Table 1 Molecular-targeted agents being tested in HCC

Agent	Antiangiogenic targets					Antiproliferative targets				Antiepigenetic targets				Developmental status	Company
	VEGF	FGF	VEGFR	PDGFR	FGFR	EGFR	Raf	MEK	mTOR	RAR	RXR	HDAC	Heparanase		
Sorafenib[a] (Nexavar)			●	●			●							Approved	Bayer
Sunitinib[a] (Sutent)			●	●										Phase III 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
Linifanib			●	●										Phase III initiated Abott	
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

Sources: Trial Trove, ClinicalTrials.Gov (NCI), Evaluate Pharma, IMS Knowledge Link, Esplcom, IDdB3, BioPharm Insight, MedTrack

[a] Sorafenib and sunitinib also have antiproliferative affects through multi-tyrosine kinase inhibition

PI3K/Akt/mTOR pathway

The PI3K/Akt/mTOR pathway also plays an important role in cell growth, survival regulation, metabolism, and anti-apoptosis. The membrane lipid phosphatidylinositol 4,5-bisphosphate (PIP_2) is phosphorylated by phosphatidylinositol 3-kinase (PI3K) into phosphatidylinositol 3,4,5-triphosphate (PIP_3), which binds to and activates the serine/threonine kinase Akt. The tumor-suppressor gene product PTEN (phosphatase and tensin homolog deleted on chromosome) is antagonistic to PI3K activity. PTEN is a lipid phosphatase that dephosphorylates inositol phosphates such as PIP_3. The inactivation of PTEN through gene deletion increases PIP_3 levels, and activates Akt, which inhibits apoptosis, leading to the development of tumors. The serine/threonine kinase mTOR is an important mediator in the PI3K/Akt pathway that binds intracellularly to a protein called raptor or rictor, and exists as two different complexes, complex 1 and 2 (mTORC1 and mTORC2). mTORC2 (mTOR-rictor) activates Akt whereas mTORC1 (mTOR-raptor) is activated downstream of Akt; thus, both molecules regulate protein synthesis [23].

A study of 528 HCC samples showed that expression of pAkt, PTEN, p27, and S6 ribosomal protein (pS6) was a poor prognostic factor for survival [24]. A tissue microarray analysis of HCC samples revealed that the loss of PTEN and overexpression of pAkt and p-mTOR were correlated with tumor grade, intrahepatic metastasis, vascular invasion, TNM stage, Ki-67 labeling index, and matrix metalloproteinase (MMP)-2 and (MMP)-9 upregulation, Meanwhile, PTEN mRNA expression in the cancerous tissue was downregulated, compared with that in the non-cancerous tissue. The levels of PTEN, MMP-2, and MMP-9 mRNA expression were correlated with tumor stage and metastasis, and the levels of PTEN and MMP-9 mRNA expression were inversely correlated [25]. In an extensive analysis of 314 HCC samples in terms of mutation analysis, DNA copy number changes, mRNA levels, and immunostaining, Villanueva et al. found that activation of the IGF pathway, upregulation of EGF, dysregulation of PTEN, and aberrant mTOR signaling were present in half of the samples, and that inhibiting mTOR activity with everolimus was effective in improved survival and suppression of recurrence [26].

The PI3K inhibitor RG7321 and the Akt inhibitor perifosine target the PI3K/Akt/mTOR pathway and are in early stages of clinical development, whereas the mTOR inhibitors everolimus (RAD001), sirolimus (Rapamune), and temsirolimus (CCI-779) are at more advanced stages of development. Everolimus is used to treat sorafenib-intolerant patients or for patients showing disease progression after sorafenib administration. A phase III study to compare everolimus and a placebo (EVOLVE-1: Advanced Hepatocellular Carcinoma after Disease Progression or Intolerance to Sorafenib *Ever*O*l*imus for *Li*V*er* cancer *E*valuation) and a phase I/randomized phase II study (sorafenib + everolimus vs. sorafenib alone) to test the efficacy and tolerance of sorafenib in combination with everolimus are underway. Because mTOR inhibitors have cytostatic and antiangiogenic effects, they are expected to be effective in combination with other angiogenesis inhibitors such as bevacizumab, and may be appropriate for administration after transarterial chemoembolization (TACE). Furthermore, because the mTOR pathway is stimulated by factors such as EGFR, PDGFR, and TGFα, and is closely related to other signaling pathways including the Ras/Raf/MEK/ERK pathway, they are likely to show promising efficacy when used in combination with other growth factor inhibitors [27].

