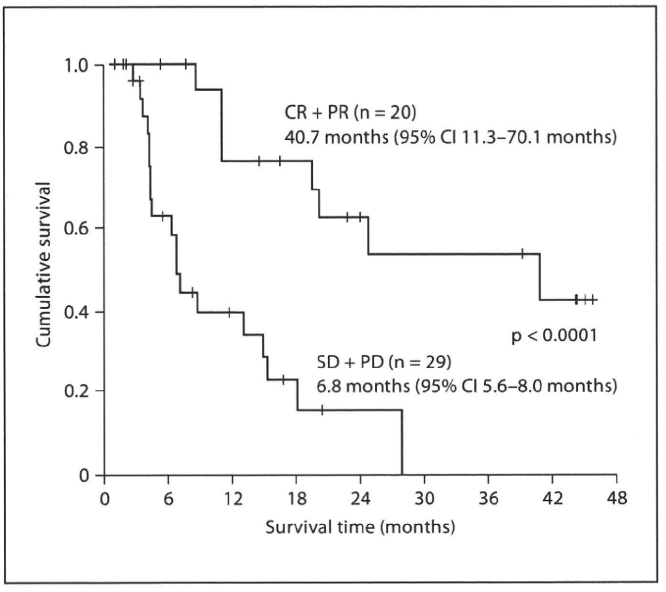

Fig. 3. The overall survival of patients with CR and PR was significantly longer than that of patients with SD and PD. The median overall survival was 40.7 months (95% CI 11.3–70.1 months) in the CR + PR group versus 6.8 months (95% CI 5.6–8.0 months) in the SD + PD group ($p < 0.0001$).

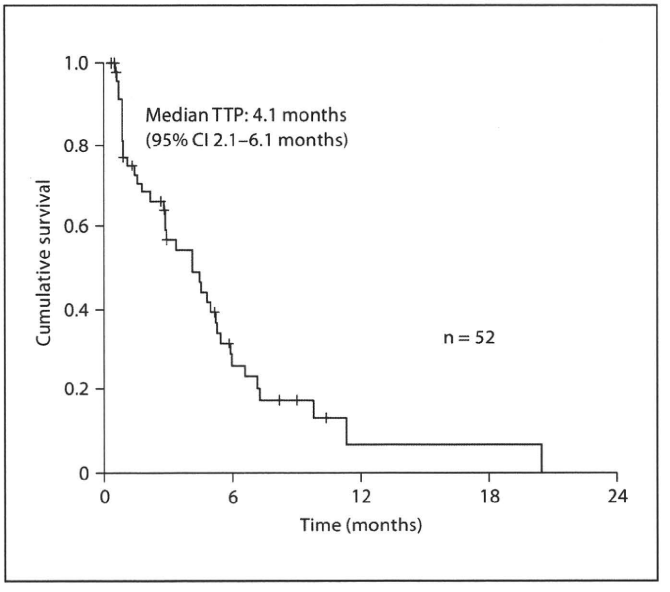

Fig. 4. Kaplan-Meier analysis of time to progression in 52 patients treated by HAIC using low-dose FP. The median time to progression was 4.1 months (95% CI 2.1–6.1).

Table 2. Adverse events

	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Leukocytes	12 (23.1)	16 (30.8)	10 (19.2)	0
Hemoglobin	30 (57.7)	10 (19.2)	5 (9.6)	0
Platelets	10 (19.2)	16 (30.8)	22 (42.3)	2 (3.8)
Neutrophil	5 (9.6)	14 (26.9)	12 (23.1)	0
Bilirubin	15 (28.8)	19 (36.5)	7 (13.5)	0
Anorexia	8 (15.4)	0	0	0
Fatigue	10 (19.2)	0	0	0
Fever	7 (13.5)	0	0	0
Mucositis	5 (9.6)	0	0	0
Diarrhea	4 (7.7)	0	0	0

Classified according to the Common Terminology Criteria for Adverse Events v3.0 (CTCAE).

Discussion

According to the Consensus-Based Treatment Algorithm for HCC of Japan Society of Hepatology [15], TACE is recommended if there are two or three tumors and their diameters exceed 3 cm, or if there are more than four tumors. However, once HCC has progressed into the portal vein, particularly the main trunk, TACE is contraindicated. Treatment with anticancer agents is necessary if the standard therapy is not indicated.

Chemotherapy as a treatment option for HCC has limitations, as follows: (1) HCC is a malignancy that is commonly less sensitive to anticancer agents, and (2) because of the pancytopenia and poor hepatic reserve caused by the underlying liver cirrhosis, it is not possible to administer adequate doses of anticancer agents to cause tumor shrinkage.

HAIC, a regional chemotherapy, offers a feasible approach to elicit a greater antitumor effect than systemic chemotherapy and can reduce toxicity against other systemic organs [16]. In addition, the HCC tends to remain in the liver, even if it advances. Accordingly, HAIC is the most suitable treatment option for locally advanced HCC.

On the other hand, there are several problems associated with HAIC, as follows: (1) skill is required to appropriately insert the catheter; (2) catheter placement is very invasive for patients; (3) infection may occur via the catheter system, and (4) the catheter system or hepatic artery may become obstructed [17]. In this study, 1 patient experienced obstruction of the hepatic artery. If injection into the port system is difficult or if the patient has any

complaint about the gastrointestinal tract, obstruction of the catheter system or hepatic artery should be considered and examined.

The pharmacokinetic rationale of HAIC using low-dose FP can be divided into two concepts. The first is the role of cisplatin as a biochemical modulator, and the second is the dose and duration of 5-FU administration.

Low-dose FP consists of a combination of low-dose cisplatin plus 5-FU, because of their synergistic effects [18, 19]. This combination is frequently used in the treatment of gastrointestinal tract malignancies. Cisplatin has a wide spectrum of antitumor effects in various malignancies. In combination with 5-FU, cisplatin plays a role as a modulator rather than an effector, and enhances the antitumor effect of 5-FU by increasing the intracellular concentration of reduced folate [20].

5-FU is also widely used to treat various malignancies. The advantage of continuous arterial infusion of 5-FU is that 5-FU acts time-dependently on tumor cells. It was reported that administration of lower doses of 5-FU for longer times was more effective in producing direct cytotoxic effects in human tumor cells than when administered at higher doses for shorter times [21]. Many investigators have reported the efficacy of this combination therapy for advanced HCC [22–25]. Okuda et al. [26] reported that the CR rate and effective response rate of HAIC using cisplatin and 5-FU were 29.0 and 71.0%, respectively. Meanwhile, Ando et al. [27] reported that the response rate of HAIC using low-dose cisplatin and 5-FU was 48.0%.

In this study, the objective response rate for low-dose FP was 38.5% and successful disease control was achieved in 65.4% of patients. This result is relatively high considering that these patients were contraindicated to standard therapies such as hepatic resection, RFA or TACE. In addition, the prognosis of the patients who achieved CR or PR was markedly improved.

Most patients with HCC have poor hepatic reserve and pancytopenia caused by underlying viral-related cirrhosis. In this study, grade 3–4 hematological toxicities were relatively common, but no subjective symptom was observed and these toxicities were improved by discontinuing the treatment. Non-hematological toxicities such as anorexia, fatigue and fever were observed but were not severe. Thus, it seems that HAIC will not deteriorate patients' quality of life.

However, HAIC has several limitations, as follows: (1) HAIC is not effective for patients with extrahepatic spread and (2) HAIC cannot be performed if the hepatic artery is obstructed. In such cases, systemic chemotherapy is required. Sorafenib, a multikinase inhibitor, was recently introduced for unresectable HCC.

Sorafenib is a low-molecular-weight compound discovered by screening inhibitors of Raf kinase. It exhibits strong inhibitory activity for tumor progression and angiogenesis [28, 29]. Positive results of a phase III study for HCC (SHARP trial) [30] has had a marked impact on the treatment strategy for HCC. Therefore, sorafenib will likely be used in various stages of HCC, and various clinical trials such as in an adjuvant or combination setting are ongoing.

It is still unclear whether HAIC using low-dose FP or systemic chemotherapy using sorafenib should be used in patients with vascular invasion, such as in the presence of a portal vein tumor thrombus, without extrahepatic spread. Our results indicate that the overall survival of patients with CR and PR was significantly longer than that of patients with SD and PD. The SHARP trial [30] revealed that sorafenib prolonged the overall survival and time to progression, but the response rate of sorafenib was extremely low (CR and PR were 0 and 2%, respectively) compared with that of HAIC using low-dose FP (CR and PR were 7.7 and 30.8%, respectively). Accordingly, we suggest that HAIC using low-dose FP might be more efficacious than systemic chemotherapy using sorafenib in this clinical setting.

HAIC using low-dose FP is an effective treatment option for locally advanced HCC and offers advantages over sorafenib, such as tumor shrinkage. However, low-dose FP may not be well tolerated hematologically because of potent pancytopenia and poor hepatic reserve. Therefore, this regimen should be performed carefully with regular monitoring of hematological function. Sorafenib in combination with HAIC using low-dose FP might provide greater clinical efficacy for advanced HCC and we have started a phase I/II study to investigate this approach.

Disclosure Statement

The authors declare that they have no financial conflict of interest.

