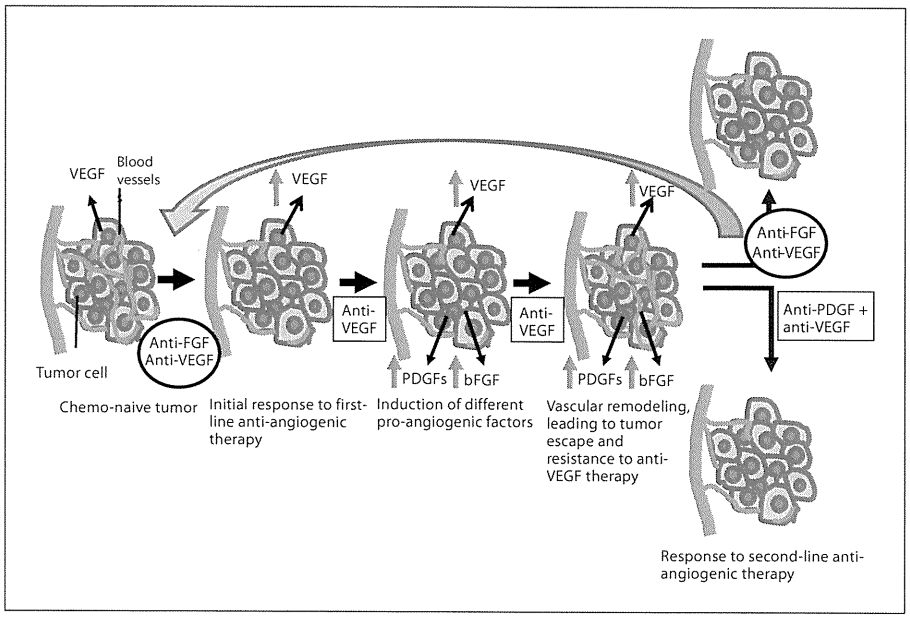

Fig. 1. Targeting angiogenesis: mechanisms of resistance. Brivanib may be effective for the failure or resistance of first-line antiangiogenic therapy for VEGF.

naling with inhibition of VEGFR signaling might provide a potential mechanism to overcome anti-VEGF resistance in HCC (fig. 1). With this in mind, it is worthwhile considering the potential future impact of brivanib on the treatment of advanced HCC. Brivanib, a small-molecule tyrosine kinase inhibitor, is the first oral selective dual inhibitor of FGF and VEGF signaling. In multiple preclinical models of human xenograft tumors, including patient-derived HCC xenografts, brivanib has shown potent antitumor activity and no overt toxicity when dosed orally [21, 22]. Furthermore, brivanib has demonstrated promising antitumor activity and acceptable tolerability in a phase 2, open-label study in patients with unresectable locally advanced or metastatic HCC [23, 24]. Crucially, within this trial, brivanib showed activity both as first-line therapy (overall survival: 10 months) or as second-line therapy in patients who had failed prior antiangiogenic treatment, primarily with sorafenib (overall survival 9.5 months) [24]. Of note, the incidence of all-grade hand-foot syndrome was only 8% in this study.

Phase I and II Data of Brivanib

Additional retrospective studies and subanalyses have also confirmed that brivanib is effective in patients from the Asia-Pacific region. In a subanalysis performed to evaluate the effects of brivanib among Asian versus non-Asian patients enrolled in the aforementioned phase II study, median overall survival was 10.6 months among Asian patients treated with first-line brivanib (versus 5.7 months in non-Asian patients) and 9.8 months among Asian patients receiving brivanib as second-line therapy (versus 9.4 months in non-Asian patients) [25]. Another subanalysis, this time including only patients who received first-line brivanib therapy in the phase 2 study, indicated that overall tolerability was similar or slightly better in the Asian population versus non-Asian patients [26]. A further subanalysis comparing 125 Asian and non-Asian patients enrolled in separate phase I and II studies [23, 27] confirmed that exposures in these patient subpopulations were similar following brivanib doses of 800 mg daily [28]. Finally, a phase 1 study of brivanib in Japanese patients with advanced or metastatic solid tumors, including HCC, has shown manageable tolerability and a similar safety profile at the same 800-mg once-daily dose as used in Caucasian patients [29]. Moreover, the study provided evidence of antitumor activity in this uniquely Japanese population, with 8 of 13 patients (62%) showing stable disease.

Design of Phase III Global Study

To further investigate the benefits of brivanib for advanced HCC, a broad-spectrum, global, phase III development plan, the Brivanib studies in HCC patients at

RISK (BRISK) clinical program, has been initiated. The global BRISK program will enroll patients from countries in Africa, Asia (including Japan), Australasia, Europe, and North, South, and Central America, and will include investigations of brivanib in a variety of clinically relevant settings, including first-line head to head with sorafenib, second-line post-sorafenib, and TACE adjuvant settings. In addition, it is noteworthy that the BRISK study of brivanib as adjuvant treatment to TACE therapy is being led by Japanese investigators and is one of the first global registration programs to be led from Japan.

Conclusion

HCC continues to be a major healthcare burden in Japan. Although it is detected in the early stages in most Japanese patients and treated accordingly, there remains a population of patients with advanced HCC who have limited therapeutic choices. With the recent approval of the antiangiogenic agent sorafenib, options for these patients have improved, but clinical studies to date suggest only a modest survival benefit with sorafenib and there is potential for safety/tolerability issues and the development of resistance to the anti-VEGF blockade. Clinical benefits seen with brivanib in the first-line setting, and following the failure of sorafenib therapy, highlight the potential to improve the clinical course of patients with advanced HCC, and this agent may provide a novel therapeutic option for the growing population of patients for whom no other treatment choice exists.

Disclosure Statement

The author has no conflict of interest to declare.

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Des-γ-Carboxyprothrombin May Be a Promising Biomarker to Determine the Therapeutic Efficacy of Sorafenib for Hepatocellular Carcinoma

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Key Words

Des-γ-carboxyprothrombin · Protein-induced vitamin K absence II · Hepatocellular carcinoma · Antiangiogenic therapy · Hypoxia · Sorafenib

Abstract

Objective: The purpose of this study was to evaluate the role of des-γ-carboxyprothrombin (DCP) as a marker for the efficacy of sorafenib therapy for hepatocellular carcinoma (HCC). ***Methods:*** Patients with advanced HCC treated with sorafenib were retrospectively evaluated, focusing on DCP levels and clinical characteristics. ***Results:*** 50 patients with advanced HCC were treated with sorafenib alone. In 25 of these patients, the serum levels of DCP were evaluated twice (pretreatment and within 2 weeks after starting therapy). The time to progression was significantly longer in patients in whom the DCP level at 2 weeks after starting sorafenib was ≥2-fold higher than the pretreatment levels, as compared with patients without an increase in DCP ($p = 0.0296$). ***Conclusions:*** The serum level of DCP is a surrogate marker for tissue hypoxia and can be a predictive marker to assess the tumor response to sorafenib therapy.

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies in Japan and is the fifth most common cancer worldwide [1, 2]. It is well known that HCC is less sensitive to chemotherapeutic agents than other tumors. Furthermore, because of pancytopenia and poor hepatic preservation caused by underlying hepatic cirrhosis, systemic chemotherapy is unsuitable for patients with HCC. Thus, locoregional therapies such as hepatic resection, radiofrequency ablation and transcatheter chemoembolization (TACE) have been developed and are widely used. However, more effective systemic chemotherapy is necessary for patients who are refractory to locoregional therapy or who progress to advanced stage cancer with extrahepatic spread and/or vascular invasion.