VEGF/VEGFR, PDGFR, FGFR

Angiogenesis is an important event not only for HCC but also for cancer growth and metastasis, and occurs because of complex alterations involving promoting factors such as VEGF, angiopoietin, and FGF, inhibitory factors including thrombospondin (TSP) and angiostatin and the surrounding tissue. The VEGF family consists of VEGF-A, B, C, D, and E, and placental growth factor (PIGF). The VEGFR family comprises VEGFR-1 (flt-1), VEGFR-2 (flk-1/KDR), and VEGFR-3 (flt-4). VEGF-A binds to VEGFR-1 and VEGFR-2 and is involved in angiogenesis and the maintenance of mature blood vessels, whereas VEGF-C and VEGF-D mainly bind to VEGFR-3, are involved in lymphangiogenesis [28, 29]. VEGF isoforms such as $VFGF_{121}$ and $VEGF_{165}$ have been identified, and isoform subtypes also exist, for example $EGF_{166}b$. Thus, it is clear that these growth factors do not exhibit angiogenesis-promoting effects alone, and they have attracted attention as new therapeutic targets [30].

HCC typically exhibits active angiogenesis. During the progression from early to well, and to moderately differentiated HCC, angiogenesis increases and cancer cells acquire the ability to invade vessels and metastasize. Scientific and clinical studies have revealed that, during the progression from hepatitis to cirrhosis, angiogenesis and disruption of the vascular architecture are linked to the progression of HCC, and contribute to increased hepatic vascular resistance and portal hypertension, and decreased hepatocyte perfusion [31]. In addition, a meta-analysis has demonstrated that VEGF expression is a prognostic factor in HCC [32].

Phase II studies have been started to test the usefulness of bevacizumab (Avastin®), which directly targets VEGF, in TACE-treated HCC, and the use of bevacizumab in

combination with erlotinib (Tarceva®), an EGFR tyrosine kinase inhibitor.

Sunitinib (Sutent®) is a multi-kinase inhibitor that inhibits tyrosine kinases such as VEGFR-1, 2, 3, PDGFR-α, β, and c-Kit. A phase II study of sunitinib in 37 advanced HCC patients showed that the median progression-free survival (PFS) and median overall survival (OS) were 3.7 and 8 months, respectively. In that study, adverse events included grade 3/4 thrombocytopenia in 37.8% of patients, neutropenia in 24.3%, asthenia in 13.5%, and hand–foot syndrome in 10.8% [33]. Because sunitinib has a lower IC_{50} for each target than sorafenib, it is expected to have greater antitumor activity. However, this factor may be responsible for the higher incidence of adverse events with sunitinib. The main evaluation item in the above phase II trial was the response rate, which did not reach the expected value, leading to the conclusion that it was a negative study [34]. In that study sunitinib was administered at 50 mg/day for 4 weeks followed by 2 weeks of rest per cycle [33], whereas Zhu et al. [34] used a dosing schedule of 37.5 mg/day for 4 weeks followed by 2 weeks of rest per cycle, and reported that the median PFS and OS were 3.9 and 9.8 months, respectively. An ongoing global cooperative phase III controlled clinical trial to compare sorafenib and sunitinib head-to-head and to seek approval for first-line indications for advanced HCC adopted a sunitinib dosing schedule of 37.5 mg/day. However, in a "Reflection and Reaction" regarding these trial results, Forner et al. cast doubt on whether the drugs at this dose could maintain tolerance and ensure efficacy [35]. Because recruitment is progressing well, the results are expected to be available soon.

Brivanib is a kinase inhibitor that selectively inhibits VEGFR-1, 2, and 3, and FGFR-1, 2, and 3. As for sunitinib, an international global phase III clinical trial to compare brivanib and sorafenib head-to-head and to seek approval for first-line therapy for advanced HCC has already been started, and the results are eagerly awaited. Japanese centers are participating in this clinical trial. Because brivanib targets FGF and VEGF, and is associated with relatively mild adverse effects, a second-line study of brivanib in sorafenib-ineffective and sorafenib-intolerant patients and a trial to evaluate the use of brivanib in combination with TACE are underway. Depending on the results of these trials, indications for use in HCC may be obtained; therefore, positive results are eagerly anticipated. The results have been reported for a phase II study of brivanib in 55 patients (cohort A) who had not received systemic therapy for curatively unresectable HCC and 46 patients (cohort B) previously treated with angiogenesis inhibitors such as sorafenib or thalidomide [36]. The median TTP and OS were 2.8 and 10 months, respectively, in cohort A versus 1.4 and 9.8 months, respectively, in cohort B. Adverse events included fatigue (51.5%), diarrhea (41.6%), hypertension (42.6%), anorexia (41.6%), and nausea/vomiting (40.6/30.7%). Thus, these results demonstrated the efficacy of brivanib as a second-line treatment. The results of three phase III clinical trials, BRISK-PS (sorafenib failure or sorafenib-intolerant patients; brivanib + best supportive care (BSC) vs. placebo + BSC), BRISK-FL (advanced HCC; brivanib vs. sorafenib), and BRISK-TA (patients with unresectable HCC, brivanib vs. placebo as post-TACE adjuvant therapy) are awaited. Japanese centers participated in all three trials.

