longer durations of therapy are necessary to confirm the effect of extended duration of therapy on reduction of relapse among patients with cEVR.

Previous reports did not consider the effects of age in setting the optimal dose of RBV. In the present study, the relapse rate decreased with an increase in RBV dose from <2.5 to 3.0–3.5 g/kg of body weight, but remained relatively stable despite a further increase in the RBV dose in older patients. Thus, a total RBV dose ≥3.0 g/kg of body weight should be the target dose for patients ≥60 years with cEVR. By contrast, ≥3.0 g/kg of body weight of RBV was associated with lower risk of relapse in patients <60 with cEVR (16% versus 32%), and a further increase in RBV dose led to a more profound reduction in relapse rates, as low as 11% in patients who received ≥4.0 g/kg of body weight. Thus, a total dose of ≥4.0 g/kg of body weight or even greater should be the target dose in patients <60 years.

In the near future, more potent therapies, such as direct antiviral agents [34,35], may become available. These drugs require RBV and PEG-IFN in combination. However, not all patients may be able to tolerate this triple combination therapy due to adverse drug reactions, such as severe anaemia or skin eruption. In particular, it may be difficult to administer a full dose of triple drugs to older patients. Thus, personalizing the PEG-IFN and RBV combination therapy based on this model may be beneficial to patients who were intolerant to triple combination therapy.

In the present study creatinine was an independent predictor of relapse by multivariable logistic regression analysis. However creatinine was not selected as a splitting variable in decision tree, which may be due to the unique property of data mining analysis. In data mining analysis, limitation is imposed to stop the analysis when the number of patients is <20. This limitation is used to avoid dividing patients into too small subgroups which lead to the generation of rules that only apply to the model derivation population and not reproduced when applied to other populations. This phenomenon is called the over-fitting of the model. Due to this limitation, the variables selected in the data mining analysis are not necessarily identical to the variables that are significant by ordinary multivariable analysis. In a separate analysis, lower level of creatinine was associated with higher rate of relapse in each subgroup of patients with cEVR. The reason for this association is not clear, but lower creatinine level may be related to more efficient clearance of RBV leading to lower serum level of RBV. Further research is needed to confirm this speculation.

A potential limitation of the present study is that data mining analysis has an intrinsic risk of showing relationships that fit to the original dataset, but are not reproducible in different groups. Although internal and external validations showed that our model had high reproducibility, we recognized that further validation on a larger external validation cohort, especially in groups other than Japanese, may be necessary to further verify the reliability of our model.

In conclusion, we built a decision tree model for the prediction of relapse among patients with EVR to PEG-IFN plus RBV. The result of the present study shows that older age and insufficient dose of RBV are significant and independent risk factors for relapse. The target dose of total RBV can be set at 3.0 g/kg of body weight in patients who achieved cEVR. A further increase in RBV dose up to 4.0 g/kg of body weight may be warranted in patients <60 years.

Acknowledgements

This study was supported by a Grant-in-Aid from the Ministry of Health, Labor and Welfare, Japan (H20-kanen-006).

Disclosure statement

The authors declare no competing interests.

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Accepted 18 April 2011; published online 21 October 2011

REVIEW ARTICLE

Clin Drug Investig 2012; 32 Suppl. 2: 37-51
1173-2563/12/0002-0037/$49.95/0

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Current Status of Hepatocellular Carcinoma Treatment in Japan

Case Study and Discussion-Voting System

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Abstract

The Toward Integrated Treatment of Advanced Hepatocellular Carcinoma with Nexavar (TiTAN) Symposium was held in August 2010 in Tokyo, Japan, during which the position of sorafenib (Nexavar®) in the treatment of HCC in Japan (for which it received approval in 2009) was discussed by a panel of eight expert hepatologists in a session chaired by Dr Kudo. The following article focuses on the discussion that went on during this session, including question and answer sessions regarding the experiences of the 350 conference attendees in treating patients with HCC, as well as some of the more challenging disease management issues.

Since 2008, when the phase III Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) trial demonstrated an increase in the median overall survival (OS) for patients with unresectable HCC treated with sorafenib compared with placebo, international and Japanese guidelines recommend sorafenib as a first-line option for patients with advanced HCC Child–Pugh liver function class A who have extrahepatic metastasis. Sorafenib is also recommended for patients unresponsive to transarterial chemoembolization (TACE) or hepatic arterial infusion chemotherapy (HAIC). Importantly, if HCC is judged to be unresponsive to TACE, treatment should be switched to sorafenib in a timely manner.

Almost half of the conference attendees said that they used both the Japan Society of Hepatology clinical practice guidelines and the clinical practice

guidelines for HCC when determining treatment strategies for individual HCC patients. Sorafenib should currently not be used as adjuvant therapy or in combination with TACE or HAIC until evidence from ongoing clinical trials shows that it is beneficial in these settings.

1. Introduction

Numerous patients with hepatocellular carcinoma (HCC) have been treated with sorafenib (Nexavar®, Bayer, Berlin, Germany) in clinical practice in Japan following its approval for this indication on 20 May 2009.[1]

The Toward Integrated Treatment of Advanced Hepatocellular Carcinoma with Nexavar (TiTAN) Symposium was held on 28 August 2010 in Tokyo, Japan, during which the position of sorafenib in the treatment of HCC in Japan was discussed by a panel of eight experts (Dr Ryosuke Tateishi, Dr Tatsuya Yamashita, Dr Masafumi Ikeda, Dr Junji Furuse, Dr Kenji Ikeda, Dr Norihiro Kokudo, Dr Namiki Izumi and Dr Osamu Matsui) in a session chaired by Dr Masatoshi Kudo. During this session, approximately 350 conference attendees were questioned regarding their experiences in treating patients with HCC, with answers given by means of a wireless voting system. Some of the more challenging issues in the management of HCC were also discussed. The following article focuses on the discussion that went on during this session, with particular emphasis on sorafenib.

2. Current Practice Guidelines for Hepatocellular Carcinoma

2.1 Asian-Pacific Association for the Study of the Liver Guidelines

The first meeting of the Asian-Pacific Association for the Study of the Liver (APASL) working committee was held in Bali, Indonesia, in December 2008 to develop consensus recommendations for the management of HCC; 21 experts from Japan, Hong Kong, Korea, Taiwan, China, Pakistan, Singapore, India and Indonesia attended the meeting.[2]

The APASL treatment algorithm for HCC (figure 1a) is similar to that proposed in the evidence-based Japan Society of Hepatology (JSH) clinical practice guidelines for HCC[3] (see figure 1b). In the APASL algorithm, sorafenib is a first-line option for the treatment of HCC with extrahepatic metastasis or extensive portal invasion (main portal vein tumour thrombus) in Child–Pugh class A or B patients. APASL has the following recommendations regarding systemic therapy:[2]

- As a systemic treatment, sorafenib is strongly recommended for the treatment of advanced-stage patients who are not suitable for loco-regional therapy and who have Child–Pugh liver function class A (quality of evidence level 1b, strength of recommendation grade A).
- Sorafenib 'may be used' with caution in patients with Child–Pugh liver function class B (4, C).
- Cytotoxic drugs are not routinely recommended but may be considered in highly selected patients whose general and hepatic conditions are adequate (3, C).