Sorafenib (Nexavar®; Bayer HealthCare Pharmaceuticals-Onyx Pharmaceuticals) is a small molecule that inhibits tumor proliferation and angiogenesis. It inhibits serine-threonine kinase Raf-1, a member of the RAF/MEK/ERK signaling pathway, and several receptor tyrosine kinases involved in neovascularization and tumor progression, including vascular endothelial growth

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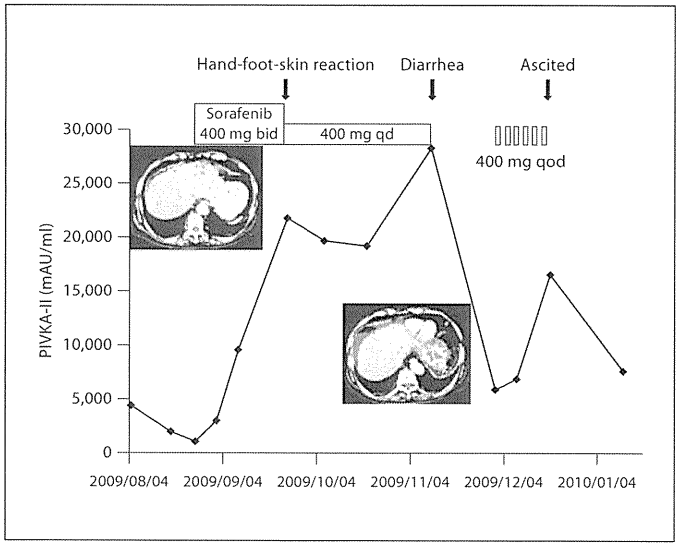

Fig. 1. Discrepancies between the changes in serum DCP levels and clinical findings for a 76-year-old man with advanced HCC. The serum DCP level rapidly increased after starting sorafenib but decreased after reducing or discontinuation of sorafenib therapy. CT showed that the HCC decreased and became necrotic, despite increased DCP levels.

factor receptor (VEGFR)-2, VEGFR-3, platelet-derived growth factor receptor-β (PDGFRβ), Flt-3 and c-KIT [3–7]. Sorafenib-based chemotherapy is used for HCC because HCC is a hypervascular tumor that expresses VEGF and the VEGFR [8], and the survival of tumor cell depends on its vascularity. A meta-analysis has shown that tissue and serum VEGF levels are prognostic factors in HCC [9].

The SHARP study, a phase III randomized trial for advanced HCC, revealed that sorafenib prolonged the overall survival time to progression (TTP) [10]. Based on such findings, sorafenib is now used worldwide. On the other hand, tumor shrinkage was infrequently observed in the SHARP study because the partial response in that study was only 2%. However, stable disease was achieved in 76% of patients, and the overall disease control rate was 78%. The tumoristatic effect of sorafenib contributes to prolongation of overall survival.

Cases of complete response or partial response have frequently been observed since sorafenib was approved in Japan in May 2009. It is thought that the Japanese race has some genetic characteristics that improve the efficacy of sorafenib therapy.

Dynamic computed tomography (CT) and dynamic magnetic resonance imaging (MRI) are often used to evaluate the antitumor effect in the treatment of HCC. However, since the introduction of molecular-targeted therapy, tumor necrosis without tumor regression is often observed. Tumor necrosis is not always induced by a cytotoxic antitumor agent. It was recently suggested that the Response Evaluation Criteria for Solid Tumors (RECIST) [11, 12] and the World Health Organization Criteria [13] are unsuitable for the evaluation of the anticancer effects of molecular-targeted therapy, which inhibits angiogenesis. To overcome the limitations of these criteria, a modified RECIST [14] for HCC was proposed, and evaluates the size of the viable tumor tissue. The validity of the modified RECIST or RECICLE [15] has been discussed, but their utility is still not established. Tumor markers have also been used to evaluate the antitumor effects of therapy. α-Fetoprotein (AFP), the lens culinaris agglutinin-reactive fraction of AFP (AFP-L3), and des-γ-carboxyprothrombin (DCP) are the most widely used tumor markers and are well established for the diagnosis and follow-up of HCC [16–18]. These tumor markers indicate the activity of HCC and are useful for patient follow-up [19]. In particular, tumor markers can be used to examine the efficacy of antiangiogenic molecular-targeted agents.

At our institute, we have experienced discrepancies between changes in DCP levels and clinical findings during sorafenib therapy (fig. 1). Therefore, we retrospectively evaluated the associations between changes in DCP levels and clinical findings.

Patients and Methods

Sixty-two consecutive patients with advanced HCC treated with sorafenib at Kinki University Hospital between May 2009 and April 2010 were included in this study. The criteria for sorafenib therapy were as follows: (1) patients with HCC refractory to TACE or the presence of major vascular invasion or extrahepatic spread; (2) ECOG Performance Status Score of 0 or 1, and (3) Child-Pugh score of ≤7 (Child-Pugh A and some B patients). Patients with laboratory values meeting the following criteria were also eligible for sorafenib: (a) hemoglobin ≥8.5 g/dl, (b) neutrophil count >1,500/mm^3, (c) platelet count >50,000/mm^3, (d) total bilirubin <3 mg/dl, (e) ALT and AST <5 times the institutional upper limits of normal, and (f) serum creatinine <1.5 times the institutional upper limits of normal.

Patients continuously received 400 mg of oral sorafenib (two 200-mg tablets) twice daily. If adverse effects were observed, the sorafenib dose was reduced according to the treatment guidelines.

Tumor response was evaluated by RECIST version 1.1. TTP was constructed by the Kaplan-Meier method and was compared using the log-rank test. Statistical analysis was conducted using SPSS version 11.5.1J for Windows.

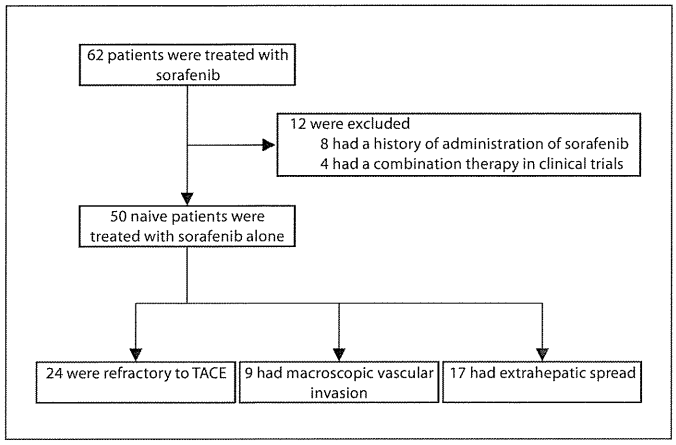

Fig. 2. Patient disposition.

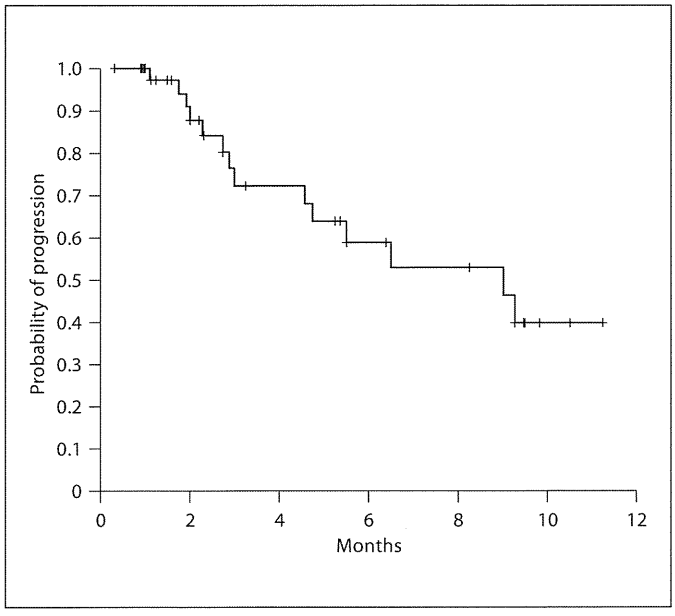

Fig. 3. TTP in 50 patients with HCC treated with sorafenib.