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Positioning of a Molecular-Targeted Agent, Sorafenib, in the Treatment Algorithm for Hepatocellular Carcinoma and Implication of Many Complete Remission Cases in Japan

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Key Words

Hepatocellular carcinoma · Liver cancer treatment algorithm · Molecular-targeted therapy · Sorafenib · Complete remission · Tyrosine kinase inhibitor

Abstract

Sorafenib, a molecular-targeted agent that inhibits tumor cell proliferation and angiogenesis by inhibiting RAF serine-threonine kinase and VEGF, PDGF, Flt-3, c-Kit receptor tyrosine kinase, was approved in Europe and North America in 2007 and in Japan on May 20, 2009. In the 10 months since its approval, sorafenib has been prescribed for more than 3,700 patients with advanced hepatocellular carcinoma (HCC), and its efficacy has been confirmed in many cases. According to the consensus statements of the Japan Society of Hepatology in 2010, sorafenib is recommended for advanced HCC with extrahepatic spread or major vascular invasion such as invasion of the 1st branch of the portal vein or the main portal branch of the portal vein in patients with Child-Pugh A liver function. In addition to that, transcatheter arterial chemoembolization (TACE) or hepatic arterial infusion chemotherapy (HAIC) refractory HCC patients with Child-Pugh A liver function are also candidates of sorafenib monotherapy as a second-line treatment option. To date, 15 cases with complete remission (CR) to sorafenib in metastatic advanced HCC patients have been reported in Japan, an event that is rarely reported in other countries. Of the 90 cases treated by ourselves, 2 achieved CR. Factors indicating systemic cancer spread, including multiple liver lesions, lymph node metastases, adrenal metastases, lung metastases and vascular invasion, were completely absent in both cases of CR by 2 and 1 year, respectively. Similarly, three tumor markers (AFP, PIVKA-II, and AFP-L3) completely returned to normal values. Although cases of CR are rare, it seems that there might be racial differences in terms of gene mutations. Clinical trials for other molecular-targeted agents, including sunitinib, brivanib, or linifanib, are ongoing and their outcomes are eagerly awaited. According to a subanalysis of the SHARP study, it is expected that sorafenib in combination with resection, ablation, TACE or HAIC will markedly prolong the overall survival in early-, intermediate- and advanced-stage HCCs.

Introduction

Sorafenib is a multikinase inhibitor that targets tumor growth (RAF-MEK-ERK) and angiogenesis (VEGFR, PDGER) signal transduction pathways. Two global phase III trials (SHARP [1] and Asia-Pacific Study [2]) showed

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Table 1. Comparison between the Asia-Pacific and SHARP studies

End point	Asia-Pacific		SHARP	
	hazard ratio (95% CI)	p value	hazard ratio (95% CI)	p value
OS	0.68 (0.50–0.93)	0.014	0.69 (0.55–0.87)	<0.001
TTSP	0.90 (0.67–1.22)	0.498	1.08 (0.88–1.31)	0.768
TTP	0.57 (0.42–0.79)	<0.001	0.58 (0.45–0.74)	<0.001
PFS	0.62 (0.46–0.82)	<0.001	0.65 (0.52–0.79)	<0.001

OS = Overall survival; TTSP = time to symptomatic progression; TTP = time to progression; PFS = progression-free survival.

that sorafenib prolonged the survival of patients with advanced hepatocellular carcinoma (HCC). The results of these studies were rapidly disseminated worldwide and were enthusiastically accepted by physicians specializing in liver cancer treatment. Based on the positive results of the SHARP trial [1], the EU and USA approved sorafenib for advanced HCC in October and November 2007, respectively.

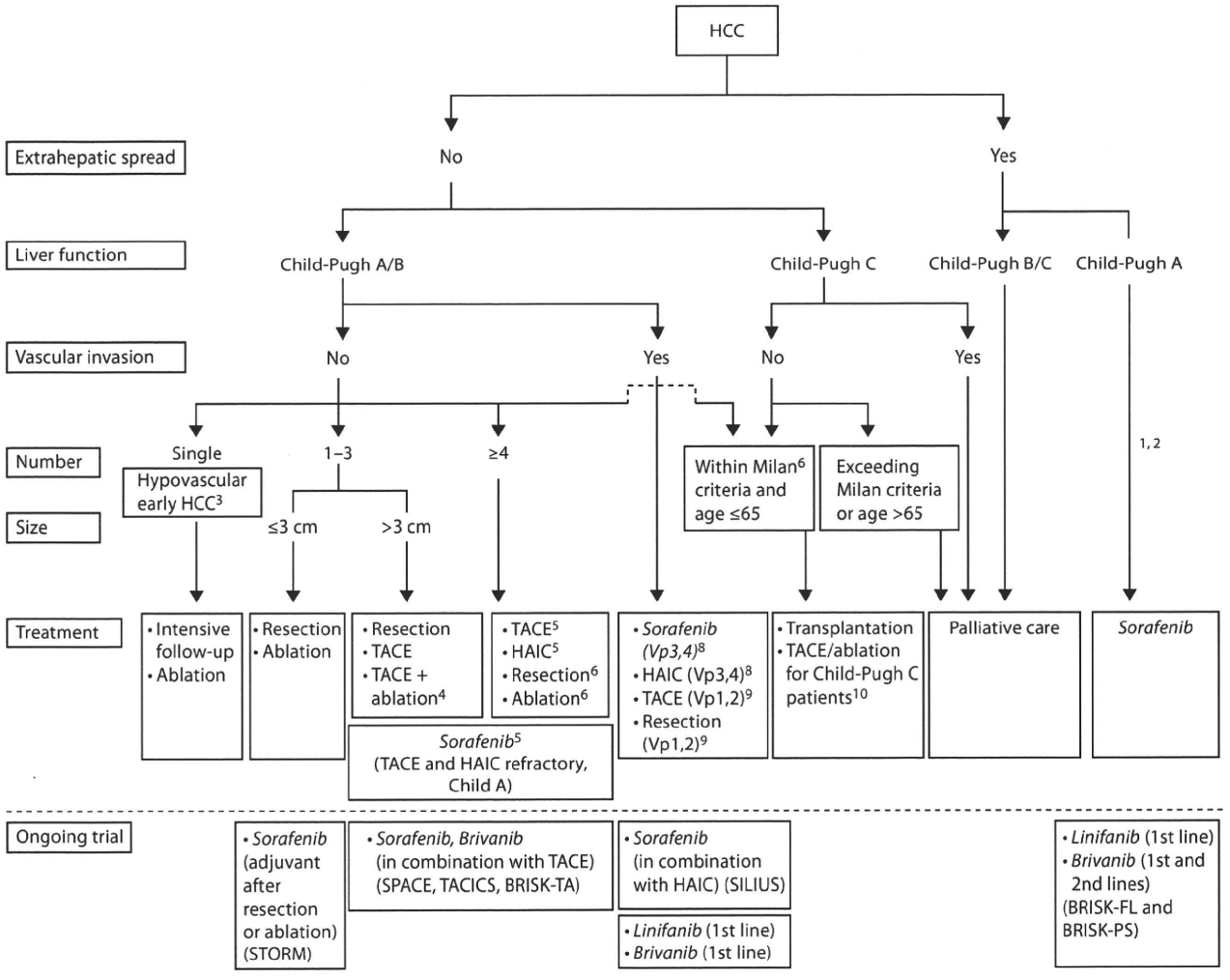
The following four factors may explain why the results of this study were well accepted worldwide, particularly in Japan. First, the study quashed the strong assumption or belief held by physicians specialized in liver cancer that systemic chemotherapy is not effective for liver cancer, unlike other cancers. Although no effective systemic chemotherapeutic drug was available before the introduction of sorafenib, very effective locoregional therapy was available for unresectable HCC, unlike other cancers, and survival for locoregional therapy was similar to that for resection. This is a major difference between liver cancer and other cancers. The commonly held view for liver cancer therapy is that 'treatment by physically destroying cancer cells' is effective and, thus, preferred over chemotherapy. Locoregional interventional treatments include transcatheter arterial chemoembolization (TACE), ethanol injection therapy, microwave coagulation therapy, and radiofrequency ablation (RFA), and physically destroying cancer cells.

In addition, HCC is often complicated by liver cirrhosis, and the accompanying pancytopenia rapidly results in excess toxicity, such as bone marrow suppression, of systemically administered cytotoxic anticancer drugs, limiting their doses and reducing their therapeutic effect. Thus, poor tolerability is a significant problem of systemic anticancer therapy and explains the poor efficacy of these drugs for HCC.

Table 2. Molecular-targeted agents for HCC under development

Agent	Anti-angiogenic targets					Antiproliferative targets				Antiepigenetic targets				Developmental status	Company
	VEGF	FGF	VEGFR	PDGFR	FGFR	EGFR	Raf	MEK	mTOR	RAR	RXR	HDAC	Heparanase		
Sorafenib[1] (Nexavar)			●	●			●							Approved	Bayer
Sunitinib[1] (Sutent)			●	●										Stopped	Pfizer
NIK-333 (Acyclic Retinoid)										●	●			Phase II/III complete	Kowa
Brivanib			●		●									Phase III ongoing	Bristol-Myers Squibb
TSU-68			●	●	●									Phase II complete	Taiho
TAC-101										●				Phase II stopped	Taiho
Erlotinib (Tarceva)						●								Phase II complete	Roche
Bevacizumab (Avastin)	●													Phase II ongoing	GenentechA
AZD2171 (Cediranib)			●											Phase II recruiting	AstraZeneca
Gefitinib (Iressa)						●								Phase II complete	AstraZeneca
Lapatinib						●								Phase II ongoing	GlaxoSmithKline
Thalidomide	●													Phase II ongoing	TTY BioPharm
ZD6474 (Zactima)			●				●							Phase II ongoing	AstraZeneca
AZD6244								●						Phase II ongoing	AstraZeneca
PI-88	●	●										●		Phase II complete	Progen
Cecuximab						●								Phase II complete	Merck
RAD001									●					Phase III initiated	Novartis
PXD101 (Belinostat)												●		Phase I/II ongoing	Curagen

[1] Sorafenib and sunitinib also have antiproliferative effects through multi-tyrosine kinase inhibition.
Sources: Trial Trove, ClinicalTrials. Gov (NCI), Evaluate Pharma, IMS Knowledge Link, Esplcom, IDdB3, BioPharm Insight, MedTrack.



1 Treatment should be performed as if extrahepatic spread were negative, when extrahepatic spread is not regarded as a prognostic factor.

2 Sorafenib is the first choice of treatment in this setting as a standard of care.

3 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.

4 Even for HCC nodules >3 cm in diameter, combination therapy of TACE and ablation is frequently performed when resection is not indicated.

5 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 (5-FU+CDDP) or intra-arterial 5-FU infusion combined with systemic interferon therapy. Sorafenib is also recommended for TACE refractory patients.

6 Resection is sometimes performed even when there are >4 nodules. Furthermore, ablation is sometimes performed in combination with TACE.