2.2 American Association for the Study of Liver Diseases Practice Guidelines 2010

The American Association for the Study of Liver Disease practice guidelines, which were updated in 2010,[5] have gained wide acceptance throughout the USA and Europe. The 2010 guideline update recommends sorafenib for stage C (advanced) HCC with portal invasion, tumour status N1, M2 or performance status test 1–2 according to the Barcelona Clinic liver cancer[6] staging system (see figure 1a in article 1 of this supplement). Similar to the 2005 version, sorafenib is recommended (based on grade 1 level of evidence) as a first-line option in patients who cannot benefit from resection, transplantation, ablation or transarterial chemoembolization (TACE), and still have preserved liver function.[5]

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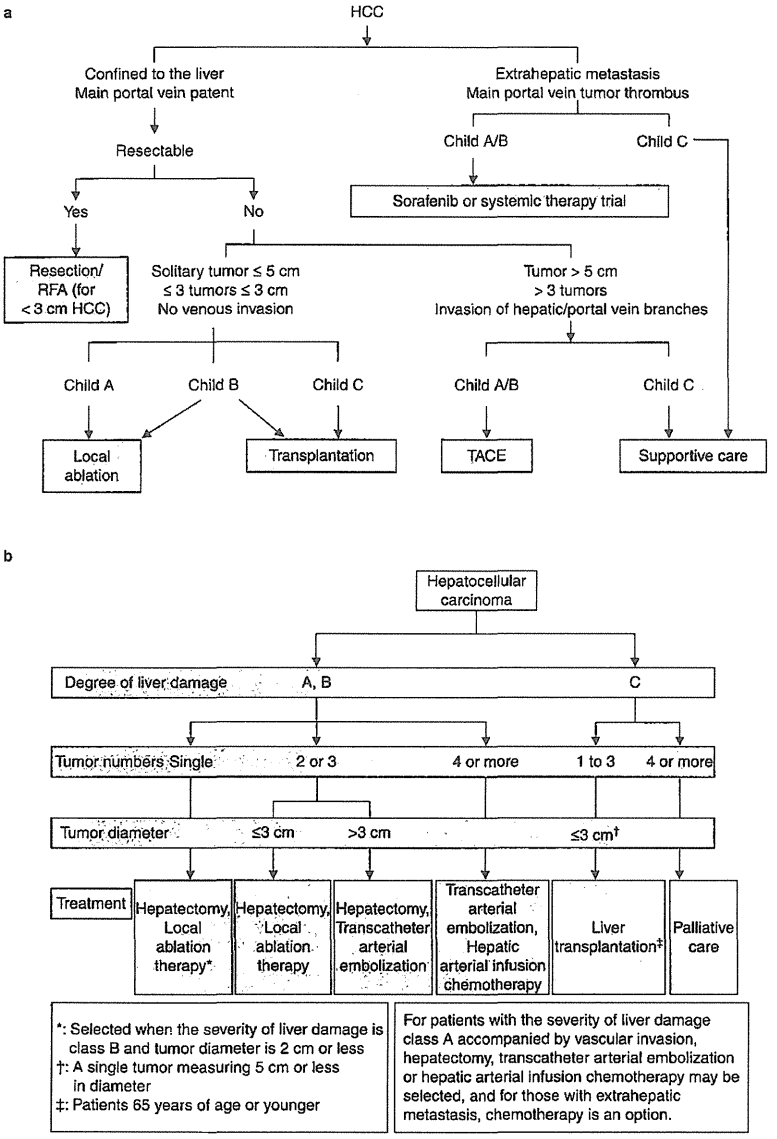

Fig. 1. Treatment algorithms for hepatocellular carcinoma (HCC) from (a) the Asian-Pacific Association for the Study of the Liver (reproduced with permission from Omata et al.),[2] (b) the evidence-based Japan Society of Hepatology (JSH) Clinical Practice Guidelines for HCC[3] and (c) the consensus-based JSH clinical practice guidelines for hepatocellular carcinoma 2010 update.[4] **HAIC** = hepatic arterial infusion chemotherapy; **RFA** = radiofrequency ablation; **TACE** = transarterial chemoembolization.

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c

Fig. 1. Contd

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2.3 Japanese Guidelines (Evidence and Consensus-Based Clinical Practice Guidelines for Hepatocellular Carcinoma)

The evidence-based JSH clinical practice guidelines for HCC 2009 update[3] (issued in November 2009) are based on data obtained up to mid-2007 and therefore do not reflect the results of the phase III Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP)[7] trial published in 2008.

If updated, the JSH clinical practice guidelines for HCC would list sorafenib as an important treatment choice. In the current version, hepatic arterial infusion chemotherapy (HAIC) is recommended for the management of advanced HCC (see figure 1b in article 1 of this supplement);[3] sorafenib therapy is now a suitable option for the management of advanced HCC.

The consensus-based JSH clinical practice guidelines for HCC 2010 update,[4] which is based on both evidence and consensus, recommends sorafenib for the management of patients with HCC and Child–Pugh liver function class A in the following cases: patients without extrahepatic metastasis with or without vascular invasion who have either four of more nodules and are unresponsive to TACE/HAIC or who have one to three nodules and a tumour size of more than 3 cm and are unresponsive to TACE; and patients with extrahepatic metastasis (figure 1c).

When conference attendees were asked which guidelines they referred to when determining treatment strategies for individual HCC patients, 30% of the 319 respondents said that they used the JSH clinical practice guidelines for HCC,[3] 11% said the JSH consensus-based clinical practice guidelines for HCC[4] and 43% said both the JSH clinical practice guidelines and consensus-based clinical practice guidelines. None of the attendees used the Barcelona Clinic liver cancer staging and treatment strategy, while 14% used strategies devised at their institutions and 1% of attendees opted to use other guidelines.

3. Treatment of Hepatocellular Carcinoma with Extrahepatic Metastasis

Conference attendees were asked how they would treat HCC Child–Pugh class A patients with extrahepatic metastasis. From the 326 attendees who responded, 85% said they would use oral sorafenib, 5% said an oral fluoropyrimidine (5-fluorouracil, uracil-tegafur or TS-1), 3% said interferon plus an oral fluoropyrimidine (5-fluorouracil, uracil-tegafur or TS-1), 4% said intravenous chemotherapy, 1% best supportive care and the remaining 3% said they would use another undefined method.

Dr Tateishi commented that although the presence of extrahepatic metastasis is a strong predictor of poor prognosis, extrahepatic metastasis itself rarely affects patient prognosis. It is still controversial whether we should concentrate on intrahepatic lesions in patients with extrahepatic metastasis when the vast majority of the tumour burden is located in the liver.

The SHARP trial was a placebo controlled phase III study of sorafenib in 602 previously untreated HCC patients in Europe, North/South America and Australia.[7] In a subset analysis of 421 patients with vascular invasion and/or extrahepatic metastasis, sorafenib significantly inhibited disease progression and prolonged OS compared with placebo; median time to disease progression was 4.1 months versus 2.7 months (hazard ratio [HR] = 0.64; 95% confidence interval [CI] 0.48, 0.84) and the median survival time was 8.9 months versus 6.7 months (HR = 0.77; 95% CI 0.60, 0.99).[8] This result supports the theory that sorafenib is a suitable first-line option for advanced HCC with vascular invasion and/or extrahepatic metastasis.