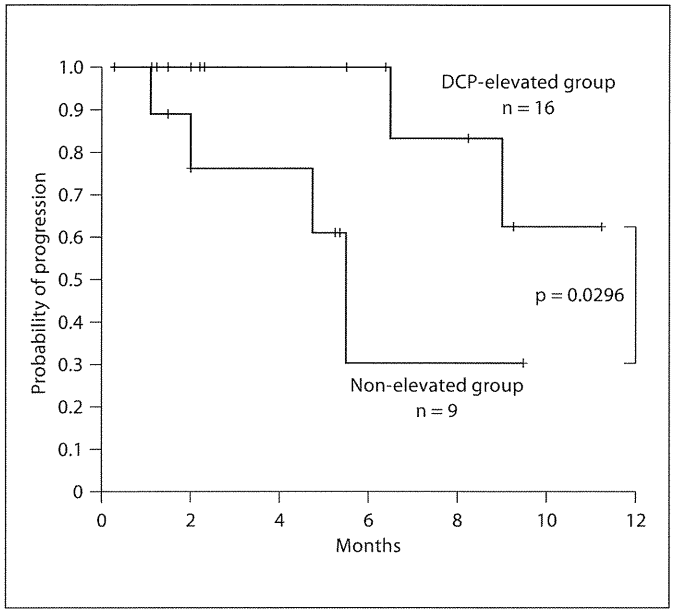

Fig. 4. Comparison of TTP between patients with (elevated) and patients without (non-elevated) an increase in DCP by ≥2-fold at 2 weeks after starting sorafenib therapy compared with pretreatment.

Results

Eight of 62 patients were excluded because they had already been treated with sorafenib before it was approved in Japan. Four patients were excluded because they participated in other clinical trials. Thus, 50 patients were evaluated in this study: 24 were refractory to TACE, 9 had major vascular invasion, and 17 had extrahepatic spread (fig. 2).

The mean duration of treatment was 5.2 months (95% confidence interval (CI) 4.1–6.8 months). The mean dose of sorafenib was 480.0 mg daily, overall survival was 9.5 months (95% CI 8.1–10.8 months), and TTP was 9.0 months (95% CI 4.75–13.25) (fig. 3).

In 25 of the patients treated with sorafenib, the serum levels of DCP were evaluated twice, i.e. before and within 2 weeks after starting treatment. The TTP in the patients in whom the DCP level at 2 weeks was ≥2-fold greater than the pretreatment level was significantly longer than that in patients without elevated DCP (i.e. <2 times the pretreatment levels) (p = 0.0296) (fig. 4). There were no statistically significant differences in other clinical characteristics between the two groups of patients (table 1).

Discussion

Sorafenib shows the significant activity against several receptor tyrosine kinases including VEGFR-2, VEGFR-3, PDGFRβ, Flt-3, and c-KIT, and inhibits angiogenesis. Antiangiogenic activity plays a very important role in HCC therapy because HCC is a typical hyper-

Table 1. Characteristics of patients according to change in DCP

Characteristics	Elevated group (n = 16)	Non-elevated group (n = 9)	p value[1]
Age	73.06 ± 6.03	68.22 ± 6.40	0.065
Male/female	12/4	7/2	0.876
Serum albumin, g/dl	3.44 ± 0.56	3.64 ± 0.32	0.329
Serum bilirubin, mg/dl	0.93 ± 0.51	0.91 ± 0.36	0.803
Prothrombin time, %	86.55 ± 17.65	84.18 ± 10.12	0.978
Child-Pugh score (5/6/7/8)	6/7/2/1	6/3/0/0	0.413
Platelet count	15.90 ± 7.00	16.21 ± 11.18	0.598
Etiology, NBNC/HBV/HCV	4/3/9	4/1/4	0.593
Stage, III/IV	10/6	6/3	0.835
MVI, with/without	3/13	2/7	0.835
EHS, with/without	3/13	4/5	0.170
AFP, ng/ml	977.0 (2–35,014)	304.5 (6–721,260)	0.728
DCP, mAU/ml	2,327.5 (41–34,170)	2,088.0 (46–357,580)	0.846

Elevated: DCP increased by ≥2-fold at 2 weeks compared with pretreatment; non-elevated: DCP increased by <2-fold at 2 weeks compared with pretreatment.

MVI = Macroscopic vascular invasion; EHS = extrahepatic spread.

[1] All values were non-significant.

vascular tumor. In other words, HCC induces angiogenesis to maintain adequate blood supply.

Liebman et al. [20] were the first to report the utility of DCP as a tumor marker for the diagnosis of HCC. DCP, also known as PIVKA-II (proteins induced by vitamin K absence or antagonist-II), is an abnormal prothrombin induced by vitamin K deficiency. Vitamin K-dependent coagulation factors such as prothrombin are synthesized in hepatocytes and contain γ-carboxy-glutamic acid (Gla residues), which can bind calcium. Normal prothrombin contains 10 Gla residues at the amino terminal. However, in the vitamin K-deficient state the Gla residues at the amino terminal are not fully γ-carboxylated. This incomplete prothrombin is known as DCP and is functionally inactive.

It is unclear why DCP is elevated in patients with HCC. Several reports have proposed mechanisms for DCP production, which include: (1) vitamin K deficiency [21]; (2) decreased activity of γ-glutamyl carboxylase in the HCC tissue because of a point mutation in the γ-glutamyl carboxylase gene [22, 23]; (3) abnormal vitamin K metabolism [24]; (4) overexpression of the prothrombin precursor in HCC cells [25, 26], and (5) abnormal uptake of vitamin K into HCC cells. We have focused on the abnormal uptake of vitamin K into the HCC cells. Murata et al. [27–29] reported that hypoxia induces DCP. They explained this phenomenon as follows. The fine filamentous actin network, which plays a crucial role in clathrin-mediated endocytosis of vitamin K, is disrupted in DCP-producing cells because of hypoxia. It is considered that this offers one explanation for the elevated serum DCP level in patients with HCC, for which sorafenib is effective. In this issue, we found that HCC patients with a rapid increase in DCP within 2 weeks after starting sorafenib had a significantly better outcome than patients with no increase in DCP [30]. The CT findings for HCC with rapid DCP elevation tended to include reduced vascularity or presence of necrosis. This indicates that hypoxia was responsible for the change in DCP production. Accordingly, DCP may offer a surrogate marker for hypoxia.

Sorafenib induces hypoxia in HCC by inhibiting angiogenesis. TACE exposes the HCC to hypoxia, as does sorafenib, but this change is very rapid and most of the tumor cells become necrotic. It is thought that not enough DCP is produced after TACE. On the other hand, sorafenib induces tissue hypoxia relatively slowly and many viable HCC cells are exposed to hypoxia. During sustained hypoxia, the tumor cells gradually die and the serum level of DCP subsequently decreases.

During molecular-targeted HCC therapy using sorafenib, we found that the rapid increase in DCP after starting sorafenib does not indicate tumor progression, but rather indicates HCC tissue hypoxia. Therefore, DCP may be a useful predictive marker for the duration of tu-

mor suppression. To our knowledge, this is the first report to show that DCP could be a good biomarker to predict the therapeutic efficacy of sorafenib in HCC.

In conclusion, the serum level of DCP during sorafenib treatment may be a promising biomarker for the therapeutic efficacy of sorafenib therapy for HCC.

Disclosure Statement

The authors have no conflict of interest to declare.

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SUPPLEMENT

Tissue Biomarkers as Predictors of Outcome and Selection of Transplant Candidates With Hepatocellular Carcinoma

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Hepatocellular carcinoma (HCC) is a common cause of cancer deaths worldwide, and its annual incidence is rising. Liver transplantation (LT) is an accepted curative treatment for patients with tumors satisfying the Milan criteria (a single tumor $\leq$ 5 cm in diameter or up to 3 tumors with individual diameters $\leq$ 3 cm and no macrovascular invasion). These criteria predict an overall 5-year survival rate of 70% after LT.[1] Since the introduction of the Milan criteria, subsequent studies have explored the expansion of transplant recipient selection to include individuals with tumors exceeding the Milan criteria.[2] A recent study demonstrated an acceptable overall 5-year survival rate (71.2%) for patients who underwent transplantation for tumors that were beyond the Milan criteria but satisfied the up-to-7 rule (7 is the sum of the size of the largest tumor in centimeters and the number of tumors) in the absence of microvascular invasion.[3] This approach is based on the best data available for understanding tumor behavior after LT, but it is still based on pathological data. The tumor size and the tumor number cannot be used to define subclasses of patients with better biology and better outcomes, so biomarkers are expected to be a major step forward in this setting during the next decade.