In a Japanese phase I/II trial of TSU-68, an oral molecular inhibitor of VEGFR, PDGFR, and FGFR, to test its safety and efficacy in 35 HCC patients, the response rate was 5.6% (CR, PR, SD, PD, and NE in 1, 2, 15, 16, and 1 patients, respectively), and the disease control rate was 51.4% [37].

In addition, several phase I/II trials are being conducted to assess kinase inhibitors such as linifanib (ABT-869) and cediranib (AZD2171), which inhibit VEGFR, PDGFR, CSF-1R (cFms), Kit, and Flt3. Furthermore, axitinib, which is currently being tested in renal cell carcinoma, has also attracted attention as a promising agent for treatment of HCC because of its efficacy and mild side effects.

EGF/EGFR

EGFR is a member of the human epidermal growth factor receptor (HER) family that includes EGFR (erbB1), HER2/neu (erbB3), and HER4 (erb4). All members of this family, except HER3, have an intracellular tyrosine kinase domain, and the binding of a ligand to its extracellular domain triggers signal transduction through the above-described MAPK and PI3K/Akt/mTOR pathways. Thus, these receptors are involved in cell growth, differentiation, survival and adhesion [38]. EGFR overexpression has been reported in many cancers, and in HCC. For example, Buckley et al. reported that EGFR, detected by immunohistochemical analysis, was overexpressed in 50 (66%) of 76 HCCs, and that fluorescence in-situ hybridization (FISH) showed extra EGFR gene copies in 17 (45%) of 38 HCCs [39].

EGFR-targeting drugs, which include anti-EGFR antibodies, such as cetuximab and panitumumab, and small-molecule inhibitors of EGFR tyrosine kinases such as gefitinib, etc., have been used widely for treatment of several cancers other than HCC. Unfortunately, except for phase II trial data, there are few clinical data on the efficacy of these drugs for the treatment of HCC.

Similar to gefitinib (Iressa®), erlotinib (Tarceva®) is an oral EGFR tyrosine kinase inhibitor. Philip et al. and Thomas et al. have reported the results of phase II studies of erlotinib in HCC [40, 41]; the median OSs in their

studies were 13 and 10.7 months, respectively. A phase III clinical study (SEARCH study: *S*orafenib and *E*rlotinib, a R*a*ndomized T*r*ial Protoc*o*l for the Treatment of Patients with *H*epatocellular Carcinoma) of sorafenib in combination with erlotinib versus sorafenib plus placebo is ongoing. Because erlotinib is associated with a high incidence of skin rash, dry skin, and gastrointestinal toxicity, for example diarrhea, the results of the SEARCH study should be evaluated to assess whether this combination therapy can be used in clinical settings. Thomas et al. conducted a phase II clinical study of erlotinib in combination with bevacizumab in 40 advanced HCC patients, and reported promising results; the median PFS and OS were 9 and 15.7 months, respectively. However, they noted frequent treatment-related grade 3/4 toxicities, including fatigue (20%), hypertension (15%), gastrointestinal bleeding (12.5%), wound infection (5%), diarrhea (10%), elevated transaminase levels (10%), and thrombocytopenia (10%) [42], which necessitates further evaluation of drug tolerance. Although a clinical study of erlotinib in combination with bevacizumab (OPTIMOX-3 study) was also conducted in colorectal cancer patients, no tolerance was observed, which led to a change in the protocol [43, 44].

After the introduction of a number of molecular-targeted drugs, strategies for the inhibition of similar or different signaling pathways (vertical or horizontal inhibition) with several drugs have been proposed. However, the combined use of molecular-targeted agents has remained largely unsuccessful, including panitumumab in combination with bevacizumab for treatment of colorectal cancer [45]. Similarly, results for sorafenib in combination with bevacizumab (vertical inhibition) have been reported [46]. Although some therapeutic response was obtained, the combination therapy resulted in greater toxicity [46], suggesting the need for detailed evaluation of the dosing regimen.

Lapatinib (Tykerb®) is a dual inhibitor of EGFR and HER-2/neu, and inhibits tumor growth by downregulating MAPK, AKT, and p70S6 kinase [47]. In Japan, lapatinib is indicated for treatment of breast cancer. In a phase II clinical trial of lapatinib in 26 patients with unresectable advanced HCC, the median PFS and OS were 1.9 and 12.6 months, respectively, and adverse events included diarrhea (73%), nausea (54%), and skin rash (42%) [48].