Dr Kudo commented that an excellent response to sorafenib has been reported in several cases of lung, lymph node and bone metastases of HCC,[9] thus systemic therapy with sorafenib could effectively control extrahepatic metastasis of HCC, perhaps not in all patients but at least in some.

Dr Furuse agreed that using sorafenib to control extrahepatic metastasis of HCC is reasonable, and highlighted that 85% of the respondents chose sorafenib when asked how they would treat HCC with extrahepatic metastasis. He also noted that some other options, including fluoropyrimidines such as S-1, have shown promising activity against metastatic lesions, but that no systemic therapy other than sorafenib has been shown to

Fig. 1. Contd

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improve the prognosis in patients with advanced HCC.[10] For these reasons, Dr Furuse concluded that he had no objection to the first-line use of sorafenib for the management of extrahepatic metastasis of HCC.

Dr Izumi presented data on the survival outcome of 42 patients with advanced HCC who had been treated with sorafenib (400 or 800 mg/day) at the Musashino Red-Cross Hospital between July 2009 and June 2010. All patients had experienced repeated recurrence while being treated with a variety of therapies available for HCC before the approval of sorafenib, 12 patients had extensive vascular invasion (VP3/4) and 12 had metastases in the bone (n = 6) or lungs (n = 6). Subgroup analyses (where $p < 0.05$ was considered statistically significant), performed to identify variables predicting survival benefits with sorafenib, showed that the survival time was longer in patients without extensive vascular invasion (n = 30) than in those with vascular invasion (n = 12) at baseline ($p < 0.00001$), and in patients with (n = 12) versus those without (n = 30) extrahepatic metastasis at baseline ($p = 0.0043$).

The improved prognosis of patients with extrahepatic metastasis after treatment with sorafenib contradicts findings from a subgroup analysis of the SHARP trial in which response to sorafenib was worse in patients with extrahepatic metastasis than in those without.[11] This apparent discrepancy may be due to differences in patient characteristics, because intrahepatic lesions had been controlled in the 42 patients with extrahepatic metastasis treated by Dr Izumi.

A case study was presented of a man aged 80 years with stage IVb HCV-related HCC whose extrahepatic metastasis, which had appeared in his ribs despite control of his intrahepatic lesions, had responded to treatment with sorafenib. After 8 months' treatment with sorafenib at 800 mg/day, the bone metastatic lesions were judged as stable disease (SD) suggesting that in patients without intrahepatic lesions, extrahepatic metastasis may show a sustained response to sorafenib.

In summary, sorafenib is the only drug shown to improve the survival of HCC patients with extrahepatic metastasis and well preserved liver function. At the TiTAN Symposium 2010, consensus was reached as to the use of sorafenib as a first-line treatment of HCC with extrahepatic metastasis in Child–Pugh class A patients, as recommended in the current (2010 update) JSH clinical practice guidelines for HCC.[4]

4. Definition of Unresponsiveness to Transarterial Chemoembolization

The JSH clinical practice guidelines for HCC[4] define the following situations as being unsuitable for TACE: all vessels used for treatment have been devastated and no feeding vessels can be selectively catheterized; liver function has deteriorated to Child–Pugh class C during repeated cycles of TACE; extensive portal invasion (VP3/4) is present; or a large arterioportal shunt has formed.

As mentioned in article 3 in this supplement, 'unresponsiveness to TACE' is defined in the JSH clinical practice guidelines for HCC[4] (see also table I). An analysis of the prognosis of patients with HCC who became unresponsive to TACE or who required a further cycle of TACE to control a new lesion within 3 months showed that these patients were most likely to show worsening liver function. Furthermore, repeating TACE at intervals of 3 months or less predicted an increased risk of progression to Child–Pugh class B and a lower cumulative survival rate. Ninety-four patients with HCC, Child–Pugh class A and four of more nodules who underwent TACE as their initial treatment at Musashino Red-Cross Hospital had a cumulative survival rate of 86% at 1 year, 54% at 3 years and 30% at 5 years.[12] These rates are lower than the corresponding values observed in

Table I. Definition of unresponsive to TACE as defined in the Japan Society of Hepatology clinical practice guidelines for hepatocellular carcinoma[4]

Poor accumulation (<50%) of lipiodol in intrahepatic lesions as assessed by CT immediately (at least 1 month) after two consecutive cycles of TACE
New multiple intrahepatic lesions detected by CT immediately (minimum 1 month) after two successive cycles of TACE
Appearance of vascular invasion
Appearance of extrahepatic metastasis
A continuous increase of tumour marker level only with an initial decrease immediately after a cycle of TACE

CT = computed tomography; **TACE** = transarterial chemoembolization.

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Table II. Conference attendee responses regarding TACE for the treatment of HCC

Question		No. of respondents	How attendees responded
QA4	How long do you wait to administer a cycle of TACE after the previous cycle?	318	1 month: 6% 3 months: 59% 6 months: 31% 9 months: 4% 12 months: 1%
QA5	How many cycles of TACE on average do you administer to a single HCC patient?	320	1–2 cycles: 2% 3–4 cycles: 53% 5–7 cycles: 43% ≥8 cycles: 3%
QA6	How do you treat HCC that has recurred at progressively decreasing intervals on TACE and seems to be unresponsive to TACE?	318	TACE repeated at shorter intervals: 8% TACE with another cytotoxic drug: 27% HAIC: 33% Sorafenib: 29% Systemic chemotherapy: 2% Others: 1%
QA7	Do you think that unresponsiveness to TACE should be defined?	328	Yes: 93% No: 7%
QA8	Do you think that the proposed definition of unresponsiveness to TACE is appropriate?	320	Appropriate: 60% Partly inappropriate: 39% Inappropriate: 1%
QA9a	Do you switch TACE to another treatment when judging the disease as unresponsive to TACE?	315	Yes: 98% No: 2%
QA9b	Which treatment do you choose for HCC unresponsive to TACE?	317	Sorafenib: 56% HAIC: 44% Others: 0%
QA10	Which treatment do you choose for HCC unsuitable for TACE?	322	Systemic chemotherapy – oral: 5% Systemic chemotherapy – intravenous: 3% Sorafenib: 79% BSC: 2% Others: 11%

BSC=best supportive care; **HAIC**=hepatic arterial infusion chemotherapy; **HCC**=hepatocellular carcinoma; **TACE**=transarterial chemoembolization.

similar patients receiving surgical resection or radiofrequency ablation[13] as their initial treatment. Forty patients died, including 34 (85%) from HCC, one (2.5%) from hepatic failure and five (12.5%) from an unrelated condition. Thirteen patients (14%) had extrahepatic metastasis in bone (n = 10) or lung (n = 3). The calculated cumulative probability of progression from Child–Pugh class A to class B was 18.6% at 1 year, 63.0% at 3 years and 88.1% at 5 years. TACE repeated at intervals of 3 months or less was significantly associated with a risk of progression to Child–Pugh class B ($p = 0.023$) and shorter survival after TACE ($p = 0.016$).