7 Milan criteria: tumor size ≤3 cm and tumor numbers ≤3; or a solitary tumor ≤5 cm. Even when liver function is good (Child-Pugh A/B), transplantation is sometimes considered for frequently recurring HCC patients.

8 Sorafenib and HAIC are recommended for HCC patients with Vp3 (portal invasion at the first portal branch) or Vp4 (portal invasion at the main portal branch).

9 Resection and TACE is frequently performed when portal invasion is minimal such as Vp1 (portal invasion at the third or more peripheral portal branch) or Vp2 (portal invasion at the second portal branch).

10 Local ablation therapy or subsegmental TACE is performed even for Child-Pugh C patients when transplantation is not indicated as 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.

Fig. 1. Consensus-based treatment algorithm for hepatocellular carcinoma proposed by the Japan Society of Hepatology in 2010. The positioning of sorafenib and the ongoing trials on sorafenib or other molecular-targeted agents are shown.

Table 3. Molecular-targeted agents for hepatocellular carcinoma: study results

Agent	Type	Target	Number of patients	RR %	PFS months	TTP months	OS months	References
Phase III								
Sorafenib	s.m.	C-Raf, B-Raf, PDGFR, VEGFR	602 (299*)	2.0	–	5.5	10.7	Llovet et al. [1], 2008
			271 (150*)	3.3	–	2.8	6.5	Cheng et al. [2], 2009
Phase II								
Sorafenib	s.m.	C-Raf, B-Raf, PDGFR, VEGFR	137	2.2	–	5.5	9.2	Abou-Alfa [18], 2006
Sunitinib	s.m.	VEGFR, PDGFR, SCFR, FLT3	37	2.7	3.7	5.3	8.0	Faivre et al. [15], 2007
			34	2.9	3.9	4.1	9.8	Zhu et al. [16], 2009
Brivanib	s.m.	VEGFR, FGFR	55	n.r.	–	2.8	10	Raoul [19], 2009
Linifanib	s.m.	VEGFR, PDGFR	44	6.8	–	5.7	9.3	Toh [20], 2009
Bevacizumab	MoAb	VEGF	46	13	6.9	–	12.4	Siegel [21], 2008
Erlotinib	s.m.	EGFR	38	9	–	3.2	13	Philip [22], 2005
			40	0	–	–	10.7	Thomas [23], 2007
Gefitinib	s.m.	EGFR	31	3.2	2.8	–	6.5	O'Dwyer [24], 2006
Lapatinib	s.m.	EGFR	40	5	2.3	–	6.2	Ramanathan [25], 2009
			26	0	1.9	–	12.6	Bekaii-Saab [26], 2009
Cetuximab	MoAb	EGFR	30	0	1.4	–	9.6	Zhu [27], 2007

n.r. = Not reported; s.m. = small molecule; MoAb = monoclonal antibody.

Table 4. Subanalysis of the SHARP study

	Advanced HCC with vascular invasion or extrahepatic spread	Advanced HCC without vascular invasion or extrahepatic spread
Hazard ratio	0.77 (95% CI 0.60–0.99)	0.52 (95% CI 0.32–0.85)
Median overall survival (MST)		
Sorafenib, months	8.9 (n = 209; 95% CI 7.6–10.3)	14.5 (n = 90; 95% CI 14.0–N/E)
Placebo, months	6.7 (n = 212; 95% CI 5.2–8.0)	10.2 (n = 91; 95% CI 8.6–15.5)

N/E = Not evaluable. Sherman et al., ASCO 2008.

Second, although Japanese HCC specialists have been active, believing that their treatment historically leads the world in liver cancer therapy since most of the treatment options including TACE, ablation, hepatic arterial infusion chemotherapy (HAIC), and systematic hepatectomy (anatomical resection) were invented in Japan, there has been no effective treatment for advanced-stage HCC with extrahepatic spread for the reason described above. Therefore, the finding that sorafenib prolongs the survival of patients with advanced-stage HCC, particularly those with distant metastases, was unexpected and surprising.

Third, unlike the current developmental process for cytotoxic anticancer agents, sorafenib was the first drug to have been developed by identifying the target molecule through researching the molecular mechanisms involved in carcinogenesis and progression, resulting in drug development. Although it is well known that molecular-targeted agents for lung cancer (gefitinib, erlotinib), renal cancer (sorafenib, sunitinib), and colorectal cancer (bevacizumab, cetuximab) have been introduced into clinical practice, liver cancer specialists never expected that such a marked survival-prolonging effect could be achieved by a drug for HCC, which is a completely different situation from solid tumors in other organs as described above.

Fourth, the results of the SHARP and Asia-Pacific studies dispelled the common belief that the response rate is a

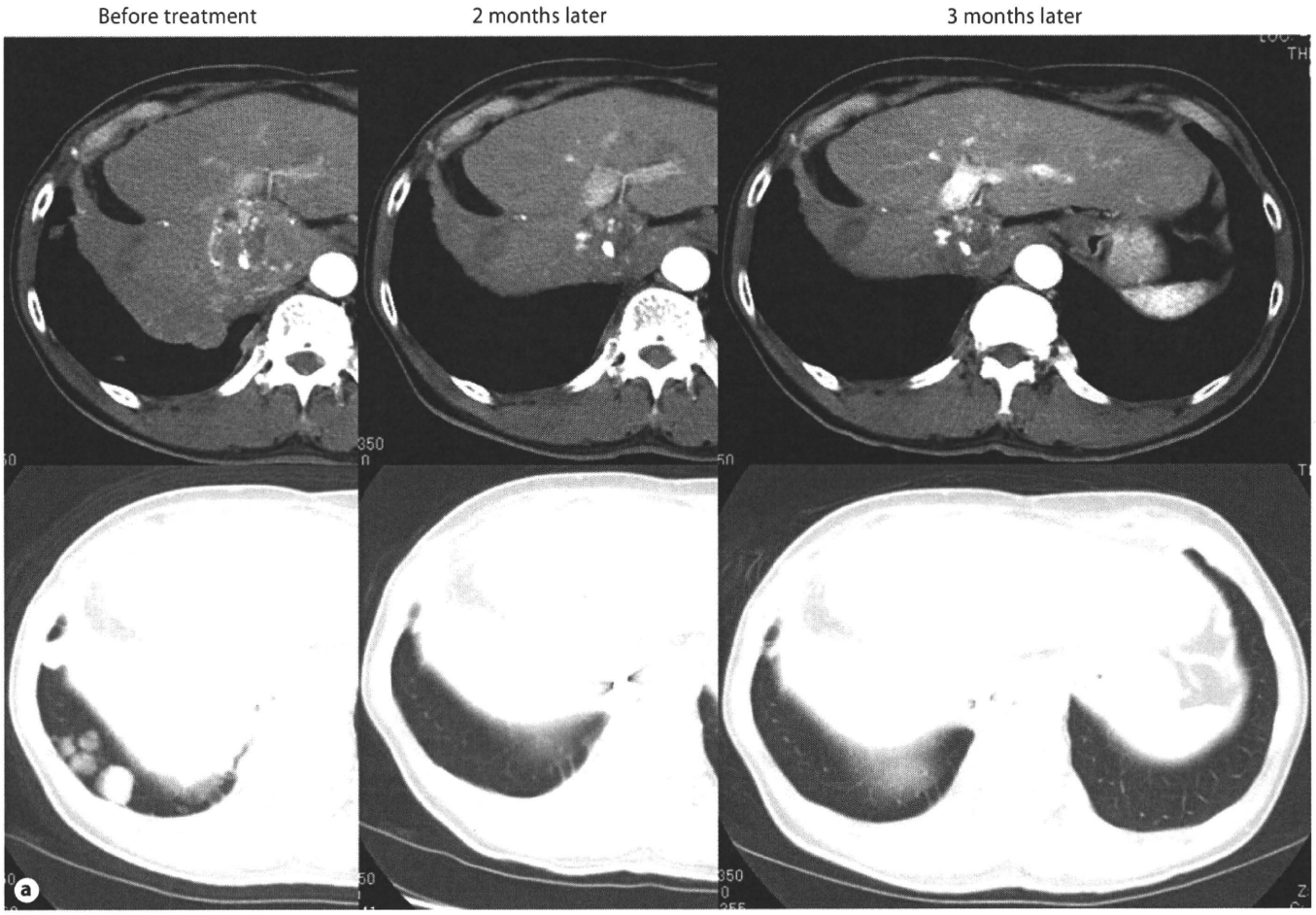


Fig. 2. Complete remission case 1. A 68-year-old male with chronic hepatitis B and stage IVB HCCs and Child-Pugh A liver function. **a** In 2004, the patient underwent surgery followed by nine sessions of TACE. In 2009, HCC invasions were found in the inferior vena cava and multiple metastases were found in the lung. Sorafenib monotherapy (800 mg) was then started. 2 months later, all tumors including a tumor in the inferior vena cava and lung disappeared completely.

surrogate of survival. Physicians treating liver cancer have endeavored to increase the local control rate, believing that the presence of a tumor response prolongs survival, while a poor response indicates treatment failure of TACE, RFA, or HAIC. However, the results of the SHARP study proposed a new concept: patients live longer on molecular-targeted therapy, even though the objective response rate is low, leading to a paradigm shift in liver cancer therapy.

In this review, we discuss the positioning of sorafenib in the treatment algorithm in Japan, complete remission (CR) cases treated with sorafenib, and the future perspectives including current ongoing clinical trials of molecular-targeted agents.