Cetuximab (Erbitux®) is a human/mouse chimeric monoclonal antibody consisting of the variable region of a mouse anti-human EGFR monoclonal antibody and the human IgG1 constant region. Cetuximab inhibits the binding of endogenous EGFR ligands, for example EGF and TGFα, to EGFR. In a phase II clinical trial of cetuximab in 30 patients with unresectable or metastatic HCC, the median PFS and OS were 1.4 and 9.6 months, respectively, and treatment-related toxicities included grade 3 hypomagnesemia (3.3%) and grade 1/2 acne-like rash (83.3%), which was observed for the duration of anti-EGFR therapy in that study [49].

The EGFR is a very interesting therapeutic target. As described above, use of erlotinib in combination with sorafenib is still in the research stage. However, on the basis of results from phase II studies, the efficacy of cetuximab or lapatinib as monotherapy seems to be limited, and the results of further studies evaluating their efficacy in sorafenib-refractory or intolerant patients are awaited with interest.

HGF/c-Met pathway

Because the hepatocyte growth factor (HGF)/Met pathway is involved in tumor growth, invasion, and angiogenesis in a wide range of neoplasms, HGF and Met have recently attracted attention as therapeutic targets. HGF is a heterodimer consisting of α and β chains bound together by a disulfate bond. The α chain contains four kringle domains, and the β chain contains a serine protease-like domain. Met is a receptor tyrosine kinase for the HGF ligand, and contains a semaphorin-like domain. HGF or Met overexpression and Met gene mutations and duplications have been reported in various cancers, and abnormalities due to HGF/Met pathway activation have also been noted [50]. These abnormalities activate the downstream signaling cascade, leading to epithelial-mesenchymal transition and increased proliferative, migratory, invasive and metastatic potentials of cancer cells [50].

HGF/c-MET-targeted drugs, including kinase inhibitors, HGF inhibitors, and decoy c-Met receptor molecules, are being developed. Of particular interest is ARQ-197, a c-Met receptor tyrosine kinase inhibitor which is a non-ATP-competitive molecule that binds near the ATP-binding site. A randomized phase II study of ARQ-197 versus placebo is ongoing in patients with unresectable HCC after systemic therapy failure.

IGF/IGFR

The IGF/IGFR system is involved in cell growth and the chemotherapeutic response. The ligands IGF-I and II bind to their receptors IGF-1R and IGF-2R, and are involved in DNA synthesis and cell growth. Abnormalities in IGF and IGF-1R or their overexpression have been reported in various cancers, including HCC. Their associations with disease stage, metastasis, and survival [51] and the functions of IGF and IGFR in HCC [52] have been reported.

IGF-targeting drugs are currently being developed, and mainly include anti-IGF-1R antibodies, for example BIIB022, AVE1642, and cixutumumab (IMC-A12). A phase II study of cixutumumab, a phase Ib/II study of

Table 2 Results of 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

sorafenib versus sorafenib plus BIIB022, and phase I/II studies of AVE1642 as monotherapy or in combination with sorafenib or erlotinib are ongoing.

Sorafenib: trial results and clinical experience

Clinical results for sorafenib in HCC

As described above, sorafenib is a multi-kinase inhibitor of tumor growth and angiogenesis, and has a strong inhibitory effect on C-Raf and B-Raf serine/threonine kinases (comprising the Raf/MEK/ERK pathway), VEGFR and PDGFR tyrosine kinases, and FLT-3 and c-kit [20]. To date, sorafenib is the only molecular-targeted agent approved for treatment of HCC, on the basis of the results of two large-scale clinical trials, namely the SHARP (Sorafenib HCC assessment Randomized Protocol) study [53] and the Asia–Pacific study [54]. The median OSs for the sorafenib group in the SHARP and Asia–Pacific studies were 10.7 months (vs. 7.9 months for the placebo group, $P < 0.001$; HR: 0.69) and 6.5 months (vs. 4.2 months for the placebo group, $P = 0.014$; HR: 0.68), respectively, indicating that sorafenib prolongs survival by approximately 50% (Table 2). These data should compel HCC specialists to challenge their preconception that systemic anticancer drug therapy is not effective for HCC.

Current status regarding the use of sorafenib in Japan

Sorafenib was approved in Japan in May, 2009. A survey has confirmed that, at the time of writing (March, 2010), over 3,700 patients have been prescribed sorafenib. Across several centers, 15 Japanese patients have achieved CR, which was not observed in the SHARP or Asia–Pacific trials. This suggests that some Japanese patients may be very sensitive to sorafenib [55]. The reason for this, and predictive biomarkers, are now actively under investigation.