Numerous molecular pathways involved in the pathogenesis of HCC have been identified. These include activation pathways that are involved in angiogenesis [vascular endothelial growth factor (VEGF)], in cell proliferation and survival (epidermal growth factor, insulin-like growth factor, and hepatocyte growth factor/Met), and in cell differentiation and proliferation (Wnt/β-catenin and hedgehog signaling). The activation of

Abbreviations: AFP, alpha-fetoprotein; Ang2, angiopoietin 2; HCC, hepatocellular carcinoma; LT, liver transplantation; miRNA, microRNA; mRNA, messenger RNA; REMARK, Reporting Recommendations for Tumor Marker Prognostic Studies; VEGF, vascular endothelial growth factor.

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VEGF,[4] Serine/threonine protein kinase Akt (Bombyx mori) [AKT],[5] and met proto-oncogene (hepatocyte growth factor receptor) [MET][6] has been correlated with an aggressive phenotype and a poor prognosis after liver resection. Similarly, several gene signatures have been used to predict the outcomes of patients with HCC.[7] Gene expression profiling with formalin-fixed, paraffin-embedded tissue samples from HCC resection specimens has been described and validated for the prediction of survival outcomes for patients after resection for HCC.[8] This profiling technique offers the ability to perform retrospective studies with stored histological specimens. In addition, it potentially offers a practical clinical application through the ability to perform gene profiling with common formalin-fixed biopsy specimens rather than frozen tissue.

This article summarizes 3 areas in which molecular tissue biomarkers should be considered for the management of HCC in LT patients:

1. Role of tissue biomarkers in the diagnosis of HCC.
2. Role of biomarkers in the prediction of prognosis (ie, the use of gene signatures or tissue biomarkers to predict a patient's prognosis and thus aid in the extension of the Milan criteria for HCC).
3. Role of biomarkers in the prediction of the response to molecular-targeted therapies.

Serum markers such as alpha-fetoprotein (AFP), angiopoietin 2 (Ang2), and des-gamma-carboxyprothrombin are not analyzed here.

ROLE OF TISSUE BIOMARKERS IN THE DIAGNOSIS OF HCC

The diagnosis of HCC is based on pathological or noninvasive criteria.[9] The pathological differentiation of dysplastic nodules (particularly high-grade nodules) from very early HCC is sometimes difficult, especially with a cirrhotic background. Few studies have tested the accuracy of the molecular diagnosis of early HCC in this setting. For instance, gene signatures have allowed molecular demarcations between low-grade dysplastic nodules, high-grade dysplastic nodules, and early HCC in both Asian[10] and Western patients.[11] More specifically, a 3-gene signature (including glypican 3, lymphatic vessel endothelial hyaluronan receptor 1, and survivin) has been reported to distinguish early HCC (<2 cm) from dysplastic nodules with an accuracy of approximately 90%.[12] Nonetheless, this signature has not yet been externally validated. More recently, an immunohistochemistry study found the expression of glypican 3, heat shock protein 70, and glutamine synthetase to be useful in detecting well-differentiated HCC in biopsy samples,[13] and this is currently being considered for HCC management guidelines.[9]

ROLE OF BIOMARKERS IN THE PREDICTION OF PROGNOSIS

Patients who develop HCC with cirrhosis and undergo resection have a high rate of recurrence (approximately 70% at 5 years).[2,14] A molecular assessment of the prognosis could determine which patients with HCC would benefit from adjuvant therapy after resection or radio frequency ablation (2 curative treatments with a high risk of relapse). Moreover, it could be used to refine the group of patients who should undergo transplantation for HCC beyond the Milan criteria. Whether the risk of tumor seeding counterbalances the advantages of tissue-based molecular profiling is still an area of discussion. In a recent meta-analysis, the risk of tumor seeding after liver biopsy was 2.7% with a median time of 17 months between biopsy and seeding.[15] These data also include large tumors, so the risk of complications with small, early tumors is expected to be significantly lower and thus acceptable.

Biomarkers predicting a patient's prognosis or response to therapy are crucial in modern oncology. Novel prognostic biomarkers enabling tumor classification, disease state monitoring, or both could advance our efforts to realize the potential of personalized medicine in cancer.[16] Besides reports on AFP levels and outcomes,[17-19] recent studies have correlated various types of markers, such as gene expression, microRNAs (miRNAs), and methylation changes, with the survival of HCC patients; this topic has been reviewed elsewhere[20] (see Table 1). Five markers or signatures (epithelial cell adhesion molecule [EPCAM signature], which is a hepatic stem cell marker in tumor tissue[21,22]; the G3 proliferation subclass[23]; the expression status of the miR-26 miRNA precursor[24]; and 2 prognostic gene signatures in nontumor hepatic tissue[8,25]) have emerged as more consistent ones. Finally, both VEGF and Ang2 were shown to have independent prognostic value in a large cohort of patients with advanced HCC.[26] Although these results support the possibility of using these genetic and molecular markers as prognostic biomarkers for patients with HCC, they require external validation before they can be included in staging systems and/or incorporated into clinical management guidelines. The fractional allelic imbalance, which is used to measure chromosomal instability, has been associated with outcomes for patients with HCC and with recurrence after LT; this observation requires attention in future studies.[27,28] Similarly, data about $CD90^+$ circulating cells may lead to a tractable supply of tissue for molecular characterization, but this is still under investigation.[29]

In this era of limited organ availability, better predictors of HCC recurrence are needed for selecting appropriate LT candidates whose tumors exceed the Milan criteria. The identification of a subgroup of patients whose tumors are beyond the Milan criteria but who have a favorably low risk of recurrence after transplantation offers a potential cure to those who would otherwise be excluded according to current organ allocation policies. Whether any of the aforementioned biomarkers or gene signatures can be used to identify those patients with better biological profiles needs to be elucidated in molecular studies addressing this point. Only a small study has addressed this

TABLE 1. Main mRNA-Based, miRNA-Based, Epigenetic, and Structural Alterations Whose Prognostic Impact for HCC Patients Needs to Be Tested or Confirmed

Molecular Alteration	Clinical Significance	REMARK Recommendation	Current Status*
mRNA-based (gene signatures)†			
Poor survival signature	Poor survival	Okay	Lacks external validation
Epithelial cell adhesion molecule signature	Poor survival	Okay	Lacks external validation
Venous metastasis signature	Hepatic metastasis	Okay	Lacks external validation
Class A/hepatoblast signature	Poor survival	Okay	Lacks internal and external validation
G3 subclass	Poor survival	—	Lacks internal and external validation
AFP and Ang2	Poor survival	Okay (unclear cutoff)	Lacks external validation
miRNA-based			
Down-regulation of miR-26a	Poor survival	Okay	Lacks external validation
20-miRNA signature	Venous metastasis, overall survival	Okay	Lacks external validation
Down-regulation of miR-122	Poor survival	—	Lacks internal and external validation
Down-regulation of Drosophila melanogaster members	Early recurrence	—	Lacks internal and external validation
Up-regulation of miR-125a	Better survival	—	Lacks internal and external validation
19-miRNA signature	Poor survival	—	Lacks internal and external validation
Epigenetic			
Genome-wide hypomethylation	Tumor progression, survival	—	Lacks internal and external validation
Hypermethylation of E-cadherin or glutathione S-transferase π1	Poor survival	—	Lacks internal and external validation
Structural			
Fractional allelic imbalance/ chromosomal instability	Recurrence/survival	Okay	Lacks external validation

NOTE: Adapted with permission from *Clinical Cancer Research*.[20]
*In terms of clinical implementation.
†Molecular classifications (mRNA-based) with a prognostic impact have been thoroughly discussed elsewhere.[5,6,20]

question in a specific manner, and it found that chromosomal instability (measured with the fractional allelic imbalance) independently predicted which patients beyond the Milan criteria had a low risk of recurrence.[27] Similarly, preliminary reports describing surrogates of microvascular invasion (the main predictor of HCC recurrence after LT) require independent validation in the setting of transplantation.[30]