When conference delegates were questioned regarding their use of TACE for patients with HCC, the majority reported that they would administer between three and seven cycles of TACE with an interval of 3–6 months between cycles (table II QA4–5). For patients unresponsive to TACE, almost one-third of attendees said that they would continue to use TACE, either at shorter intervals or with a different cytotoxic drug (table II QA6).

These results show that, historically, TACE has been used repeatedly to treat HCC, even if it was unresponsive, as no other effective treatments were available. Now that sorafenib provides an alternative treatment option for patients with advanced HCC, it is imperative to define 'unresponsiveness to TACE' in order to permit timely switching of TACE to other treatments. Notably, 93% of conference delegates agreed that unresponsiveness to TACE should be defined, but

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only 60% felt that the definition of 'unresponsiveness to TACE' proposed in the JSH clinical practice guidelines for HCC[4] was appropriate (table II QA7–8); the proposed definition of 'unresponsiveness to TACE' must be validated.

5. Treatment of Hepatocellular Carcinoma Unresponsive to or Unsuitable for Transarterial Chemoembolization

At least two cycles of TACE should be administered to patients with HCC before determining whether HCC is unresponsive to TACE for the following reasons: it is uncertain whether the lipiodol/embolizing agent enters and sufficiently embolizes the target vessel; any collateral circulation cannot be found before TACE;[14,15] and HCC unresponsive to TACE with one drug may respond to TACE with another drug.[16,17]

An early study, which reported response to serial cycles of TACE in 142 patients with HCC, showed that the complete response rate was significantly higher after more than three cycles of TACE compared with only one cycle (28% vs 12%; $p < 0.001$)[15] supporting that one cycle of TACE is insufficient to determine whether HCC is unresponsive to TACE.

Dr K. Ikeda presented the following case studies of long-term HCC survivors who received repeated cycles of TACE:

- An 84-year-old man with liver cirrhosis and HCC concurrent with bladder cancer had received approximately two cycles of TACE per year since 1996. He was diagnosed with progressive disease during 1998 and died in 1999 (figure 2a). If an assessment of 'unresponsive to TACE' had been made at the time of diagnosis of progressive disease alternative treatments could have been considered. This case study suggests that although the decision to switch from TACE to another treatment should not be made before administering at least two cycles, this decision should not be left too late.
- A 61-year-old woman with liver cirrhosis and HCC had ascites and was in Child–Pugh class B. Her HCC was controlled by four cycles of TACE performed from 1998 to 1999 but began to grow rapidly in 2000 (figure 2b). The patient died without responding to the fifth cycle of TACE given over 6 months after the fourth.

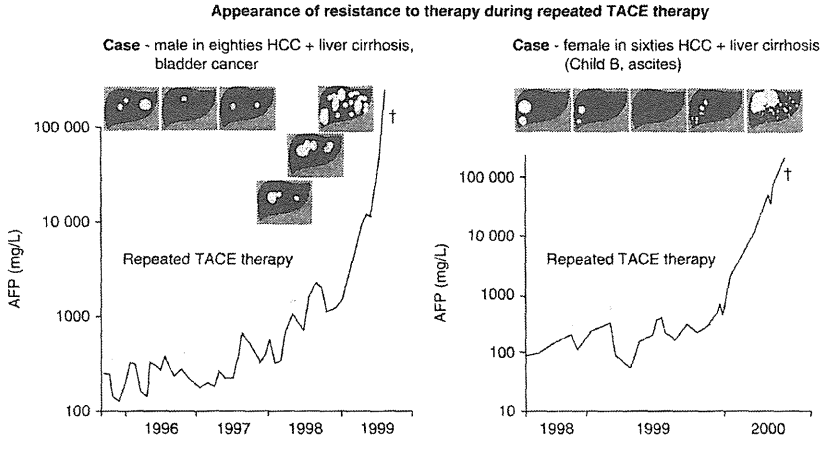

Fig. 2. Two case studies that represent long-term hepatocellular carcinoma (HCC) survivors who received repeated cycles of transarterial chemoembolization (TACE): (**a**) An 82-year-old man with liver cirrhosis and HCC concurrent with bladder cancer received approximately two cycles of TACE per year since 1996, his disease worsened during 1998 and he died in 1999. (**b**) A 61-year-old woman with liver cirrhosis and HCC with ascites and in Child–Pugh class B had her HCC controlled by four cycles of TACE performed from 1998 to 1999, but which began to grow rapidly in 2000 resulting in death. **AFP** = alpha fetoprotein, † Patient died.

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The current provisional definition of 'unresponsiveness to TACE' suggests that the initial assessment of tumour response to each cycle of TACE may be performed 'a minimum of 1 month' after treatment. This case study illustrates that if response to TACE is assessed at 3–6 months after treatment, it may be too late for further treatment options.

Dr K. Ikeda concluded that it was appropriate that the current provisional definition of 'unresponsiveness to TACE' in the JSH clinical practice guidelines for HCC[4] requires 'two successive cycles of TACE' for observing 'poor lipiodol accumulation' and the 'appearance of a new lesion' and stated that as TACE is curative, we should try to repeat TACE for as long as possible.

The majority (98%) of conference attendees said that when judging HCC as unresponsive to TACE they would switch to another treatment, with 56% stating that they would choose sorafenib and 44% HAIC as the alternative treatment (table II QA9a–b).

In the SHARP trial, the subgroup of patients who had previously undergone TACE represents patients with HCC unresponsive to TACE. In these patients, the median time to progression (TTP) was significantly longer for the sorafenib arm (n = 86) than the placebo arm (n = 90) (HR = 0.57; 5.8 months vs 4.0 months), although the median survival time was similar between treatment groups (HR 0.75; 11.9 months vs 9.9 months).[18] The results of this subgroup analysis suggest that sorafenib may be effective for HCC unresponsive to TACE.

Dr Kudo presented two case studies of patients with HCC unresponsive to TACE who had received sorafenib for over 1 year, depicting the effectiveness of sorafenib for HCC unresponsive to TACE:

- A 79-year-old woman with stage III non-B, non-C type HCC in Child–Pugh class A had a large lesion that was unresponsive to TACE. In June 2009, sorafenib was started at 800 mg/day and then downtitrated to 400 mg/day. As of May 2010, the patient was still receiving sorafenib and was in good condition (Eastern Cooperative Oncology Group performance score was 0) without experiencing any adverse reactions. The HCC was assessed as SD (Figure 3a).
- In June 2009, sorafenib was started at 800 mg/day in an 81-year-old man with stage III non-B, non-C type HCC judged unresponsive to TACE because of poor accumulation of lipiodol. In July 2009, dizziness occurred and some doses were omitted. Subsequently, sorafenib was restarted at the same dose. As of 10 May 2010, the patient was still receiving sorafenib and was assessed as having a performance score of 0 and SD (figure 3b).