Mechanism of Action of Sorafenib and Results of Recent Studies

The mitogen-activated protein kinase (MAPK) cascade, located downstream of growth factor receptors, plays an important role in cell growth and survival. Raf protein is an important regulatory factor in this cascade, and sorafenib was discovered by screening for inhibitors of Raf protein activity [3, 4]. Sorafenib is a potent inhibitor not only for the RAF isoforms c-RAF (RAF1) and wild-type and mutant (V600E) b-RAF but also vascular endothelial growth factor receptor-2 (VEGFR-2), VEGFR-3, platelet-derived growth factor receptor

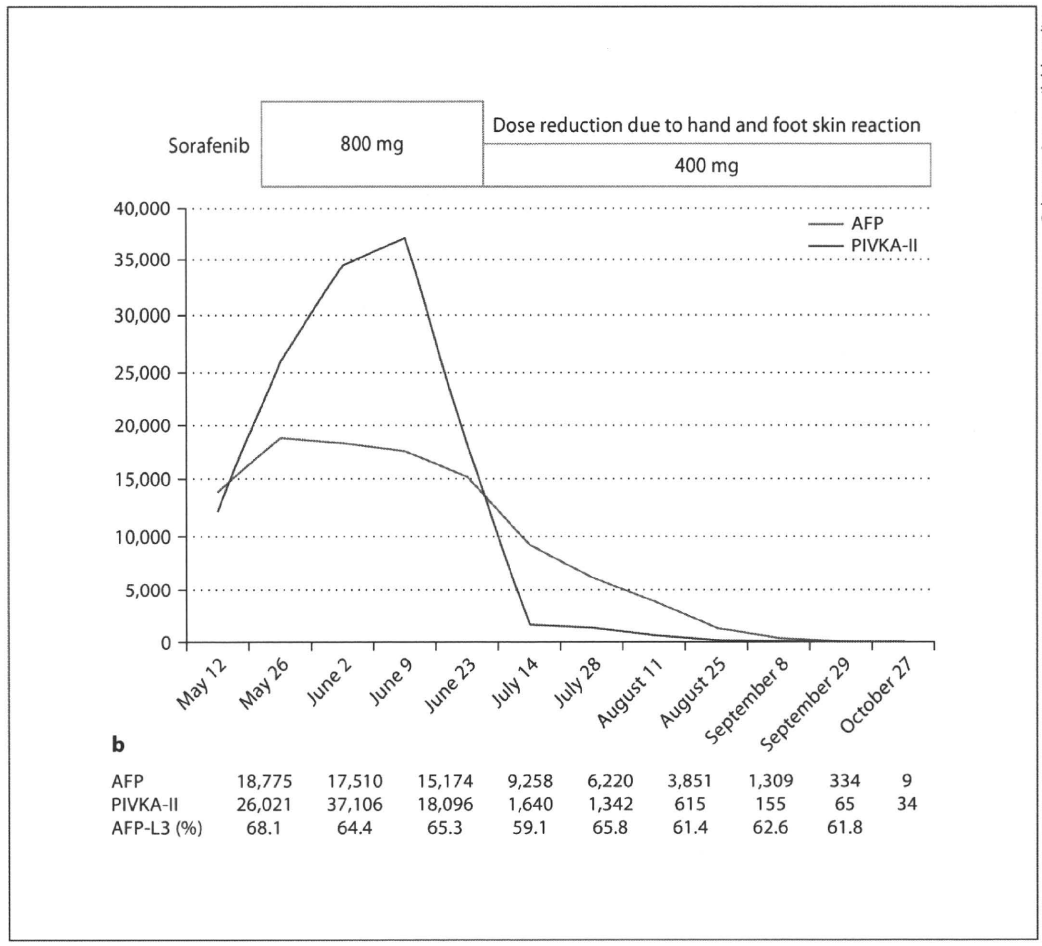


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Fig. 2. Complete remission case 1. A 68-year-old male with chronic hepatitis B and stage IVB HCCs and Child-Pugh A liver function. **b** Clinical course of the tumor markers. The AFP and PIVKA-II levels and the AFP-L3 fraction markedly decreased and normalized during sorafenib treatment. The patient is now under long-term treatment with sorafenib at 400 mg/day, and the HCC has not recurred for more than 1 year.

(PDGFR) and Fms-related tyrosine kinase-3 (Flt-3), which are involved in angiogenesis and are receptor tyrosine kinases involved in cell growth. Thus, sorafenib is a multikinase inhibitor that exhibits multiple effects: it acts directly on cancer cells to inhibit their growth, and affects the surrounding vascular endothelial cells to inhibit angiogenesis [5–10].

In the SHARP [1] and Asia-Pacific [2] studies, the median overall survival with sorafenib was 10.7 months (placebo group 7.9 months; $p < 0.01$) in the SHARP study and 6.5 months in the Asia-Pacific study (placebo group 4.2 months; $p < 0.01$), showing an apparent difference between the 2 studies. However, the hazard ratios for overall survival, time to progression, and progression-free survival were similar in both studies (table 1). Overall, sorafenib appeared to prolong patients' survival (table 1). The Asia-Pacific study tended to include more patients with advanced stage cancer compared with the SHARP study. In the SHARP study, approximately 30% of the patients did not exhibit distant metastases or vascular invasion, suggesting that patients in an intermediate stage, who are usually candidates for TACE, were included in the SHARP study. Taken together, the poorer conditions of the Asian patients in the Asia-Pacific study may at least partly explain the shorter overall survival in that study.

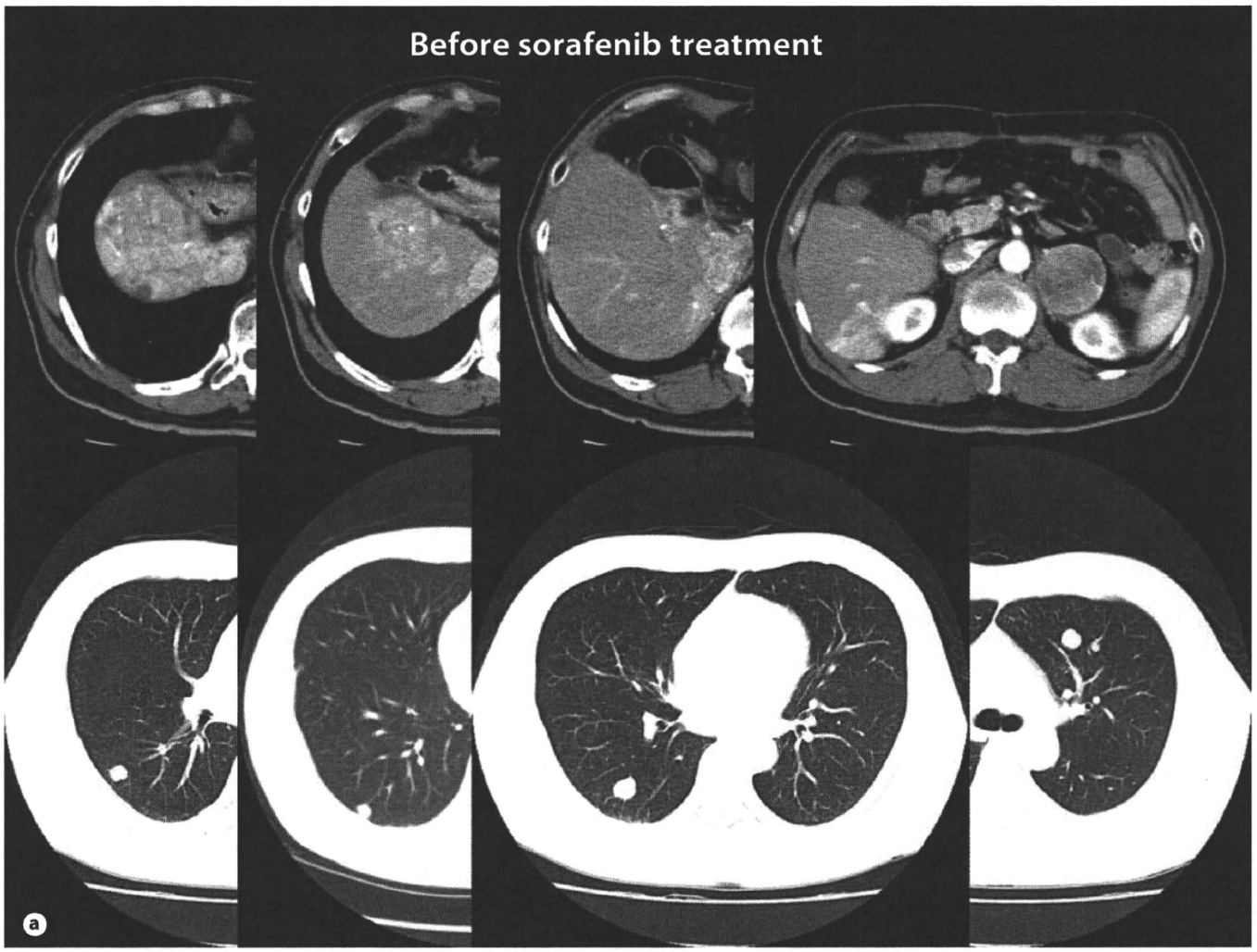

Fig. 3. Complete remission case 2. A 68-year-old male with chronic hepatitis B with stage IVB HCC and Child-Pugh A liver function. **a** The initial development of HCC was detected in February 2007, and TACE was performed. The HCC recurred in April 2007 and hepatectomy was performed, followed by intraarterial infusion chemotherapy with an implanted port, but the infusion was discontinued due to arterial obstruction. Multiple lung, lymph node, and left adrenal metastases were confirmed, and the patient was referred to our institute. At our hospital, S-1 + PEG-IFN combination therapy was performed, but the response was progressive disease (PD). Epirubicin and MMC were systemically administered, but the PD response remained. Oral administration of 800 mg sorafenib was initiated on January 5, 2008. Computed tomography (CT) before sorafenib administration shows intrahepatic multiple HCCs, portal tumor thrombus, and left adrenal, lymph node and multiple lug metastases can be seen.

Positioning of Sorafenib in the HCC Treatment Algorithm

According to the consensus statements of the Japan Society of Hepatology in 2010, sorafenib is recommended for advanced HCC with extrahepatic spread or major vascular invasion such as the 1st branch of the portal vein invasion or the main branch of the portal vein invasion in patients with Child-Pugh A liver function. In addition to that, TACE or HAIC refractory HCC patients with Child-Pugh A liver function are also candidates of sorafenib monotherapy as a second-line treatment option [11] (fig. 1).

