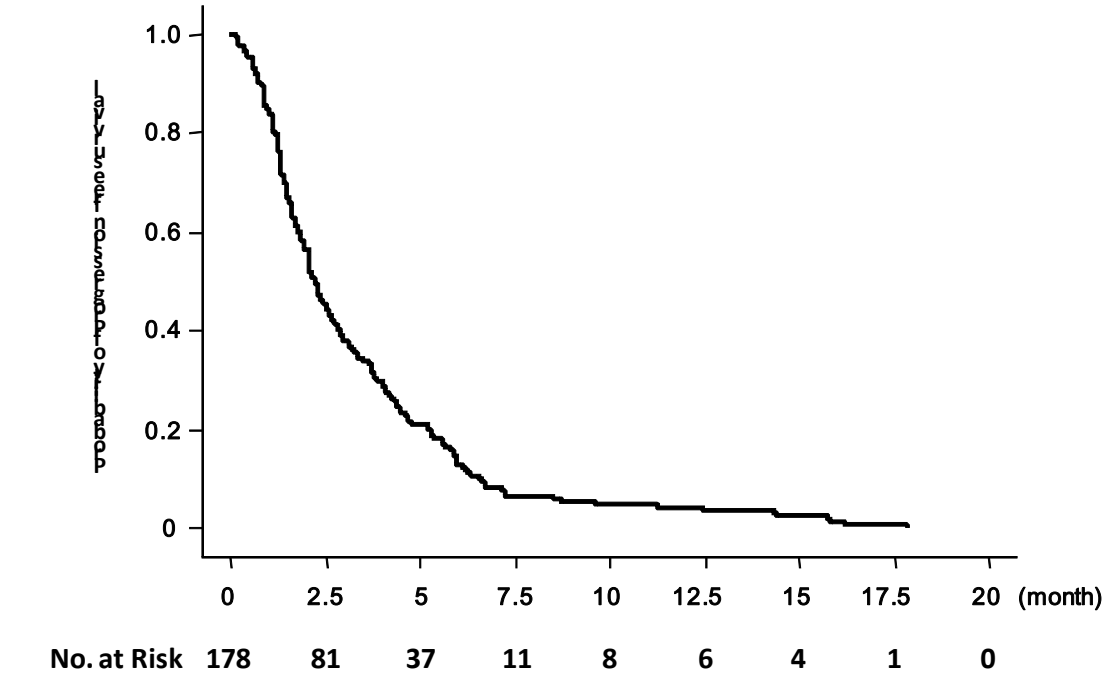


**Figure 2:** Therapeutic efficacy of miriplatin with or without embolus material