Sorafenib may also be used in combination with TACE and several clinical studies assessing the efficacy and safety of this combination are ongoing. The SPACE study (ClinicalTrials.gov identifier NCT00855218) is a randomized, placebo controlled, phase II study investigating TACE with doxorubicin-loaded DC beads (currently unavailable in Japan), with or without sorafenib 400 mg twice a day, in patients (n = 300) with intermediate-stage (unresectable) HCC at 95 to 100 centres in the USA, Europe and Asia. The primary endpoint is progression-free survival. Secondary endpoints include OS, time to untreatable progression, vascular invasion, time to extrahepatic metastasis, patient's reported treatment outcome, biomarkers and safety. That study commenced in March 2009 and is scheduled for completion by March 2012.

The randomized, controlled, phase II JLOG0903 study (Transcatheter Arterial Chemoembolization Therapy in Combination with Sorafenib [TACTICS] trial, NCT01217034) is currently in progress at approximately 40 Japanese institutions. Eligibility criteria include unresectable HCC, Child–Pugh class A, one of fewer previous TACE cycles, tumour size 10 cm or less and 10 or fewer nodules. Exclusion criteria include vascular invasion and distant metastasis. The primary endpoint of the study is time to untreatable progression. Secondary endpoints include TTP, OS, objective response rate, tumour markers and safety. Among 228 subjects planned for enrolment, those allocated to the sorafenib group will receive alternating cycles of TACE and sorafenib (400 mg/day increasing to 400 mg twice a day) until progression. Study completion is expected in approximately September 2016.

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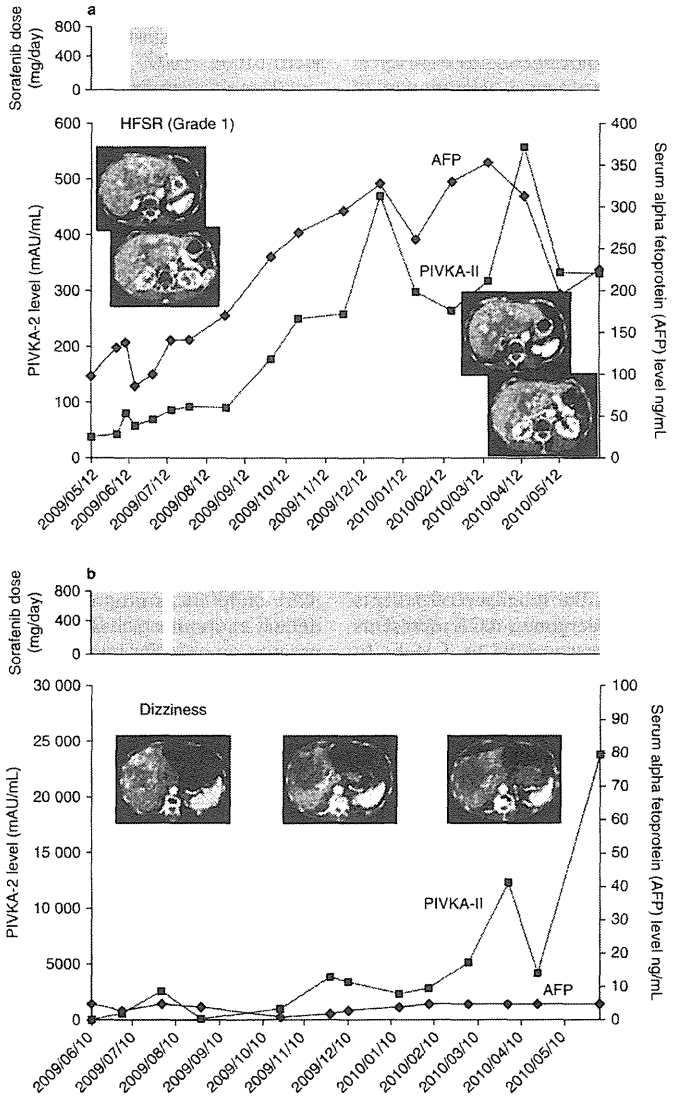

Fig. 3. Two case studies of patients with hepatocellular carcinoma (HCC) unresponsive to transarterial chemoembolization (TACE) who have received sorafenib for more than 1 year showing the effectiveness of sorafenib in this setting. (**a**) A 79-year-old woman with stage III non-B, non-C type (NBNC) HCC in Child–Pugh class A with a large lesion that was unresponsive to TACE. (**b**) An 81-year-old man, stage III NBNC HCC judged as unresponsive to TACE because of poor accumulation of lipiodol. **AFP** = alpha fetoprotein; **HFSR** = hand-foot skin reaction; **PIVKA-II** = protein induced by vitamin K absence II.

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In summary, treatment strategies for HCC unresponsive to TACE are as follows:

- Before worsening of hepatic functional reserve, sorafenib is a treatment option for HCC unresponsive to TACE, which responds poorly to HAIC.
- Conventional treatments combined with sorafenib and other molecular targeted agents (e.g. the tyrosine kinase inhibitor of the epidermal growth factor receptor, erlotinib, a multitargeted tyrosine kinase inhibitor, sunitinib, and the humanized monoclonal antibody against the antivascular epidermal growth factor, bevacizumab) may also become treatment options in the future. Such combinations are still under investigation and will not come into use until their efficacy/safety have been confirmed in clinical trials.
- The proposed definition of 'unresponsiveness to TACE' needs further review and validation for practical use.

HCC that is unsuitable for TACE is also defined in the JSH clinical practice guidelines for HCC,[4] as described above. When delegates were questioned on which treatment option they would choose for HCC unsuitable for TACE, 79% said they would use sorafenib (table II QA10).

6. Treatment of Hepatocellular Carcinoma with Hepatic Arterial Infusion Chemotherapy and Sorafenib

HAIC is effective in terms of tumour response and survival for the management of HCC newly diagnosed with vascular invasion, but is much less effective against advanced HCC that has become unresponsive to TACE after repeated cycles.[19] Such cases may respond to sorafenib followed sequentially by HAIC.

As discussed in article 2 in this supplement, previous treatment with sorafenib followed sequentially by HAIC may be better than concurrent treatment with HAIC and sorafenib. It is thought that sorafenib enhances the cytotoxic effect of HAIC by inhibiting tumour vascularisation, or by normalizing anatomical vascular architecture; however, the benefit of previous treatment with sorafenib needs to be confirmed in a large clinical trial.

6.1 Differential Use of Hepatic Arterial Infusion Chemotherapy and Sorafenib

Combining sorafenib with HAIC appears promising but has not yet been approved. At present, the choice between using sorafenib or HAIC is a 'trial and error' approach because been no biomarkers have been identified that can predict response to either treatment. As response to HAIC differs among patients, a reasonable approach is to use HAIC initially and to assess response after approximately 4–6 weeks. If successful, HAIC may be continued; however, if there is no response, treatment may be switched to sorafenib.

When conference attendees were asked how they would treat HCC newly diagnosed with vascular invasion, the majority chose HAIC with (43%) or without (16%) an implanted reservoir (table III QA14). Notably, when asked how they would treat HCC with vascular invasion that had failed to respond to HAIC, 85% of respondents chose sorafenib (table III QA15).