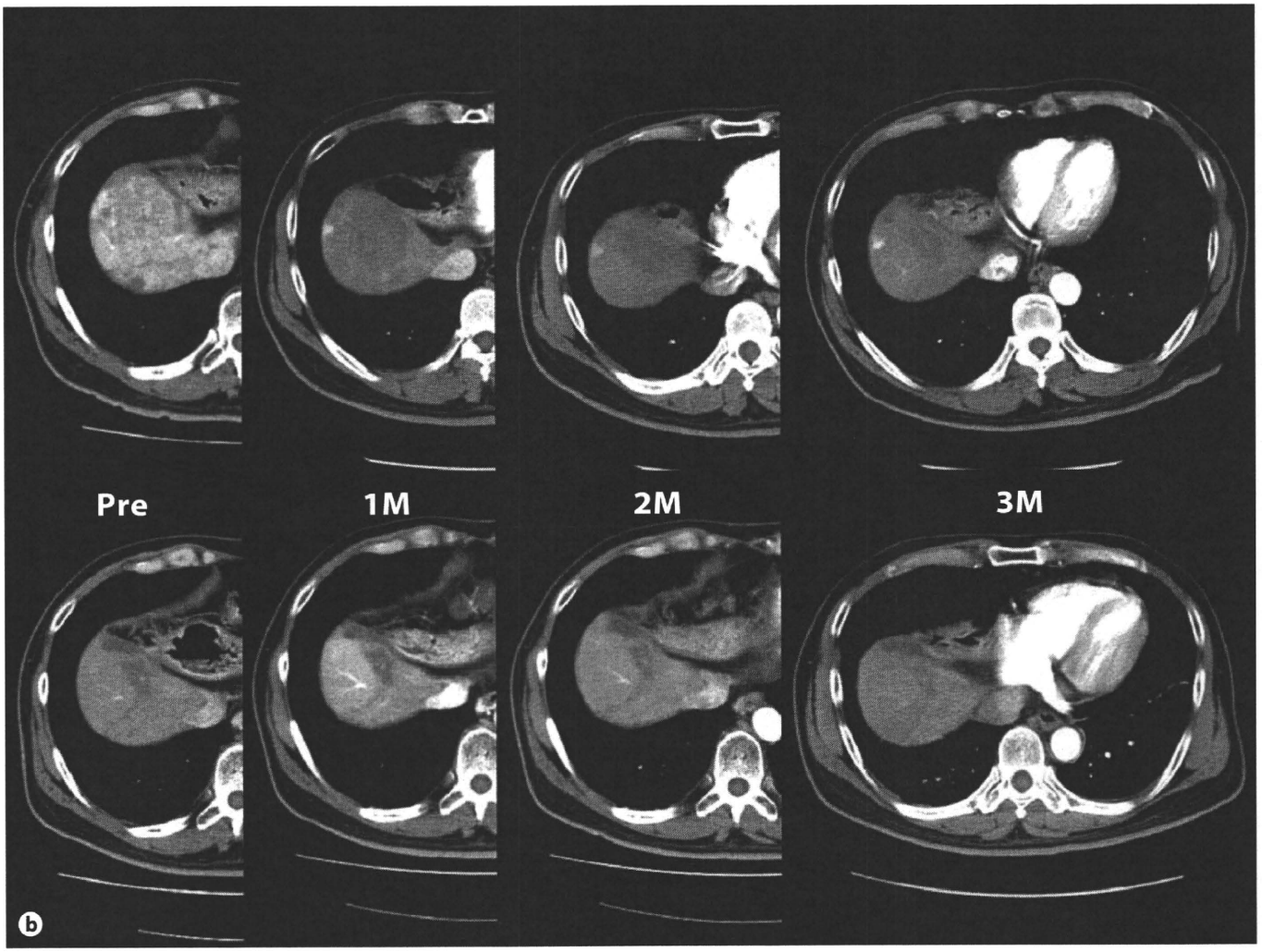

Fig. 3. Complete remission case 2. A 68-year-old male with chronic hepatitis B with stage IVB HCC and Child-Pugh A liver function. **b** One month later, all of the tumors in the lung, liver and the lymph node metastases completely disappeared except in left adrenal gland.

Clinical Experience of Complete Remission Cases with Sorafenib

Many patients with advanced-stage HCC accompanied by distant metastases that is considered untreatable at many hospitals visit our institution and are willing to have any potential treatment. Since the approval of sorafenib in Japan on May 20, 2009, it has been used to treat more than 3,700 patients with advanced HCC in Japan. Of these, 15 patients have been reported to achieve CR [12]. To date, we have treated 90 patients at our institution with sorafenib monotherapy, and 2 achieved CR (fig. 2, 3). By contrast, there have been very few reports of cases achieving CR in other countries [13, 14]. Based on these findings, there might be a racial difference concerning gene mutation that influences the response to sorafenib, differing between ethnic groups, similar to the EGFR mutation for gefitinib.

Clinical Trial Status of Molecular-Targeted Agents for HCC

The agents shown in tables 2 and 3 are currently under development. Drugs that have entered phase III clinical trials are briefly outlined here. Molecular-target-

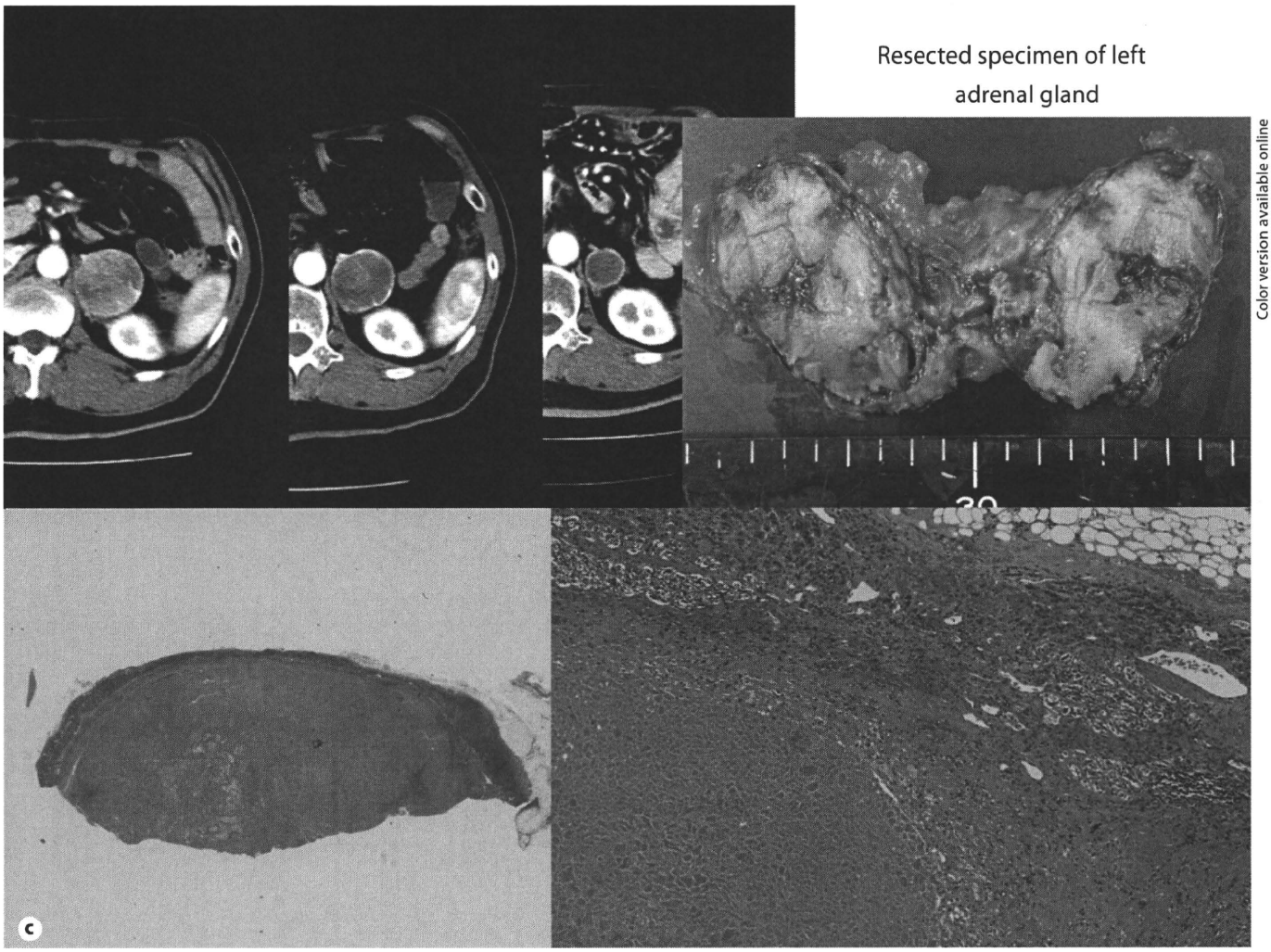

Fig. 3. Complete remission case 2. A 68-year-old male with chronic hepatitis B with stage IVB HCC and Child-Pugh A liver function. **c** Left adrenal metastasis became small during 6-month follow-up; however, there remains enhancing thin layer at the peripheral area. Therefore, the left adrenal gland was surgically resected. Pathological study of the resected specimen showed entire necrosis at the central area with normal adrenal gland at the periphery of the adrenal gland. Cancer-free status was therefore confirmed.

ing drugs for liver cancer and their target molecules are shown in figure 4 [15]. The results of clinical trials of molecular-targeted agents for HCC are summarized in table 3 [16–27].

Sunitinib (Sutent®; Pfizer)

Sunitinib is a low-molecular-weight oral tyrosine kinase inhibitor, which not only inhibits VEGFR and PDGFR but also Flt-3 and C-Kit. Compared with sorafenib, sunitinib slightly more frequently showed grade 3–4 toxicity in phase II studies [16, 17], including thrombocytopenia, neutropenia, and hemorrhage. Sunitinib also strongly inhibits angiogenesis, which is thought to be involved in its strong efficacy.

On a global basis, a head-to-head study of sunitinib versus sorafenib as a control in patients with advanced HCC has unfortunately been terminated in April 2010 because of its toxicity and insufficient efficacy based on the recommendation by an independent data monitoring committee.