On the other hand, it has been reported that hand–foot syndrome occurs early after sorafenib administration [56] more often than was noted in the SHARP and Asia–Pacific studies, and the drug is often discontinued because of the adverse effects in many patients [56]. As demonstrated in the SHARP and Asia–Pacific studies, sorafenib is only used to achieve stable disease; it is, therefore, important to improve drug efficacy by extending the period of administration for as long as possible. Therefore, it is no exaggeration to say that, in the case of sorafenib, the "successful management of side effects" is equal to "successful treatment." According to "post-TACE phase III clinical study [56]" performed in Japan and Korea, it is strongly speculated that physicians who are unaccustomed to prescribing molecular-targeted agents and who fail to see marked efficacy, as induced by conventional chemotherapeutic agents, often do not understand the properties of this drug, and they (and the patients) do not fully comprehend therapeutic efficacy. Moreover, they feel too anxious about side effects that have not been encountered before. These circumstances may result in treatment discontinuation in many patients. Clearly, greater awareness among physicians for therapeutic efficacy and approaches to manage adverse effects is needed to improve treatment outcomes.

Experience of sorafenib use at our institute

Since the approval of sorafenib on May 20, 2009, we have treated 90 patients with sorafenib, and few have discontinued therapy because of adverse effects or patient refusal to continue. Of these 90 patients, two achieved CR [55]. These two CR patients, in whom pulmonary and adrenal metastases and intrahepatic lesions all disappeared, survived free of recurrence for more than 2 years and 1 year, respectively, at the time of writing (March, 2010), i.e., they are still alive at present. In other patients who apparently achieved SD, the tumor marker levels reached a plateau after sorafenib administration, when their levels were rising rapidly before sorafenib administration. Even if hepatic lesions do not show a clear tendency to undergo necrosis or regression on CT images, three tumor markers (AFP, PIVKA-II, and AFP-L3) are widely considered to serve as surrogate markers. In fact, there are very few data on serum tumor markers, except for AFP, outside Japan. Nevertheless, Japanese researchers have demonstrated the value of changes in these markers and the antitumor efficacy of sorafenib [55].

Interestingly, it has previously been demonstrated that the levels of PIVKA-II or DCP tend to be increased by

inducing hypoxia [57]. Therefore, PIVKA-II or DCP may be a good predictive marker for evaluating the hypoxic response to antiangiogenic therapy for HCC.

Only 17 of the 90 patients showed PD on computed tomography (CT) images although follow-up period is still short (less than 10 months). However, because the speed with which the patient develops progressive disease may slow down due to tumor growth inhibition, it is very difficult to determine when to discontinue treatment because of tumor refraction. Important issues for future studies include:

1 identification of biomarkers that can be used to predict therapeutic responses, including CR or PR, in patient groups;
2 evaluation of the role of tumor markers in the determination of therapeutic responses;
3 establishing response evaluation criteria that can determine the therapeutic responses to molecular-targeted agents; and
4 development of effective second-line therapies after sorafenib failure (Figs. 2, 3).

In the treatment algorithm (Figs. 2, 3) approved by the Consensus Meeting of the 2009 Annual Meeting of the Japan Society of Hepatology (Congress chair: Professor Masatoshi Kudo), sorafenib is indicated for treatment of patients with Child-Pugh A HCC with extrahepatic metastasis, vascular invasion, or refractoriness to TACE or arterial infusion chemotherapy.

In addition to the pharmaceutical-sponsored clinical trials of sunitinib and brivanib as first and second-line therapy in sorafenib-refractory patients, investigator-initiated trials (IIT) of sorafenib in combination with hepatic arterial infusion chemotherapy (SILIUS trial), pharmaceutical and IIT trials of sorafenib in combination with TACE (SPACE, TACICS and BRISK-TA trials), and a trial to test the inhibitory effect of sorafenib on tumor recurrence after curative treatment (STORM trial) are ongoing, and the results of these trials are eagerly awaited (Figs. 2, 3). The working hypotheses in these studies can be deduced by extrapolating the MST and hazard ratios in overall survival (OS) calculated in a subanalysis of the SHARP study (Table 3). The results obtained suggest that starting treatment with molecular-targeted drugs at an earlier tumor stage in combination with standard treatment options such as resection, ablation, TACE, or hepatic arterial infusion chemotherapy can improve the prognosis of HCC. Thus, sorafenib has the potential to induce a change of emphasis in the treatment of HCC. For example, in a subanalysis of the SHARP trial, the hazard ratios for OS and MST ratio in intermediate stage HCC without vascular invasion or extrahepatic spread were 0.52 and 1.50, respectively (Table 4). This suggests that survival of early stage HCC and intermediate stage HCC may be prolonged from 5 years to 7.5–10 years by using sorafenib in an adjuvant setting after curative treatment, and from 3 years to 4.5–6 years by using sorafenib in combination with TACE (Fig. 4).