When asked whether they would consider using sorafenib before HAIC to treat HCC newly diagnosed with portal invasion in a Child–Pugh class A patient, more hepatologists than expected chose to consider using sorafenib before HAIC (68%) (table III QA16). Interestingly, 84% of respondents said they would consider using the combination of HAIC with sorafenib, even though it has not yet been approved (table III QA17).

Dr Kudo concluded that Japanese hepatologists often use HAIC to manage HCC with vascular invasion, and many want to try it in combination with sorafenib. However, sorafenib cannot be used in combination with any cytotoxic drug at present, because the efficacy and safety of such a combination has not been established, as stated in the prescribing information.[20] In addition, as HAIC is used only in Japan, an international study cannot be expected to provide evidence for the combination of HAIC with sorafenib. Therefore, a well-designed prospective study should be conducted in Japan in order to establish the efficacy and safety of this combination, as described below.

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Table III. Conference attendee responses regarding the use of HAIC for the treatment of HCC

Question		No. of respondents	How attendees responded
QA14	How will you treat HCC newly diagnosed with vascular invasion?	293	Surgical resection: 18% TACE: 6% HAIC without an indwelling catheter: 16% HAIC with an implanted reservoir: 43% Sorafenib: 13% Oral fluoropyrimidine (5FU, UFT or TS-1): 0% Interferon plus fluoropyrimidine (5FU, UFT or TS-1): 0% Intravenous chemotherapy: 0%; Others: 4%
QA15	How will you treat HCC with vascular invasion failing to respond to HAIC?	309	Sorafenib: 85% Surgical resection: 6% TACE: 1% HAIC without an indwelling catheter: 0% HAIC with an implanted reservoir: 2% Oral fluoropyrimidine (5FU, UFT or TS-1): 0% Interferon plus fluoropyrimidine (5FU, UFT or TS-1): 2% Intravenous chemotherapy: 0%; Others: 3%
QA16	Do you consider using sorafenib before HAIC to treat HCC newly diagnosed with portal invasion in a Child–Pugh class A patient?	310	Yes: 68% No: 32%
QA17	Do you want to consider combination use of HAIC with sorafenib, which has not been approved yet?	309	Yes: 84% No: 16%

5FU = 5-fluorouracil; HAIC = hepatic arterial infusion chemotherapy; HCC = hepatocellular carcinoma; TACE = transarterial chemoembolization; UFT = uracil-tegafur.

6.2 Ongoing Trials to Assess the Combination of Hepatic Arterial Infusion Chemotherapy and Sorafenib in Japan

Although there is widespread belief in Japan that HAIC is extremely effective for HCC with vascular invasion, there is no evidence to support this. Therefore, robust evidence for its efficacy must be derived from a domestic study. As current international guidelines recommend sorafenib as a first-line option for HCC with vascular invasion, a series of clinical trials have been established to evaluate the potential benefit of combining HAIC with sorafenib with the primary objective being to establish the efficacy of sorafenib plus HAIC with cisplatin in comparison with sorafenib alone. A small (n = 21) phase I study (UMIN Clinical Trials Registry identifier UMIN000001496), which has completed recruitment, will determine the recommended dosage regimen for sorafenib plus HAIC with cisplatin. After this study, randomized phase II and III studies will be conducted to evaluate the efficacy/safety and clinical benefit of this combination, compared with sorafenib alone.

The phase Ib/II Sorafenib in Combination with Low-dose FP Intra-arterial Infusion Chemotherapy (SILIUS) trial (JLOG0901; NCT00933816), which was completed in October 2010, assessed the combination of sorafenib and HAIC with low doses of 5-fluorouracil and cisplatin (FP). HAIC with low-dose FP is administered via an implanted reservoir. That study included patients with advanced HCC and assessed dose-limiting toxicities (phase Ib) and TTP (phase II) as primary outcome measures. The phase Ib part of the study was completed in August 2010.[21] As the TTP with sorafenib plus HAIC with low-dose FP was found to be much better than with low-dose FP alone, the data monitoring committee recommended progressing directly to a phase III study. The ongoing phase III SILIUS randomized controlled study, being conducted at 25 Japanese centres, is comparing sorafenib plus low-dose FP with sorafenib alone (ClinicalTrials.gov identifier NCT01214343; UMIN Clinical Trials Registry identifier UMIN000004315). The study has a planned completion date of September 2013. If this study successfully shows the superiority of sorafenib combined with low-

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dose FP over sorafenib alone, the combination may be presented as a novel treatment option for HCC with vascular invasion.

The treatment of HCC with vascular invasion can be summarized as follows:

- For the management of HCC newly diagnosed with vascular invasion in Child–Pugh class A patients: HAIC may be used first, and if this fails, switch to sorafenib; previous treatment with sorafenib followed by HAIC may be a reasonable option depending on the patient's clinical profile.
- For the management of HCC with vascular invasion or with multifocal disease that has become unresponsive to TACE, sorafenib may be used first.

7. Optimum Dose of Sorafenib

The current recommended dose of sorafenib is 800 mg/day,[20] although excellent responses to 400 mg/day have recently been reported.[22] Some studies have suggested better efficacy and tolerability of sorafenib 400 mg/day in Japanese patients, while others have reported that 800 mg/day is well tolerated and maintains high dose intensity for prolonged periods.[22]

When asked what starting dose they would prescribe, 48% of attendees replied that they would initially prescribe sorafenib at 800 mg/day; however, the majority (80%) of attendees who would start sorafenib at doses lower than 800 mg/day would uptitrate to 800 mg/day if tolerated (table IV QA18–QA19). Concern regarding unmanageable, potentially serious adverse reactions was the most frequent reason for using lower doses (table IV QA20).

Sorafenib is a first-line option for the treatment of patients with advanced HCC and extrahepatic metastasis in Child–Pugh liver function class A. As sorafenib has caused hepatic encephalopathy and hand–foot skin reaction more frequently in Japanese HCC patients,[23] Japanese hepatologists not experienced in using sorafenib may become concerned about its potential adverse effects at 800 mg/day. For some patient populations (e.g. elderly patients, those with low body weight or significant comorbidities), it may be prudent to start sorafenib at lower doses; however, as the drug has been shown to be effective at 800 mg/day (400 mg twice a day), if well tolerated, its dose should be uptitrated to 800 mg/day after several weeks.

8. Future Prospects

8.1 Sorafenib as Neoadjuvant or Adjuvant Chemotherapy

A promising strategy is neoadjuvant treatment with sorafenib followed by hepatic resection in

Table IV. Conference attendee responses regarding the optimum dose of sorafenib for the treatment of HCC

Question		No. of respondents	How attendees responded
QA18	At which dose do you currently start sorafenib?	300	800 mg/day: 48% 600 mg/day: 1% 400 mg/day: 33% 200 mg/day: 2% Individualized: 16%.
QA19	To those who start sorafenib at any other dose than 800 mg/day: how do you modify the dose after starting sorafenib?	175	Not modified: 20% Uptitrated to 800 mg/day if tolerated: 80%
QA20	To those who start sorafenib at any other dose than 800 mg/day: why do you start sorafenib at doses other than 800 m/day?	180	Adequate efficacy even at a reduced dose in Japanese patients, unlike in US/European patients: 6% Concern about unmanageable potentially serious adverse reactions at 800 mg/day: 61% Efficacy even at a reduced dose after sustained treatment: 14% Better compliance to treatment at a lower dose: 19%

HCC = hepatocellular carcinoma.