Brivanib (Bristol-Myers)

Brivanib is a low-molecular-weight oral kinase inhibitor that selectively inhibits VEGFR and FGFR. In a phase

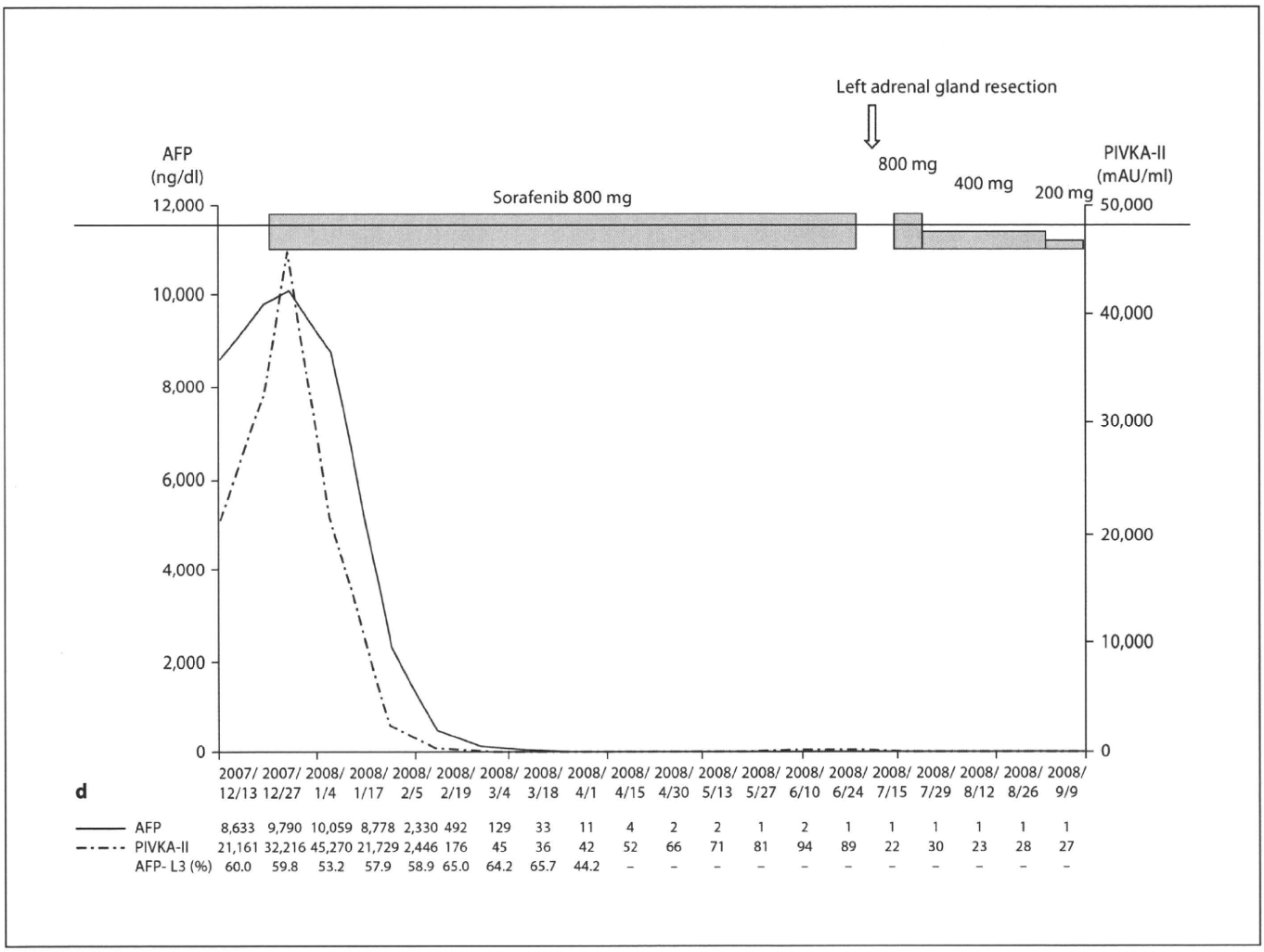

Fig. 3. Complete remission case 2. A 68-year-old male with chronic hepatitis B with stage IVB HCC and Child-Pugh A liver function. **d** For more than 1 year, there was no recurrence (sustained cancer-free status) and the patient is now under longterm treatment with sorafenib at 200 mg/day. Clinical course of the tumor markers: 5 months after sorafenib administration, the high AFP level (10,559 ng/ml) returned to normal (1 ng/ml). Similarly, the high PIVKA-II level (45,270 mAU/ml) returned to normal (27 mAU/ml) and the high AFPL3 fraction (60.0 %) returned to normal (<10%). The patient is now under long-term treatment with sorafenib at 200 mg/day.

II study of 36 Asian and 20 non-Asian patients with advanced HCC, the overall survival rate in the Asian patients was 10.0 months, showing a favorable outcome compared with that (6.2 months) achieved by sorafenib in the Asia-Pacific study. However, a simple comparison of the 2 studies is not appropriate because of differences in patient characteristics.

Three global trials of brivanib are now ongoing: one, a placebo-controlled study, is for adjuvant therapy after TACE (BRISK-TA trial); the second is a first-line clinical trial for brivanib versus sorafenib for advanced HCC (BRISK-FL trial); and the third is a second-line, placebo-controlled clinical trial in sorafenib-resistant HCC (BRISK-PS trial).

Retinoid (NIK-333; Kowa)

Retinoids represent a broad range of compounds that bind to and activate retinoic acid (RAR) and retinoid (RXR) receptors, two nuclear hormone receptors. Retinoid-333 is an acyclic retinoid that was developed in Japan. It activates transcription via RAR and RXR, and induces differentiation, and is expected to induce apoptosis

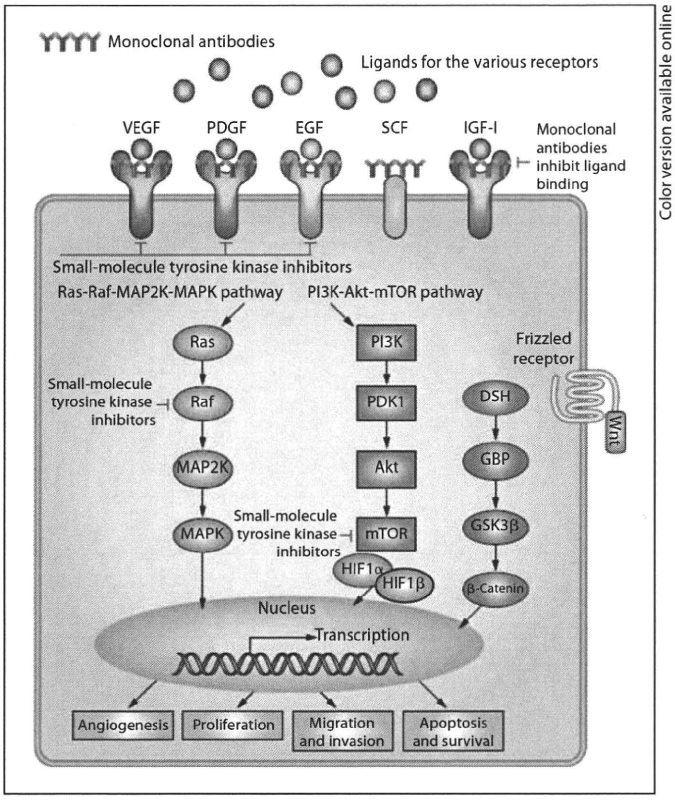

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Fig. 4. Signaling pathways and molecular-targeted agents. Monoclonal antibodies (VEGFR: bevacizumab, EGFR: cetuximab), tyrosine kinase inhibitors (VEGFR: sorafenib and sunitinib, EGFR: erotinib, lapatinib), serine/threonine kinase inhibitors (Raf: sorafenib, mTOR: rapamycin and everolimus, PIK: KL-755). Cited from Spangenberg et al. [15]. Reproduced with permission.

of precancerous HCC cells, and inhibit carcinogenesis by inducing differentiation [28, 29]. In Japan, a phase II/III study of adjuvant therapy with retinoid after resection or RFA was recently completed and the results were presented at the annual meeting of the American Society of Clinical Oncology (ASCO) in 2010. Although the study did not reach its primary endpoint, the results in recurrence-free survival were favorable to some extent.

Other Drugs

A phase II study of TSU-68 (Tiho Pharmaceuticals) in combination with TACE was recently completed and presented at ASCO in 2010. At present, the feasibility of a phase III study is being investigated. C-met inhibitor and mTOR inhibitor (RAD001) is also entering a phase III clinical study as a second-line therapy in patients with sorafenib-intolerant or resistant cancer (table 2).

Future Perspectives of Molecular-Targeted Therapy for HCC

The SHARP study showed that sorafenib inhibits the growth and progression of HCC and inhibits angiogenesis. What do these findings mean? Even cases of liver cancer indicated for curative treatment, such as resection, RFA or TACE, show the similar phenotype of advanced cancer, including hypervascularity, vascular invasiveness, and a high recurrence rate of intrahepatic metastasis. Although the therapeutic policy varies depending on the cancer stage, all of hypervascular HCCs are included in the same category; so-called 'advanced cancer' which has a strong potential to recur at a yearly rate of 15–20%. In other words, the treatment policy is dictated by the cancer stage; however, the existence of these characteristics indicates that the cancer should be treated as an advanced cancer. Accordingly, it may be possible to extrapolated the results of the SHARP study to most HCC cases classified into various stages. Of course, this should be evaluated in prospective clinical trials and, in fact, global trials are already underway, which are expected to show that sorafenib improves prognosis in the following settings: (1) adjuvant therapy after curative treatment (STORM trial); (2) TACE combination therapy (global SPACE trial and Japanese TACTICS trial), and (3) combination therapy with HAIC (Japanese SILIUS trial). Indeed, when considering a subanalysis of the SHARP study presented at ASCO in 2008 by Sherman et al. [30], the hazard ratio for overall survival in patients without extrahepatic spread or vascular invasion was 0.52, indicating that sorafenib improved survival twofold relative to the placebo group. Furthermore, the median survival time of these patients was approximately 15 months with sorafenib compared with 10 months in the placebo group (table 4). These results indicate that when sorafenib is used in combination with TACE or adjuvant therapy after resection or ablation, overall survival should be much prolonged as presented in figure 5.