ROLE OF BIOMARKERS IN THE PREDICTION OF THE RESPONSE TO MOLECULAR-TARGETED THERAPIES

Biomarkers for treatment responses are still rarities in oncology; only a few have made their way into routine clinical use. Well-defined biomarkers are believed to characterize an oncogenic addiction loop (the proposed mechanism by which a tumor cell becomes largely reliant on a single activated oncogene[31]) and define particular tumor subtypes that respond to specific molecular-targeted therapies. Examples of oncogenic addiction include an amplification of human epidermal growth factor receptor 2 in patients with breast cancer responding to trastuzumab,[32] mutations in epidermal growth factor receptor that distinguish patients with non–small cell lung cancer responding to erlotinib,[33] and v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog (c-KIT)–positive gastrointestinal stromal tumors responding to the multikinase inhibitor imatinib.[34] In addition, wild-type v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) has recently emerged as a marker of a response to cetuximab and panitumumab in patients with colorectal cancer, although the mechanism is entirely different and involves the downstream regulation of epidermal growth factor receptor signaling.[35] Moreover, a new step in personalized medicine has been achieved recently with the development of a specific inhibitor of mutated V600E v-raf murine

sarcoma viral oncogene homolog B1 (BRAF); this inhibitor has shown impressive clinical efficiency with few adverse events in a recent phase 2 study of melanoma.[36] In the future, therefore, mapping the genetic alterations of tumors before the treatment or after treatment failure will improve the clinical care of patients with cancer.[37]

The use of biomarkers for HCC is somewhat more complex because HCC is a very heterogeneous disease for which oncogenic addiction loops have yet to be characterized. Initial approaches for defining a molecular classification have not yet been linked to specific treatment responses.[38,39] So far, only 1 small molecule, sorafenib, has been shown to improve the survival of HCC patients.[40] Sorafenib is a multikinase inhibitor that targets a number of kinases; these kinases include VEGF receptors 2 and 3, platelet-derived growth factor receptor β, c-KIT, Ret proto-oncogene (RET), fms-related tyrosine kinase 3, and Raf kinase, efector of Ras (RAF).[41] Isolated reports have described the use of sorafenib in the adjuvant setting after LT. In a companion biomarker study of the pivotal Sorafenib HCC Assessment Randomized Protocol trial, 10 serum markers and 1 tissue marker were tested, but none of them succeeded in identifying subclasses of responders.[26] Nonetheless, the fast development of new biotherapies and the growing number of clinical trials for HCC are expected to lead to the use of the molecular features of tumors in defining types of treatment. In this setting, we have to reevaluate the utility of tumor biopsy for easy access to tissue and its frequency.

FUTURE PROSPECTS

Novel molecular data may change our approach to the diagnosis, staging, and prognosis of HCC in this decade. For prognosis assessments, recently reported prognostic gene signatures and miRNAs may be added to staging systems to complement clinical variables once they have been externally validated by independent studies. These advances in our understanding of HCC ultimately need to be transferred to clinical practice as daily tools for selecting management and treatment methods. Moreover, treatment response predictors will emerge along with novel drugs for the treatment of HCC. Positive results with sorafenib[40] have opened a new era in HCC research. Future trends in drug development will pivot on the accurate assessment of genetic traits associated with human diseases on an individual basis (ie, personalized medicine). For HCC, the identification of these singularities will allow maximization of the therapeutic response through the selection of the best drug for the ideal candidate.

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Hepatocellular Carcinoma in 2011 and Beyond: From the Pathogenesis to Molecular Targeted Therapy

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Key Words
Hepatocellular carcinoma · Pathogenesis · Signaling pathway · Locoregional therapy · Molecular targeted therapy

Abstract
Hepatocellular carcinoma is a malignant tumor responsible for approximately 600,000–700,000 deaths worldwide, and it is becoming more prevalent not only in Southeast Asia and Africa but also in Western countries; therefore, interest in hepatocellular carcinoma has mounted in recent years in the West, where little or no interest was evident 10–20 years ago.

Introduction

The second Asia-Pacific Primary Liver Cancer Expert Meeting (APPLE) was held on July 1–3, 2011, in Osaka, Japan. A total of 73 oversea guests, all globally recognized hepatocellular carcinoma (HCC) specialists, were invited to this symposium (table 1). Numerous topics were presented followed by extensive discussions with Japanese HCC specialists. This supplement issue focuses on these topics and especially on the Asian consensus on subjects from the pathogenesis and signaling pathway to molecular targeted therapy. I firmly believe that readers will gain a deeper insight into the latest progress and updated diagnosis and treatment of HCC.

Pathogenesis

Persistent infection with hepatitis C virus (HCV) is a major risk for the development of HCC. One of the characteristics of HCV infection is the unusual augmentation of oxidative stress, which is exacerbated by iron accumulation in the liver, as observed frequently in hepatitis C patients. Using a transgenic mouse model, in which HCC develops late in life after the preneoplastic steatosis stage, the core protein of HCV was shown to induce overproduction of reactive oxygen species (ROS) in the liver. In excessive generation of ROS, HCV affects the steady-state levels of a mitochondrial protein chaperone, i.e. prohibitin, leading to an impaired function of the mitochondrial respiratory chain with the overproduction of ROS.

Combination with the other activated pathway, including an alteration in the intracellular signaling cascade of MAP kinase, along with HCV-associated distur-

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Table 1. Invited speakers at the 2nd APPLE meeting (in alphabetical order)

Western speakers (n = 18)	Asian speakers (n = 20)	Japanese speakers (n = 21)
Jacques Belghiti (France)	Subrat Acharya (India)	Yasuaki Arai
Luigi Bolondi (Italy)	Oidov Baatarkhuu (Mongolia)	Yasuhiro Asahina
John F.P. Bridges (USA)	Ding-Shinn Chen (Taiwan)	Takafumi Ichida
Jordi Bruix (Spain)	Pei-Jer Chen (Taiwan)	Tomoaki Ichikawa
Adrian Michael Di Bisceglie (USA)	Ann-Lii Cheng (Taiwan)	Namiki Izumi
Richard S. Finn (USA)	Pierce K.H. Chow (Singapore)	Shuichi Kaneko
Peter R. Galle (Germany)	Kwang-Hyub Han (Korea)	Kazuhiko Koike
Jean-Francois H. Geschwind (USA)	Yun Hwan Joseph Kim (Korea)	Shigehiro Kokubu
Riccardo Lencioni (Italy)	Jeong Min Lee (Korea)	Norihiro Kokudo
Josep M. Llovet (Spain/USA)	Sung-Gyu Lee (Korea)	Masatoshi Kudo
Vincenzo Mazzaferro (Italy)	Laurentius A. Lesmana (Indonesia)	Masatoshi Makuuchi
Valerie Paradis (France)	Shi-Ming Lin (Taiwan)	Osamu Matsui
Lewis R. Roberts (USA)	Sheng-Nan Lu (Taiwan)	Kazuto Nishio
Riad Salem (USA)	Joong-Won Park (Korea)	Kiwamu Okita
Myron E. Schwartz (USA)	Young Nyun Park (Korea)	Takuji Okusaka
Morris Sherman (Canada)	Hunchul Rhim (Korea)	Masao Omata
Augusto Villanueva (Spain)	Hui-Chuan Sun (China)	Michiie Sakamoto
Andrew X. Zhu (USA)	Hee Jung Wang (Korea)	Shuichiro Shiina
	Sheng-Long Ye (China)	Kenichi Takayasu
	Jian Zhou (China)	Ryosuke Tateishi
		Kazuomi Ueshima

bances in lipid and glucose metabolism would lead to the unusual mode of hepatocarcinogenesis, i.e. very frequent and multicentric development of HCC, in persistent HCV infection [1].

Signaling Pathways in HCC

The capability of cells to receive and correctly respond to the microenvironment is basic for their homeostasis. Each cell acts as a complex system where multiple signaling pathways intertwine in parallel circuits. Within this context, a signaling pathway represents a series of chemical reactions ending up in changes in gene expression and cellular phenotype. Information on signaling pathways is crucial to understanding how genes are connected to each other and how they influence cellular functions and behavior in normal and diseased conditions [2–4].