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patients with advanced but resectable HCC or HCC with extrahepatic metastasis; however, well-designed clinical trials are needed to establish the benefit of sorafenib in this setting. Sorafenib may also be effective against HCC following non-curative resection (including HCC with extrahepatic metastasis).

The benefit of sorafenib administered before or after hepatic transplantation is controversial. Although there has been a case report of successful downstaging of HCC by sorafenib administered before transplantation,[24] sorafenib is unlikely to cause downstaging in such cases because most responses to the drug reported to date are only SD. Furthermore, patients in Child–Pugh class B or C are not suitable for sorafenib therapy. Therefore, it is questionable whether sorafenib is effective for HCC patients with reduced liver function who are candidates for transplantation.

Sorafenib may be considered as neoadjuvant or adjuvant therapy to reduce the risk of recurrence after transplantation. Concerns regarding the use of sorafenib in this setting include sorafenib-induced hepatic damage and graft rejection, as well as interactions between sorafenib and immunosuppressants.[25] After liver transplantation, HCC recurs at a rate of approximately 10%, and it is widely accepted that recurrent HCC after liver transplantation is incurable. There have been several reports of an excellent response to sorafenib in patients with recurrent HCC following liver transplantation.[25-27]

8.1.1 Sorafenib as Adjuvant Treatment in the Prevention of Recurrence of Hepatocellular Carcinoma Trial

The Sorafenib as Adjuvant Treatment in the Prevention of Recurrence of Hepatocellular Carcinoma (STORM) trial (NCT00692770) is designed to evaluate the benefit of sorafenib as postoperative adjuvant therapy. This phase III study has recruited 1065 intermediate to high-risk patients following hepatic resection, radiofrequency ablation, or percutaneous ethanol injection therapy, who will be allocated to receive oral treatment with sorafenib (400 mg twice a day) or placebo for up to 4 years. The primary endpoint is recurrence-free survival; secondary endpoints include time to recurrence and OS. The estimated study completion date is October 2014.

9. Conclusions

Sorafenib is recommended as a first-line option for patients with HCC with extrahepatic metastasis in both international and Japanese guidelines. Its use should be restricted to patients in Child–Pugh class A. Sorafenib is also a first-line option for HCC unresponsive to TACE in Child–Pugh class A patients, because HCC unresponsive to TACE responds poorly to HAIC, and is also indicated for the treatment of HCC with four or more nodules or vascular invasion.

It is important to minimize the risk of treatment discontinuation with sorafenib due to adverse reactions. To avoid serious adverse events, dose reductions or interruptions may be useful. If HCC is judged as unresponsive to TACE, treatment should be switched to sorafenib in a timely manner. Sorafenib should not be used as adjuvant therapy or in combination with TACE or HAIC until evidence from clinical trials shows it is beneficial in these settings.

The SHARP trial demonstrated an increase in the median OS for patients with unresectable HCC treated with sorafenib compared with placebo. Clinical studies are currently planned or ongoing to evaluate the benefit of sorafenib as an adjunct to HAIC, TACE, or curative therapies. It is hoped that the combination of sorafenib with conventional therapies will prolong the survival of HCC patients. Planned and ongoing clinical studies will answer the question of whether sorafenib has survival benefit for patients with HCC at any stage.

Acknowledgements

The authors would like to thank Nila Bhana and Melanie Gatt from inScience Communications, Springer Healthcare, for medical writing support funded by Bayer, Japan. Dr Kudo has received honoraria in the form of lecture fees from Bayer Healthcare, Dr Takeishi has received lecture fees from Bayer Healthcare, Dr Yamashita has received lecture fees from Bayer Healthcare, Dr M Ikeda has received lecture fees from Bayer Healthcare, Dr Furuse is a consultant of Bayer Healthcare from whom he has received honoraria, Dr K Ikeda is a member of the sorafenib proper use committee and has received lecture fees from Bayer Healthcare, Dr Kokudo has

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received grants and support for his work from Bayer Healthcare, Dr Izumi has no conflicts of interest to declare, and Dr Matsui has received lecture fees, research funding and grant support from Bayer Healthcare.

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Digestive Diseases

Dig Dis 2011;29:339–364
DOI: 10.1159/000327577

Management of Hepatocellular Carcinoma in Japan: Consensus-Based Clinical Practice Guidelines Proposed by the Japan Society of Hepatology (JSH) 2010 Updated Version

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Key Words
Clinical practice guidelines, evidence-based · Clinical practice manual, consensus-based · Hepatocellular carcinoma, prevention · Hepatocellular carcinoma, staging · Hepatocellular carcinoma, surveillance · Hepatocellular carcinoma, diagnostic algorithm · Hepatocellular carcinoma, treatment algorithm

Abstract
Hepatocellular carcinoma (HCC) is one of the leading causes of cancer death not only in Japan but also worldwide. Clinical practice guidelines for HCC were first published in 2001 by the European Society of Study of the Liver (EASL) followed by the American Association for the Study of Liver Disease (AASLD) published in 2005 and updated in 2010. However, these guidelines have proven to be somewhat unsuitable for Japanese patients. In 2005, supported by the Japanese Ministry of Health, Labour and Welfare, evidence-based clinical practice guidelines for HCC were compiled in Japan. In 2009, a revised version of evidence-based guidelines was published. Based on both 'evidence-based' guidelines and the consensus of an expert panel on HCC, the Japan Society of Hepatology (JSH) published the Consensus-Based Clinical Practice Manual in 2007 and updated in 2010. In this article, the 2010 updated version of this manual, especially issues on prevention, surveillance, pathology, diagnosis, staging, and treatment algorithm are summarized.

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Introduction

Following the publication by the European Society of Study of the Liver (EASL) in 2001 [1], the American Association for the Study of Liver Disease (AASLD) published the Clinical Practice Guidelines of hepatocellular carcinoma (HCC) in *Hepatology* in November 2005 [2] and updated in 2010 [3].