It must be noted that sorafenib is associated with some unusual adverse events that are not normally encountered with other cytotoxic chemotherapeutic agents, and include skin reactions to the hands and feet, diarrhea and hypertension. In addition, liver dysfunction, hepatic encephalopathy, acute interstitial pneumonia, or bleeding are the big issues that need to be well managed as they are life-threatening events. Hepatologists mainly prescribe this drug in Japan as opposed to other countries where oncologists prescribe sorafenib as well. To adequately prescribe and manage molecular-targeted agents, hepa-

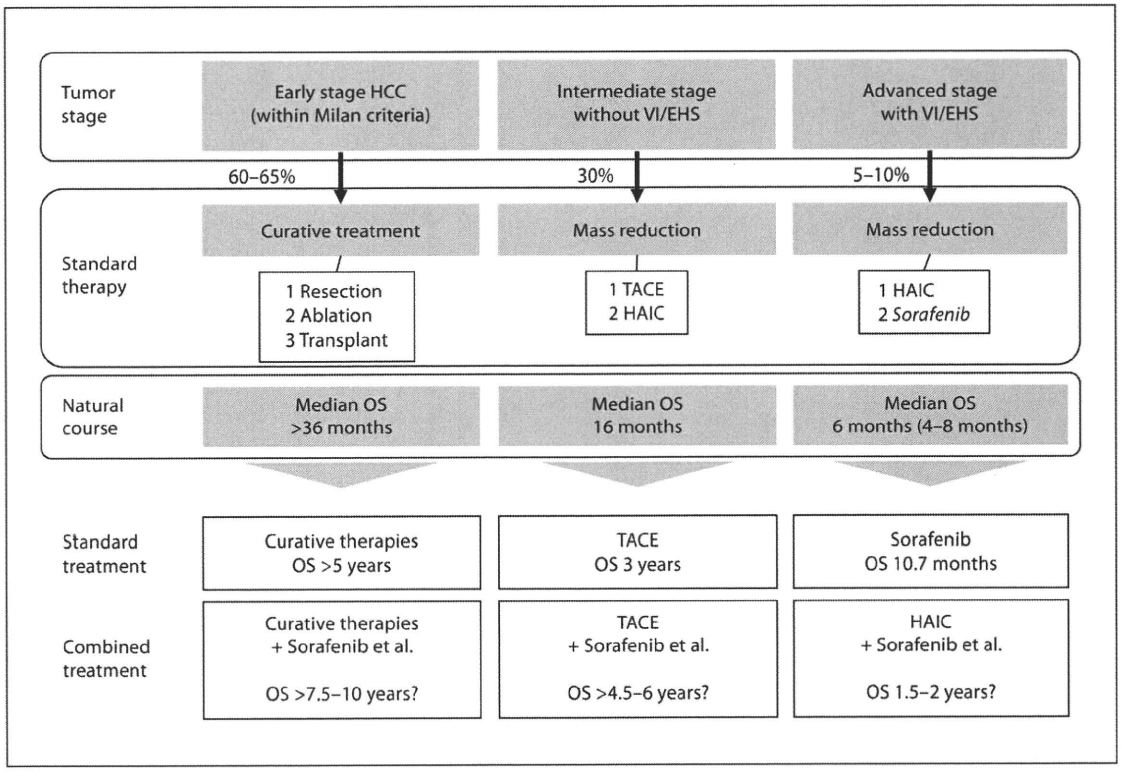

Fig. 5. Outcomes of standard treatment modalities and expected future outcomes of combination therapy with molecular-targeted agents. By combining molecular-targeted agents with resection or ablation, life expectancy is expected to be increased to 7.5–10 years. In addition, for intermediate stage HCC, the prognosis is expected to be increased to 4.5–6 years by combination with TACE. OS = Overall survival.

tologists should have a thorough knowledge of the possible adverse events and be aware of treatment options. This is important not only to avoid unnecessary adverse events, but also to maximize the efficacy of such agents by continuing drug administration for as long as possible, and thus prolonging survival.

One year has passed since sorafenib was approved in Japan on May 20, 2009. Molecular-targeted agents, such as sorafenib, may have a significant impact on the treatment of liver cancer and markedly change the algorithm originally established in 2007 for treating liver cancer in Japan, as shown in figure 5 [31, 32], and revised by the Japan Society of Hepatology in 2010 [11]. The results of the SHARP and Asia-Pacific studies and the 1-year experience in Japan with 15 CR cases among a total of more than 3,700 cases offer hope to many HCC patients, particularly those with advanced HCC with major vascular invasion or extrahepatic spread.

Disclosure Statement

The authors declare that they have no financial conflict of interest.

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Real Practice of Hepatocellular Carcinoma in Japan: Conclusions of the Japan Society of Hepatology 2009 Kobe Congress

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Key Words
Hepatocellular carcinoma · Japan Society of Hepatology · Consensus Meeting

Abstract
This article presents the current consensus on the management of hepatocellular carcinoma (HCC) formed at the 45th Annual Meeting of the Japan Society of Hepatology (June 4–5, 2009) and the 3rd International Kobe Liver Symposium (June 6–7, 2009) held in Kobe. Concluded important consensuses, which were well accepted by Japanese HCC specialists, are as follows. (1) Patients with type B or type C liver cirrhosis, who are an ultrahigh-risk group of liver cancer, should be screened every 3–4 months by ultrasonography and measurement of AFP and PIVKA-II. (2) Gd-EOB-MRI is useful for the diagnosis of early HCC. (3) The JIS score is more useful for the staging of liver cancer than the BCLC staging system, which is a global standard. (4) The TNM staging system by the Liver Cancer Study Group of Japan is superior to the TNM stage by the AJCC/UICC. (5) The therapeutic algorithm in the Japanese guidelines for the management of liver cancer is superior to the BCLC treatment algorithm. (6) Early stage. Liver cancers should be treated by radiofrequency ablation if they are ≤2 cm, and by surgical resection if they are Child-Pugh A solitary lesions. (7) Liver transplantation is only indicated for Child-Pugh C patients within Milan Criteria. In conclusion, these consensuses seem to well reflect the real practice pattern of the management of HCC in Japan and provide valuable information for other countries as well.

Introduction

A total of three Consensus Meetings were held during the 45th Annual Meeting of the Japan Society of Hepatology (JSH) on June 4–5, 2009, and the 3rd International Kobe Liver Symposium on Hepatocellular Carcinoma (HCC) (IKLS; June 6–7, 2009) held in succession in Kobe. The first one was the Consensus Meeting on HCC (participated in by Japanese HCC specialists only) of the Annual Meeting of the JSH, one held as part of the international symposium during the session of the Annual Meeting also participated in by foreign experts, and one during the 3rd IKLS, for which 20 foreign HCC experts and 200 Japanese HCC experts were selected from a total of 786 Council members representing the 10,737 members of the JSH who voted using answer pads after topic presentations.

The experts consisted of 68% internists or hepatologists, 25% surgeons, 3% radiologists, 2% pathologists, and

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2% from other fields. This report outlines the current consensus regarding the latest diagnostic and therapeutic issues for HCC in Japan by presenting excerpts of the results of these meetings.

Screening

According to Western guidelines (BCLC algorithm), the screening interval need not be changed depending on the degree of fibrosis or stage of the liver disease [1], but Japanese guidelines recommend modification of the screening intervals according to the risk of carcinogenesis [2–5]. In a questionnaire survey of 200 experts also using answer pads, a majority of experts (91%) answered that the screening interval should be changed according to the degree of fibrosis. This view, reflecting the actual contents of clinical practice in Japan, is considered reasonable. More specifically, 53% of the experts considered that patients with hepatitis B or C should be screened by ultrasonography every 6 months, with monitoring of the tumor marker levels every 3 months. However, 84% of the experts answered that patients with type B or C liver cirrhosis, who are an ultrahigh-risk group, should be screened every 3–4 months, following the Japanese algorithm. For the screening of high-risk groups, 72% simultaneously examined AFP, PIVKA-II and AFP-L3 among tumor markers, and 44% combined them with ultrasonography. These figures are considered to accurately reflect common practice in Japan (fig. 1).

ConsensusS tatement1

The surveillance interval needs to be shortened for patients at higher risk of HCC, such as hepatitis B- or C-related liver cirrhosis.

Consensus Statement 2

Surveillance should be performed using both ultrasonography and three tumor markers including AFP, PIVKA-II, and AFP-L3.

Diagnosis

HCC has usually been diagnosed by dynamic CT, but it is notable that 58% of the experts described gadolinium diethylenetriamine ethoxybenzyl-MRI (Gd-DTPA-EOB-MRI) as the primary modality, outnumbering those who answered dynamic MDCT. In addition, 91% of the experts agreed that biopsy is unnecessary when a hypervascular tumor of ≥1.5 cm shows typical features of wash-in and wash-out on imaging, and 67% stated that biopsy should be performed, in principle, for hypovascular tumors of ≤1.5 cm. These results also reflect the current Japanese standard of clinical practice for liver cancer.

Also, Western guidelines require the agreement of two dynamic studies for tumors 1–2 cm in diameter even when they present typical images [1], but 83% of the Japanese experts considered that one imaging modality suffices for tumors of any size (even those of 1–2 cm in diameter). This is a marked difference between Japan and Western countries, and it is considered that the Japanese view is more theoretically reasonable. Concerning small nodules presenting non-typical images, a majority (55%) answered, to my surprise, that they would follow-up without biopsy. This was probably because they assumed a situation in which HCC cannot be diagnosed definitively even with the extensive use of modalities including Gd-EOB-MRI or contrast-enhanced ultrasonography, and, if so, the approach may be justified.

ConsensusS tatement3

Even though a nodule is as small as 1–2 cm in size, HCC can be correctly diagnosed by the typical imaging findings by only one dynamic imaging study.