Prevention

Prevention of Hepatitis B Virus-Related HCC

About 350 million people are chronic carriers of the hepatitis B virus (HBV) worldwide. The efficacy of universal immunization has been shown in many countries, with striking reductions in the prevalence of HBV carriage in children. A nationwide vaccination program against HBV launched in Taiwan [5, 6] has drastically reduced the HBsAg carrier rate in the younger populations [7]. More importantly, follow-up results from the Taiwan vaccination programs have shown that the incidence of HCC has been significantly reduced in children. The average annual incidence of HCC in children 6–14 years of age declined from 0.70/100,000 children between 1981 and 1986 to 0.57/100,000 between 1986 and 1990 and further to 0.36/100,000 between 1990 and 1994 ($p < 0.01$) [8, 9].

Secondary Prevention of HCC by Interferon Therapy

There was one randomized controlled trial (RCT) [10], which involved 101 Taiwanese men with chronic hepatitis B, 67 of whom received interferon (IFN) and 34 of whom received placebo. During 1.1–11.5 years after completion of therapy, the incidence of HCC in untreated patients was higher than that in IFN-treated patients (12 vs. 1.5%; $p = 0.043$). The cumulative incidence of HCC was also higher in untreated patients than in treated patients ($p = 0.013$).

A meta-analysis of randomized studies comparing IFN-treated patients versus untreated patients with HBV-

related cirrhosis showed that IFN seemingly decreased the rate of HCC [11].

Secondary Prevention of HCC by the Nucleoside Analog

To date, only one RCT suggests that lamivudine (LAM) treatment of chronic hepatitis B and advanced liver disease does reduce the incidence of HCC but with marginal significance (hazard ratio 0.49; 95% CI 0.25–0.99; $p = 0.047$) [12]. A multicenter retrospective study of 2,795 patients (657 treated with LAM and 2,138 not treated with LAM) was reported from Japan [13]. The cumulative HCC incidence was significantly lower in the LAM group ($p < 0.001$). These findings suggest that LAM effectively reduces the incidence of HCC in patients with chronic hepatitis B.

Prevention of HCV-Related HCC

Primary Prevention by Prevention of Viral Transmission

It is well known that HCV infection has become prevalent recently under artificial circumstances: mother-neonate transmission and sexual transmission of the virus are possible but not common. In many countries, new acquisition of HCV infection is decreasing due to growing concern about blood-transmitted infections, especially HIV, and this trend should be further encouraged considering the absence of effective vaccination against either HCV or HIV.

Secondary Prevention by Treatment of Chronic Hepatitis C

The effect of IFN therapy on HCC incidence in noncirrhotic patients has been evaluated in nonrandomized studies. All studies agree that the risk is reduced in patients who show sustained virologic response or persistent normalization of serum ALT levels [14–17]. Although documentation is rather scarce, the combination with ribavirin will produce a stronger effect on HCC prevention among overall treated patients [18].

Surveillance for Early Detection of HCC

Definition of the Population at High Risk for HCC

Liver cirrhosis induced by causes other than HBV and HCV is a risk for liver carcinogenesis [19]. Since carcinogenesis occurs in some cases of liver cirrhosis associated with nonalcoholic steatohepatitis, alcoholic liver disease, primary biliary cirrhosis, and autoimmune hepatitis, the course of the disease should be followed paying close attention to carcinogenesis, particularly in viral liver cirrhosis. Alcohol increases the risk of chronic hepatitis B- and C-associated liver carcinogenesis.

Based on the above mentioned information, patients with chronic hepatitis B and C and nonviral liver cirrhosis are defined as high-risk populations for HCC in both the Evidence-Based Practice Guidelines [20] proposed by the Japan Society of Hepatology (JSH) and the Consensus-Based Clinical Practice Manual [21] in Japan and the Practice Guideline published by the American Association of Study of the Liver (AASLD) [22]. Patients with liver cirrhosis types B and C are defined as a super high-risk population [20, 21].

Surveillance Protocol for Early Detection of HCC

No clear evidence is available to determine the optimal interval for periodic screening, but HCCs detected in periodic screening by AFP, a protein induced by vitamin K absence or antagonist-II (PIVKA-II), AFP lectin fraction (AFP-L3) measurement, and ultrasonography are solitary and small in many cases compared to those detected in symptomatic patients. Thus, the Japanese Evidence-Based Clinical Practice Guidelines [20] and the Consensus-Based Clinical Practice Manual [21] propose ultrasonography and tumor marker measurements every 3–4 months in the super high-risk population and every 6 months in high-risk populations.

Results of Early Detection of HCC in Japan

In Japan, approximately 65% of HCCs are detected in an early stage, for which curative treatment intervention is possible according to the nationwide survey in 198,000 patients [23]. This can be attributed to the establishment of a nationwide surveillance system across Japan.

Tumor Marker: Highly Sensitive AFP-L3

Five reported studies have analyzed the diagnostic significance of highly sensitive AFP-L3 (hs-AFP-L3) at low total AFP levels [24–29]. The sensitivity and specificity of hs-AFP-L3 at different cutoff levels in these five studies are summarized in table 1. The sensitivity of hs-AFP-L3 for HCC was approximately 25–50% in patients with total AFP levels below 20 ng/ml when the cutoff was fixed between 5 and 7%. The sensitivities of AFP-L3 measured by conventional methods in the serum samples of hs-AFP-L3 from two studies were 3.6 and 5.2% (cutoff of AFP-L3: 7%) [24, 26]. Thus, the sensitivity for HCC markedly in-

creased with the use of a newly developed, highly sensitive measurement method.

An important advantage of AFP-L3 is its high specificity for HCC. Therefore, attempts to increase the sensitivity of AFP-L3 for HCC should avoid a concomitant reduction in specificity. Based on the data from reported studies among patients with low total AFP levels, the specificity of hs-AFP-L3 for HCC was over 85% when the cutoff was fixed between 5 and 7%, except in one study. The original advantage of AFP-L3 produced by conventional methods, i.e. high specificity for HCC, appeared to be maintained in the case of hs-AFP-L3. The specificity was 54.0% when the cutoff was fixed at 5% in the study by Nouso et al. [27]. This was because the control group in their study included only patients with cirrhosis; patients with minute HCC that had not been detected by imaging examination might have been included in a control group.

Another reported advantage of AFP-L3 in the management of patients with HCC is its ability to indicate an advanced nature of HCC and to identify cases with poor prognoses. Previous studies have reported that HCC with high AFP-L3 levels demonstrate characteristics of advanced HCC by pathologic [30] and imaging findings [31]. Higher recurrence rates [32] and lower survival rates [33, 34] after treatment have also been reported in patients with increased AFP-L3 at diagnosis. We sought to determine whether these benefits of AFP-L3 persist with hs-AFP-L3.

hs-AFP-L3 increased the sensitivity of HCC at diagnosis, maintaining its high specificity and indicative value for poor prognoses. This biomarker can be used as a new tool in clinical practice for the management of patients with HCC. The utility of hs-AFP-L3 for the prediction of HCC development in high-risk patients under surveillance should be further investigated.

Imaging Diagnosis

Contrast-Enhanced Ultrasound with Sonazoid

Clinical Significance of Contrast-Enhanced Ultrasound

Sonazoid is a newly introduced second-generation ultrasound (US) contrast agent exclusively approved in Japan in 2007. The important characteristics of Sonazoid are that it facilitates real-time imaging in blood flow images at a low acoustic power and stable Kupffer phase imaging, tolerable for multiple scanning from 10 to 120 min after its injection [35]; this results in the invention of the breakthrough method, defect reperfusion imaging. Sonazoid-enhanced US with defect reperfusion imaging is an innovative technology that will greatly change the daily practices of HCC [36].