In Japan, the original Evidence-Based Clinical Practice Guidelines of HCC were published in 2005 [4] and updated in 2009 [5], disclosed on the website of the Japan Society of Hepatology (JSH) [www.jsh.or.jp/], and then widely used for liver cancer treatment in Japan. An ex-

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Akio Ido	Kagoshima University
Kenji Ikeda	Toranomon Hospital
Tatsuo Inoue	Kinki University
Takao Iwasaki	Tohoku University
Namiki Izumi	Musashino Red Cross Hospital
Shuichi Kaneko	Kanazawa University
Akinori Kasahara	Osaka University
Kazuhiko Koike	Tokyo University
Masatoshi Kudo	Kinki University
Takashi Kumada	Ogaki Municipal Hospital
Yasushi Matsuzaki	Tokyo Medical University
Masahito Minami	Kyoto Prefectural University of Medicine
Yasunori Minami	Kinki University
Takeshi Okanoue	Saiseikai Suita Hospital
Masao Omata	Yamanashi Prefectural Hospital
Yukio Osaki	Osaka Red Cross Hospital
Shuichiro Shiina	Tokyo University
Masatoshi Tanaka	Kurume University Medical Center
Hidenori Toyoda	Ogaki Municipal Hospital
Yoshihide Ueda	Kyoto University
Tatsuya Yamashita	Kanazawa University
Hepato-Biliary-Pancreatic and Transplant Surgeons	
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cerpted version has also been published in an English journal by Makuuchi and Kokudo et al. [5–7]. These guidelines were prepared after critical evaluations based on about 100 reports with a high evidence level in each field selected from 7,118 reports on HCC published between 1966 and 2002. In the 2009 revised version, 2,950 articles were reviewed and 532 articles were incorporated into the new version. Since the guidelines were prepared based as much as possible on highly evidenced data, some points may slightly deviate from actual practices related to HCC routinely performed based on the experience and consensus of HCC experts in Japan.

Considering this situation, the JSH summarized HCC treatment as performed in Japan with the consensus opinions of many experts, even though clear evidence was not available, and published a simple manual in 2007 [8] and updated in 2010 [9]. This was an experience- or consensus-based manual based on evidence-based guidelines with respect to the evidence level, and summarized the consensus of expert opinions – widely reflecting the actual state of HCC treatment in Japan.

The manual was prepared in accordance with the Evidence-Based Clinical Practice Guidelines reported by Makuuchi and Kokudo et al. [5–7], and thus contains no conflict with those guidelines. Points that slightly differ are a more detailed explanation of liver cancer treatments based on expert opinions, and a summary of the consensus by the expert panel [10]. Although it may seem unusual that two different guidelines are available and followed in Japan, both have different roles and are not contradictory.

This report introduces the revised version of Consensus-Based Clinical Practice Manual of HCC published by the JSH in 2010, and focuses on prevention, surveillance, pathology, diagnosis, staging, and treatment algorithm. This constitutes a 'practice manual' summarized by the expert panel of the JSH (table 1), and is different from the Clinical Practice Guidelines. The contents of this report may be considered as the current state of the most advanced HCC treatment practices in Japan.

Prevention

Antiviral Therapy

Hepatitis B Virus-Related HCC

Preventive therapy for HCC should be indicated for these patients. In Japan, HBe antigen-positive chronic hepatitis B patients with an ALT level of ≥31 IU/l and an HBV DNA level of ≥5 log IU/ml, HBe antigen-negative

chronic hepatitis B patients with an HBV DNA level of ≥4 log IU/ml, and liver cirrhosis patients with an HBV DNA level of ≥3 log IU/ml are recommended for antiviral therapy.

Previously, a randomized controlled trial (RCT) examined the inhibitory effects of interferon (IFN) therapy on carcinogenesis in patients with chronic hepatitis B. In 1999, Lin et al. [11] randomly divided 101 HBe antigen-positive patients with type B chronic liver disease into three groups: placebo (n = 31), placebo + IFN (n = 34), and prednisolone + IFN (n = 36) groups, and continued follow-up, with a mean follow-up of 8.4 (1.1–11.5) years. HCC was detected in 1 of 67 patients treated with IFN and in 4 of 34 patients receiving a placebo. They reported that carcinogenesis was significantly inhibited in the IFN-treated groups (p = 0.013). However, when investigating only chronic hepatitis patients, excluding 12 with liver cirrhosis, there were no significant differences in the incidence of HCC between the IFN-treated and non-IFN-treated groups.

On the other hand, the incidence of HCC was compared between 233 IFN-treated and 233 untreated patients in a case-control study involving 466 HBe antigen-positive patients with type B chronic liver disease. In the IFN-treated group, carcinogenesis was significantly inhibited (p = 0.011) [12].

Camma et al. [13] conducted a meta-analysis involving seven articles, and examined whether IFN therapy reduces the risk of compensatory liver cirrhosis B-derived carcinogenesis. IFN therapy decreased the absolute risk of liver carcinogenesis by 6.4%. However, the values markedly differed among the studies. A study involving groups in Europe with slight differences reported that there were no differences.

Prevention of Chronic Hepatitis/Liver Cirrhosis B-Derived Liver Carcinogenesis with Nucleoside Analogues

Two RCTs investigated the effectiveness of nucleoside analogue on preventing liver carcinogenesis in patients with chronic hepatitis/liver cirrhosis B. One of these involved 651 patients with marked hepatitis B-related fibrosis or compensatory liver cirrhosis. During the follow-up period (32.4 months), HCC was noted in 17 (3.9%) of 436 patients treated with lamivudine and in 16 (7.4%) of 215 patients treated with a placebo. In the former, carcinogenesis was significantly inhibited [14]. The other trial involving 222 patients with liver cirrhosis B compared lamivudine-treated and additionally adefovir-treated groups with a non-treated group, and reported that HCC incidence was significantly inhibited in the former two groups (p = 0.003) [15]. Furthermore, a non-randomized, comparative study also indicated that lamivudine and additional adefovir treatments significantly inhibited carcinogenesis compared to control group [16]. Thus, antiviral therapy with nucleoside analogues is useful for preventing HCC in patients with chronic hepatitis B or compensatory liver cirrhosis B.

Hepatitis C Virus-Related HCC

Primary Prevention of Chronic Hepatitis C-Derived Liver Carcinogenesis with IFN

The risk of HCC in patients in whom IFN therapy achieved sustained viral response (SVR) was one-fifth of that in untreated patients. In non-SVR group it was significantly inhibited to one-fourth to one-half in comparison with patients with ALT normalization at the end of IFN therapy and biochemical responders (BR) with ALT normalization for ≥6 months after the completion of such therapy [17]. A meta-analysis involving 4,614 patients examined the relationship between the presence or absence of IFN therapy in patients with type C chronic liver disease, including those with liver cirrhosis, and the incidence of HCC indicated that IFN therapy decreased the risk of HCC by 13%. The effects were more marked in BR [18]. These results suggest that IFN therapy inhibits the development of HCC in comparison with untreated patients, and that not only SVR but also BR are related to the prevention of HCC. Furthermore, a retrospective cohort study regarding the inhibitory effects of combination therapy with IFN and ribavirin on HCC in patients with chronic hepatitis C showed that the risk of HCC development was significantly lower in responders to this combination therapy [19]. Based on these findings, it is recommended that antiviral therapy with IFN be performed to prevent HCC incidence in patients with chronic hepatitis C. The primary goal of IFN treatment is virus eradication (SVR). When it is impossible, the liver function should be normalized as much as possible (BR).

Recently long-term follow-up of the HALT-C study confirmed this observation [20].

Two RCTs investigated the effectiveness of IFN therapy for liver cirrhosis C on preventing liver carcinogenesis. Of these, one reported that there was no difference in the incidence of HCC between IFN-treated and non-treated groups. However, the other study indicated that IFN therapy inhibited the development of HCC. Seven non-randomized, comparative studies, in which a non-IFN-treated group was set as a control group, have been