Staging and Prognostic Stages

While the TNM staging system by the AJCC/UICC is a global standard, the TNM stage of the Liver Cancer Study Group of Japan has been used for a long time in Japan, because the cutoff size employed in the AJCC/UICC system is huge (5 cm). In Japan, many liver cancers of ≤2 cm are detected frequently due to the nationwide coverage of the screening system, and AJCC/UICC TNM staging is not adequate. Reflecting this, 97% of the participants of the International Symposium quite reasonably supported the Japanese TNM staging. Also, 65% of the experts agreed with the view that integrated staging should be employed for the staging for a predicting prognosis of liver cancer, and 69% answered that BCLC staging is inappropriate for a prognostic prediction. Indeed, the BCLC staging system is a therapeutic algorithm, and the classification of tumors and patients' conditions into early, intermediate, and advanced naturally results in the progressive exacerbation of the outcome and favorable agreement between stratification of the survival curve and the prognosis. Therefore, in a strict sense, BCLC staging is not a prognostic staging system. The view that the JIS score is appropriate as an integrated staging system for a predicting prognosis in Japan was supported by 71%.

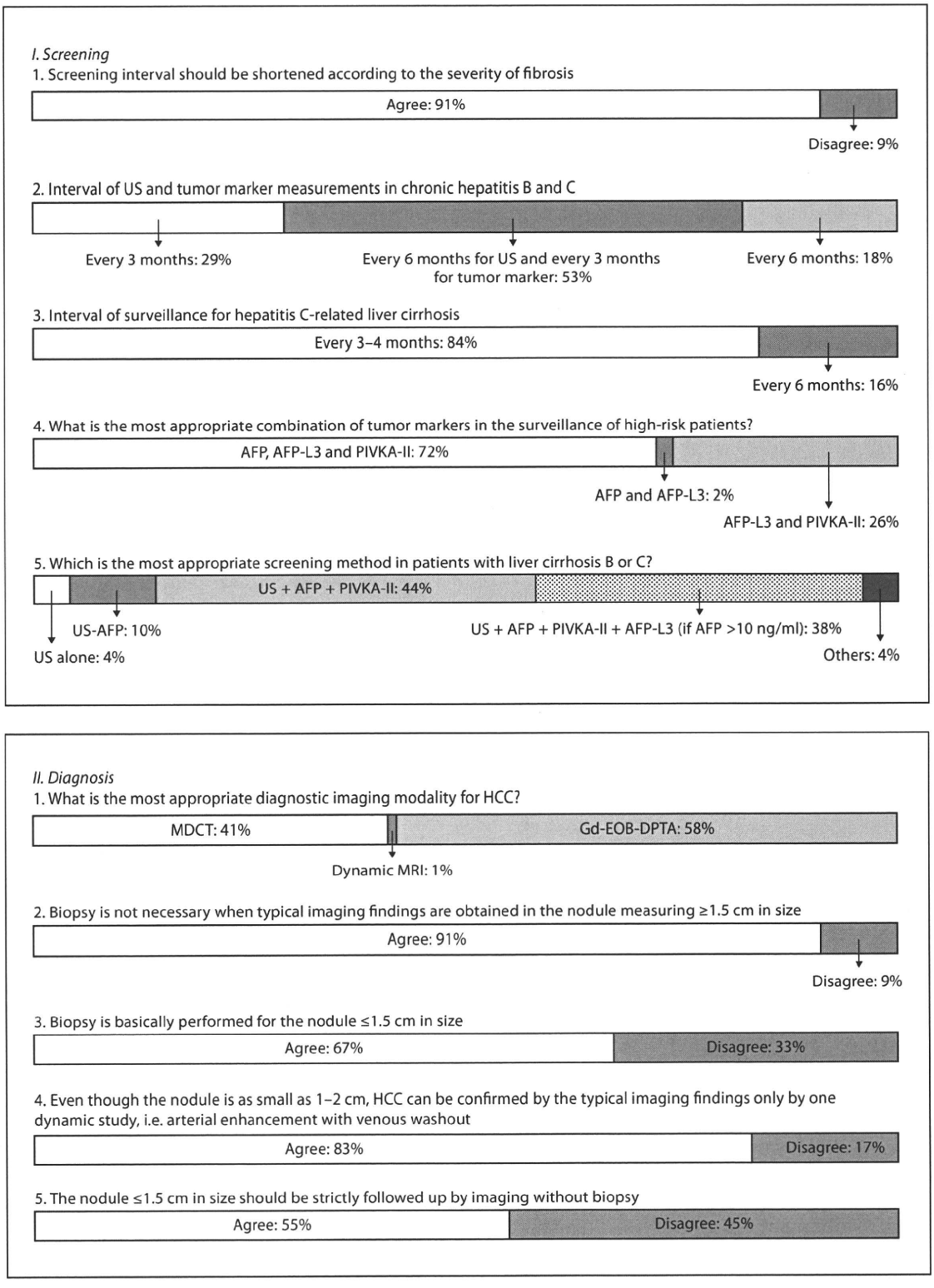

Fig. 1. Differences in many aspects of both the concept and clinical practice concerning the diagnosis and treatment of liver cancer between Japan and Western countries. AFP = Alpha-fetoprotein; PIVKA-II = protein induced by vitamin K absence or antagonist-II; AFP-L3 = AFP-L3 fraction; LCSGJ = Liver Cancer Study Group of Japan.

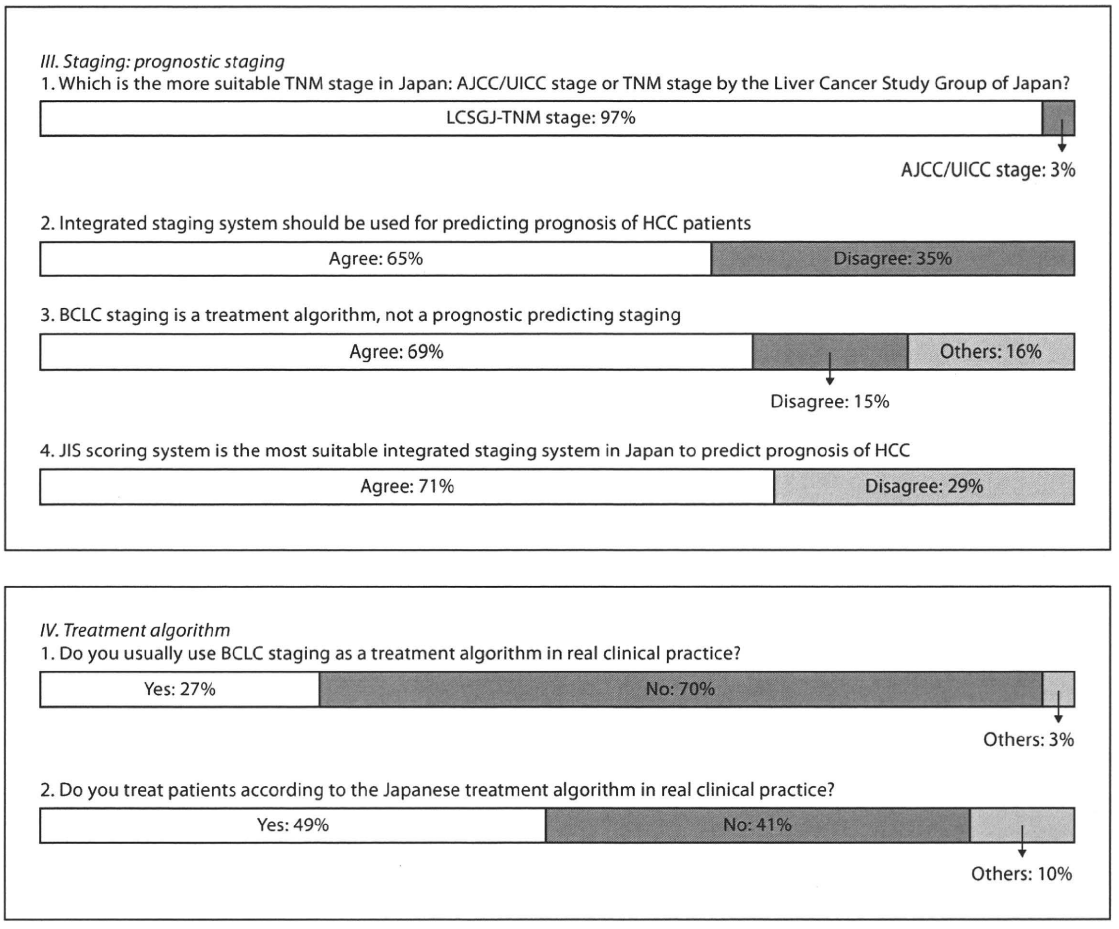

Fig. 1.

ConsensusS tatement4

TNM stage by the Liver Cancer Study Group of Japan is the more appropriate stage than the AJCC/UICC TNM stage.

ConsensusS tatement5

The JIS scoring system is the most suitable integrated staging system in Japan to predict a prognosis of HCC.

Treatment Algorithm

Concerning the treatment algorithm, 49% of the experts answered that they determined the therapeutic approach on the basis of Japanese guidelines for the management of liver cancer (fig. 1, 2) [2–4], and only 27% used the BCLC treatment algorithm. This is another marked difference in the approach to liver cancer between Western countries and Japan.

As expected, most of the experts (94%) considered that a circumferential ablative margin should be secured for ablation with the aim of the locally curative treatment of small liver cancer. This view is unique to Japanese physicians, not observable as part of the general Western practice. Also, 94% supported CT scanning at slice intervals of ≤5 mm for CT-based assessment after RFA. To my knowledge, in no country is the effect of RFA evaluated so carefully by CT, aiming at 100% necrosis and the securing of an ablative margin.

A minority (36%) answered that they would perform TACE followed by RFA for hypervascular liver cancers of ≤2 cm in diameter, but a majority (81%) answered that they would perform them, in principle, for hypervascular liver cancers of ≥3 cm, because microsatellite lesions and mircrovascular invasion are present around hypervascular liver cancers 2–3 cm in diameter, and they may lead to subsequent local recurrence even after complete necro-