Development of Defect Reperfusion Imaging (Dual Phase Fusion Imaging)

We recently developed defect reperfusion imaging [37–39] using the properties of very stable Kupffer images and real-time fine blood flow images obtained with Sonazoid for typical HCC, which is depicted by CT but not by B mode scanning. This method is a breakthrough for accurate localization and treatment guidance [38]. Until recently, diagnosis in dynamic studies was usually based on the enhancement of patterns according to a time sequence or phase; however, by introducing the novel idea of dual phase imaging with the reinjection method, both Kupffer and arterial phase images are obtained at the same slice of ultrasound plane, which is really an innovative technique. Namely, this method is performed as follows: reinjection of Sonazoid is performed in areas that show defects in the postvascular phase [35, 37–39]. The introduction of this method has led to dramatic solutions for many limitations in the diagnosis and treatment of HCC, such as detection of small HCCs [40–42], evaluation of the treatment response [43], and needle insertion guidance [44]. The detection rate of small HCCs by Sonazoid-enhanced US is even more sensitive than that by MDCT [40].

MR Imaging Using a New Contrast Agent, Gadolinium-Diethylene-Triamine-Pentaacetic Acid, in the Diagnosis of Early HCC

A newly introduced contrast agent, gadolinium-diethylene-triamine-pentaacetic acid (Gd-EOB-DTPA), approved in 2008 in Japan, is a hepatocyte-specific MRI contrast medium with a different mechanism, utilizing both dynamic and Kupffer cell imaging. This new contrast medium is useful for the diagnosis of cases which would have been difficult using previous techniques such as dynamic MRI or SPIO-MRI [45].

In well-differentiated early HCC, some nodules may not be completely shown as a defective area on CTAP, but the Gd-EOB-DTPA uptake is apparently lower than that in the surrounding normal liver parenchyma, being imaged as a low-intensity nodule. Well-differentiated early HCC having Kupffer cells with enhanced SPIO uptake and receiving portal blood flow on CTAP has been difficult to characterize by SPIO-MRI or CTAP; however, it can be imaged clearly as a hypointense nodule using Gd-

EOB-DTPA MRI in many early HCC cases due to differences in biological characteristics, indicating that this contrast agent may lead to a breakthrough in the diagnosis of early HCC [46, 47], which has been clinically difficult and difficult even by pathological diagnosis when a biopsy sample is used. In other words, this technique may be the most sensitive tool in the detection of the phenotypic change of early hepatocarcinogenesis, much more sensitive than CTAP, CTHA, or SPIO-MRI [48].

Therefore, the diagnostic algorithm will be changed by introducing Gd-EOB-DTPA MRI in hypervascular and hypovascular liver nodules [49, 50].

Hepatic Arterial Infusion Chemotherapy for Advanced HCC

No effective anticancer drug for advanced liver cancer had been demonstrated before sorafenib was introduced [51]. 'Far advanced liver cancer' represents stage IVa liver cancer accompanied by vascular invasion and stage IVb liver cancer accompanied by distant metastasis, for which low-dose FP (5FU and *cis*-platinum) [52] therapy and hepatic arterial infusion of 5FU in combination with IFN treatment [53] have been established as effective treatment options in Japan. In fact, the response rate (CR+PR) reaches 45.9% according to the nationwide survey by the LCSGJ [23]. In addition, it is well established that the overall survival (OS) of the responders is definitely better than that of the nonresponder or best supportive care group. However, the intraarterial infusion procedure is complex because establishment of a reservoir port for arterial infusion is necessary; therefore, this technique is not performed in Western counties.

Hepatic intra-arterial infusion chemotherapy is not recommended in the AASLD guidelines [22]; therefore, although the response rate is high, the efficacy and especially the survival benefit of intra-arterial infusion chemotherapy and that using an intractable delivery port system should be confirmed by further randomized studies.

Treatment Algorithm

A Consensus-Based Treatment Algorithm for HCC Proposed by the JSH

For HCC treatment, practice patterns markedly differ between Europe/the USA, and Japan. For this reason, a unique Japanese algorithm (JSH Consensus 2007) was proposed in 2007 [21]. Consequently, a revised draft was presented at the 45th meeting of the Japanese Liver Society in 2009 (congress chair: Masatoshi Kudo), and an article was published in 2010 [54] and 2011 [55] (fig. 1). The consensus-based treatment algorithm recommended by this society consists of extrahepatic lesions, hepatic reserve, vascular invasion, number of tumors, and tumor diameter. Treatment is classified into curative treatment (resection, local ablation), transcatheter arterial embolization (TACE), arterial infusion chemotherapy, liver transplantation, and best supportive care. Basically, the contents are consistent with the evidence-based treatment algorithm established by the Makuuchi group. However, consensus-based algorithms are not always based on evidence but involve a routinely employed treatment for which a consensus has been reached in Japan. For example, concerning the item of early HCC, local ablation is performed for the lesions in which biopsy diagnosis, CTHA/CTAP, or gadolinium-DTPA ethoxybenzyl (EOB)-MRI suggests malignancy. In evidence-based guidelines, hypovascular tumors are categorized as 'nontypical for HCC', reflecting lesions without an arterial enhancement. Evidence-based guidelines recommend that these lesions be followed up. However, among hypovascular tumors, 'early liver cancer' definitively diagnosed based on CTAP, EOB-MRI, or biopsy findings is known to frequently progress to classical HCC. Based on this fact, treatment is performed in many cases in a routine clinical setting; noninvasive ablation therapy is performed rather than resection, which is more invasive. With respect to hypovascular lesions without malignant findings, intensive follow-up is recommended. For management, early hypovascular HCC should be separated from other types of hypervascular liver cancer.

Initially, resection or local ablation therapy should be performed to treat 3 or fewer tumors measuring 3 cm or less in diameter without extrahepatic lesions/vascular invasion in which the liver function is good. In this group, the prognosis of curative treatment may be favorable. In 3 or fewer lesions measuring more than 3 cm in diameter, resection or TACE is recommended. Curability may be improved by adding ablation therapy to previous transarterial treatment (TACE or lipiodol TACE). Secondly, TACE and arterial infusion chemotherapy are recommended to treat 4 or more lesions. However, arterial infusion chemotherapy is performed based on expert experience, but there is no solid evidence because there is no RCT. The combination of local ablation therapy and TACE/arterial infusion chemotherapy for 5 or 6 or fewer lesions is beneficial in some cases. Furthermore, resec-