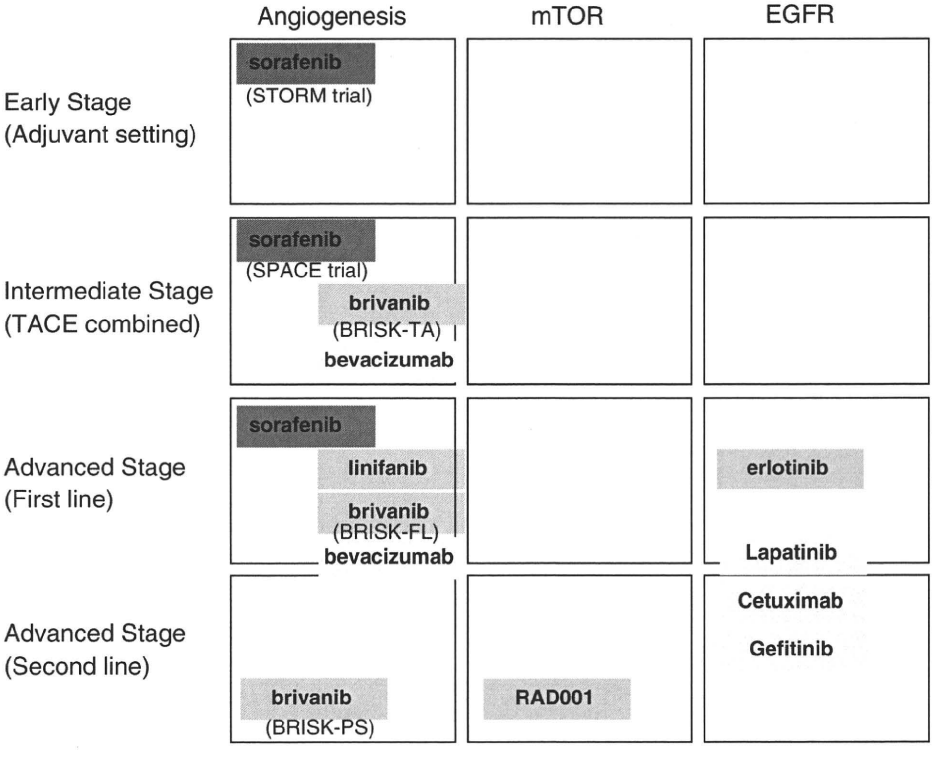

Fig. 2 Molecular targeted agents: ongoing trials in each stage of HCC

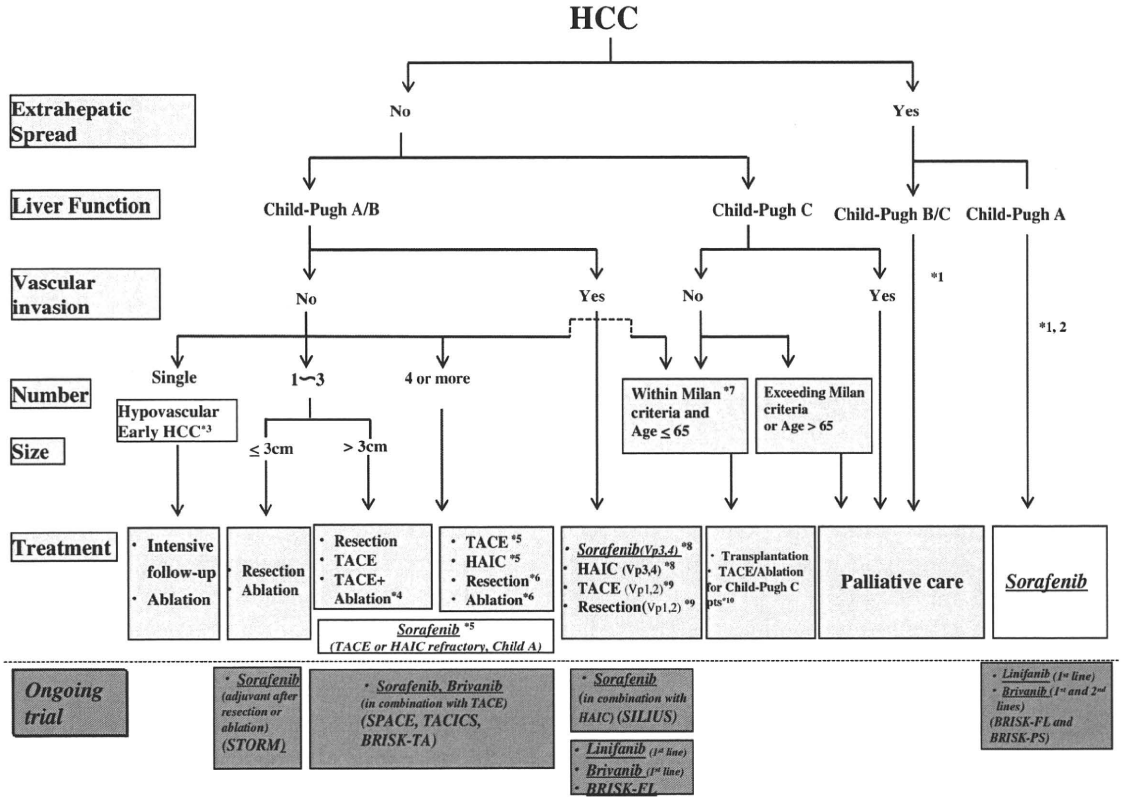

Fig. 3 Consensus-based treatment algorithm for HCC proposed by the Japan Society of Hepatology (JSH) revised in 2010. *1 Treatment should be performed as if extrahepatic spread is negative, when extrahepatic spread is not considered as a prognostic factor in Child-Pugh class A/B patients, *2 sorafenib 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 frequently progress to advanced HCC, *4 even for HCC nodules exceeding 3 cm in diameter, transcatheter arterial chemoembolization (TACE) in combination with ablation is frequently performed when resection is not indicated, *5 TACE is the first choice of treatment in this setting. Hepatic arterial infusion chemotherapy (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 interferon therapy. Sorafenib is also recommended for TACE- or HAIC-refractory patients with Child-Pugh class A liver function, *6 resection is sometimes performed when more than four nodules are detected. Ablation is sometimes performed in combination with TACE, *7 Milan criteria: tumor size ≤3 cm and tumor number ≤3, or solitary tumor ≤5 cm. Even when liver function is good (Child-Pugh A/B), transplantation is sometimes considered for patients with frequently recurring HCC, *8 sorafenib and HAIC are recommended for HCC patients with major portal invasion such as Vp3 (portal invasion in the first portal branch) or Vp4 (portal invasion in the main portal branch), *9 resection and TACE are frequently performed when portal