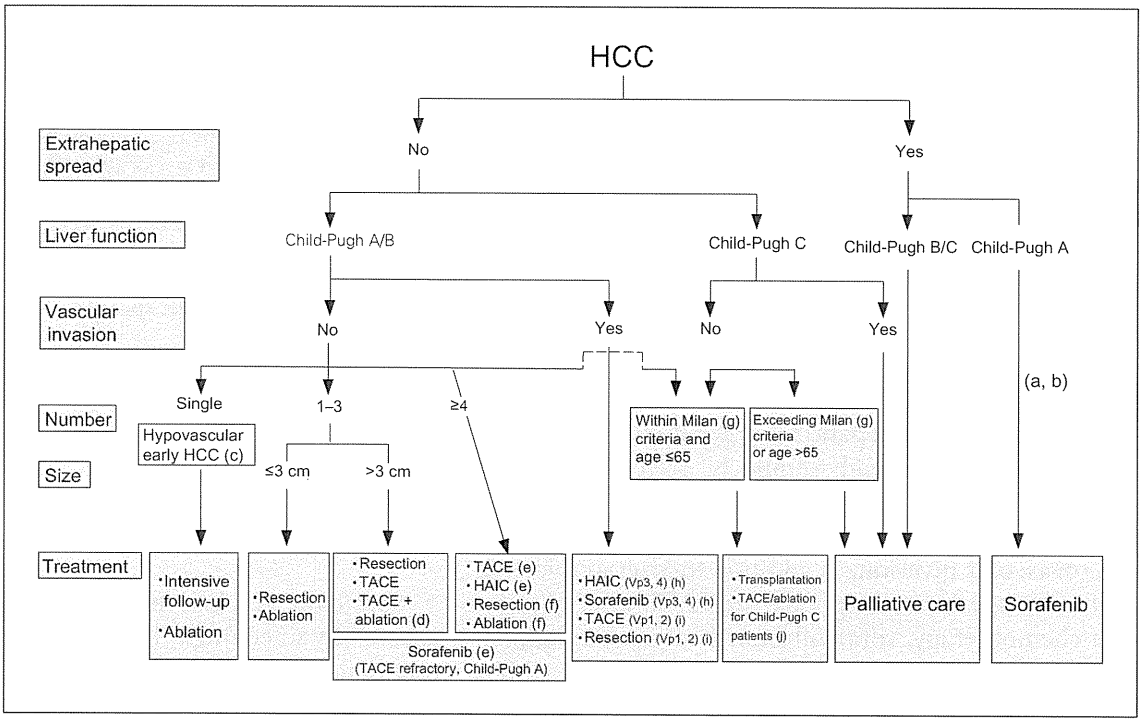

Fig. 1. Consensus-based treatment algorithm for HCC proposed by the JSH and revised in 2010. (a) = Treatment should be performed as if the extrahepatic spread is negative when extrahepatic spread is not regarded as a prognostic factor; (b) = sorafenib is the first choice of treatment in this setting as a standard of care; (c) = intensive follow-up observation is recommended for hypovascular nodules by the Japanese Evidence-Based Clinical Practice Guidelines. However, local ablation therapy is frequently performed in the following cases: (1) when the nodule is diagnosed pathologically as early HCC, (2) when the nodules show decreased uptake on Gd-EOB-MRI, or (3) when the nodules show decreased portal flow by CTAP, since these nodules are known to frequently progress to the typical advanced HCC. (d) = Even for HCC nodules exceeding 3 cm in diameter, combination therapy of TACE and ablation is frequently performed when resection is not indicated; (e) = TACE is the first choice of treatment in this setting. HAIC using an implanted port is also recommended for TACE refractory patients. The regimen for this treatment is usually low-dose FP (5FU+CDDP) or intra-arterial 5FU infusion combined with systemic IFN therapy. Sorafenib is also a treatment of choice for TACE refractory patients with Child-Pugh A liver function. (f) = Resection is sometimes performed even when the number of nodules is greater than 4. Furthermore, ablation is sometimes performed in combination with TACE. (g) = Milan criteria: tumor size ≤3 cm and tumor number ≤3, or solitary tumor ≤5 cm. Even when the liver function is good (Child-Pugh A/B), transplantation is sometimes considered for frequently recurring HCC patients. (h) = Sorafenib and HAIC are recommended for HCC patients with Vp3 (portal invasion at the 1st portal branch) or Vp4 (portal invasion at the main portal branch); (i) = resection and TACE are frequently performed when the portal invasion is minimum, e.g. Vp1 (portal invasion at the 3rd or more peripheral portal branch) or Vp2 (portal invasion at the 2nd portal branch); (j) = local ablation therapy or subsegmental TACE is performed even for Child-Pugh C patients when transplantation is not indicated when there is no hepatic encephalopathy, no uncontrollable ascites, and a low bilirubin level (<3.0 mg/dl). However, it is regarded as an experimental treatment since there is no evidence of its survival benefit in Child-Pugh C patients. A prospective study is necessary to clarify this issue. Even in Child-Pugh A/B patients, transplantation is sometimes performed for relatively younger patients with frequently or early recurring HCC after curative treatments.

tion may be considered for such lesions if possible. In young Child-Pugh A/B hepatic reserve patients with early recurrence, liver transplantation is sometimes a choice of treatment when they meet the Milan criteria. In the presence of vascular invasion, resection is performed for patients with a 3rd or 4th branch of portal venous invasion if possible. In such patients, TACE can be a choice of treatment. In patients with a main track or 1st branch of portal vein, arterial infusion chemotherapy, in addition to hepatic arterial infusion chemotherapy with implanted port, is a choice of treatment.

In Child-Pugh C hepatic reserve patients aged 65 years or younger with an unfavorable liver function in the absence of vascular invasion who meet the Milan criteria, liver transplantation is recommended [56]. Furthermore, as test therapy, local ablation or subsegmental TACE is

conducted in Child-Pugh C hepatic reserve patients without hepatic encephalopathy or refractory ascites showing a bilirubin level of 3 mg or less. However, there is no evidence regarding the survival benefits. In the future, a prospective clinical study should be conducted. In Child-Pugh C hepatic reserve patients with vascular invasion or extrahepatic lesions, the best supportive treatment is basically selected. In this case, palliative radiotherapy to resolve pain is included. However, when extrahepatic lesions are not a prognostic factor, treatment in accordance with the standard treatment algorithm may improve the prognosis.

In Child-Pugh A hepatic reserve patients with extrahepatic lesions, sorafenib should be selected as a first choice of treatment [57]. This agent is recommended for patients with vascular invasion, especially patients with macrovascular invasion, in addition to arterial injection chemotherapy. In nonresponders to TACE/arterial injection chemotherapy, sorafenib may become a treatment option when the hepatic reserve is evaluated as Child-Pugh A.

The consensus-based treatment algorithm is not always based on scientific evidence. However, it is significant because a consensus has been reached among specialists belonging to the JSH, as demonstrated by the BCLC, and therefore an own treatment algorithm is introduced. In the future, evidence-lacking parts must be revised through a prospective study. The treatment algorithm for liver cancer reflects a primary concept for treatment strategies. Basically, it is important to perform individualized treatment in individual patients, considering various conditions [58].

Definition of TACE Failure

In Japan, repeated TACE is commonly performed for multiple nodules without major vascular invasion or extrahepatic spread in Child-Pugh A or B patients. Even though recurrence is very rapid, TACE has been repeatedly performed (sometimes over 10 times). The reason for this is that there was no next treatment modality after TACE failure/refractory patients before sorafenib was introduced. Since hepatic arterial infusion chemotherapy is not effective for TACE failure patients, sorafenib is regarded as a first choice of treatment for TACE failure patients. Up to now there had been no clear definition of TACE failure. The JSH expert panel agrees that the definition of TACE is mandatory to change the treatment strategy to sorafenib if TACE failure is confirmed [55].

In this regard, the definition of TACE failure has been proposed for the first time ever as shown in table 2.

Table 2. Definition of TACE failure

Intrahepatic lesion
– More than 2 consecutive incomplete depositions (<50%) of lipiodol detected by response evaluation CT within the treated tumors at 4 weeks after adequately performed TACE
– More than 2 consecutive appearances of new lesions (recurrence) detected in the liver by response evaluation CT at 4 weeks after adequately performed TACE
Appearance of vascular invasion
Appearance of extrahepatic spread
Tumor marker
Continuous elevation of tumor markers despite prior TACE

Molecular Targeted Therapy

Sorafenib, is a low-molecular-weight compound discovered by screening inhibitors of Raf kinase, an important molecule in the MAP kinase cascade located downstream of the growth factor receptor. Sorafenib exhibits strong inhibitory activity for not only the wild-type c-Raf and V600E mutant b-Raf but also the receptor tyrosine kinases involved in angiogenesis and cell growth, such as vascular endothelial growth factor receptor (VEGFR)-2, VEGFR-3, platelet-derived growth factor receptor (PDGFR), Fms-related tyrosine kinase-3 (Flt-3), and c-Kit.

The positive results of a phase III study for HCC (SHARP trial) [59] had a strong impact on the treatment strategy of HCC. This study was performed as a randomized double-blind placebo-controlled multicenter study initiated in March 2005. The subjects were advanced HCC patients at ECOG PS 0–2 with Child-Pugh A liver function without previous systemic chemotherapy. Regarding the study design, two groups, sorafenib (400 mg b.i.d.) and placebo treatment, were established, and the primary end point was OS. The secondary end point was time to progression.

Ongoing Clinical Trials with Molecular Targeted Agents

As stated earlier, the STORM trial using sorafenib as an adjuvant setting after curative treatment such as resection or ablation is ongoing as a global trial. In addition, the SPACE trial and TACTICS trial using sorafenib in combination with TACE are ongoing in Western counties and Japan, respectively. The SILIUS trial using sorafenib in combination with hepatic arterial infusion chemotherapy (HAIC) is under investigation in Japan. Further-