invasion is minor, such as Vp1 (portal invasion in the third or more peripheral portal branch) or Vp2 (portal invasion in the second portal branch), *10 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 because there is no evidence of a survival benefit in Child-Pugh C patients. A prospective study is necessary to clarify this issue

Table 3 Subanalysis data of the SHARP study

		Advanced HCC with vascular invasion and 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 OS (MST)	Sorafenib	8.9 M (n = 209) (95% CI: 7.6–10.3 M)	14.5 M (n = 90) (95% CI: 14.0 M–N/E)
	Placebo	6.7 M (n = 212) (95% CI: 5.2–8.0 M)	10.2 M (n = 91) (95% CI: 8.6–15.5 M)

M, month

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Table 4 Results of studies of molecular-targeted agents for HCC

Agent	Type	Target	Number of patients	RR (%)	PFS (month)	TTP (month)	OS (month)	Reference
Phase III								
Sorafenib	s.m.	C-Raf, B-Raf,	602 (299[a])	2	–	5.5	10.7	Llovet [5, 53]
		PDGFR, VEGFR	271 (150[a])	3.3	–	2.8	6.5	Cheng [54]
Phase II								
Sorafenib	s.m.	C-Raf, B-Raf, PDGFR, VEGFR	137	2.2	–	5.5	9.2	Abou-Alfa [58]
Sunitinib	s.m.	VEGFR, PDGFR,	37	2.7	3.7	5.3	8	Faivre [33]
		SCFR, FLT3	34	2.9	3.9	4.1	9.8	Zhu [34]
Brivanib	s.m.	VEGFR, FGFR	55	n.r.	–	2.8	10	Raoul [36]
Linifanib	s.m.	VEGFR, PDGFR	44	6.8	–	5.7	9.3	Toh [59]
Bevacizumab	MoAb	VEGF	46	13	6.9	–	12.4	Siegel [60]
Erlotinib	s.m.	EGFR	38	9	–	3.2	13	Philip [40]
			40	0	–	–	10.7	Thomas [41]
Gefitinib	s.m.	EGFR	31	3.2	2.8	–	6.5	O'Dwyer [61]
Lapatinib	s.m.	EGFR	40	5	2.3	–	6.2	Ramanathan [62]
			26	0	1.9	–	12.6	Bekaii-Saab [48]
Cetuximab	MoAb	EGFR	30	0	1.4	–	9.6	Zhu [49]

[a] Sorafenib arm

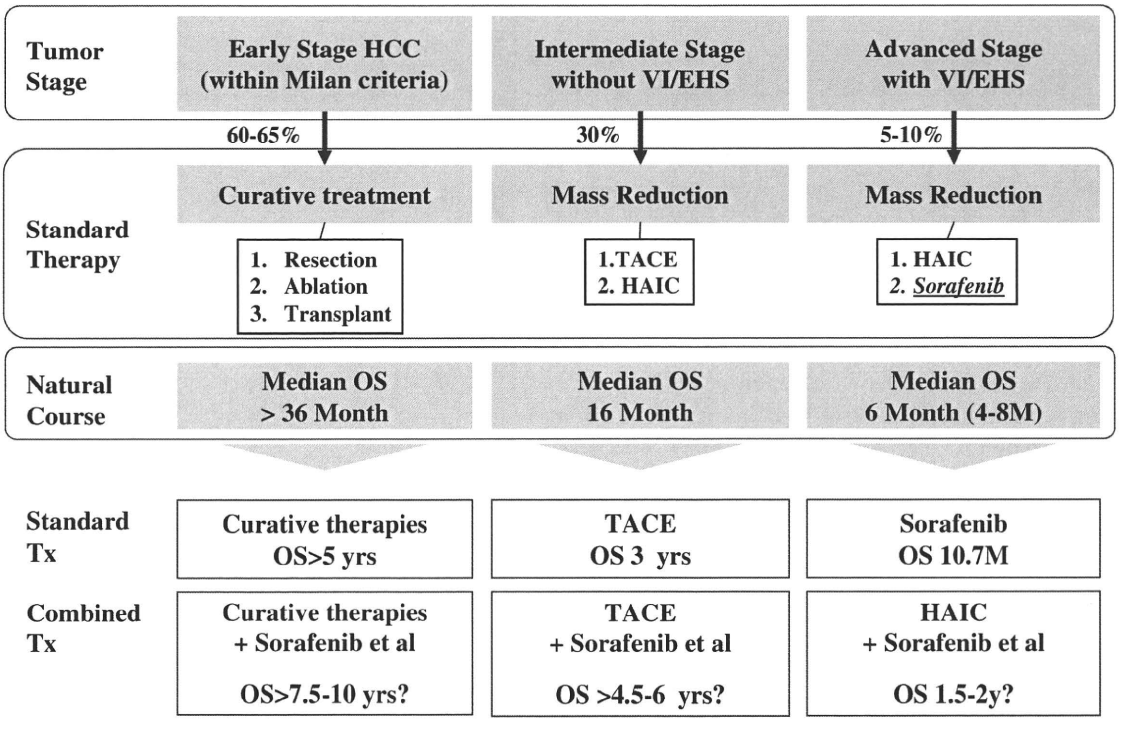

Fig. 4 Outcomes of standard treatment modalities and expected effects of combination therapy with molecular-targeted agents

Summary and future prospects

The results of clinical trials [33, 34, 36, 40, 41, 49, 58–62] of the molecular-targeted agents described above are summarized in Table 4. Angiogenesis-inhibiting drugs, particularly sorafenib, have been evaluated for HCC, and drugs targeting EGFR and mTOR are being developed. The results (numerical values) of phase II clinical trials show no marked differences in the therapeutic efficacy evaluated by time to progression (TTP) or progression-free survival

(RFS). However, results from phase II studies may be subject to patient selection bias and cannot be compared with results from other trials. Thus, when determining the therapeutic efficacy of drugs, we should review the efficacy of the respective drugs, and consider where the theoretical target molecules are present and what combinations of drugs have a theoretical rationale, and thus evaluate options for monotherapy and combination therapy based on the efficacy and safety data obtained from phase III clinical trials.

Molecular-targeted agents that have been introduced into clinical use in recent years are approved for treatment of specific cancer and are then frequently used to treat other cancers. Although not discussed here, studies to identify predictors of efficacy (i.e., biomarkers) for angiogenesis inhibitors and EGFR tyrosine kinase inhibitors, and factors involved in drug resistance, are making steady progress, and the associated therapeutic strategies are undergoing major changes. Therefore, even in the treatment of HCC, it is necessary for HCC specialists to expand their knowledge of and techniques for applying existing treatment modalities (resection, ablation, TACE, arterial infusion chemotherapy) to physically remove, destroy, or necrotize the tumor, and to better understand clinical oncology, particularly the role and mechanisms of action of molecular-targeted agents. We are entering an era in which physicians treating HCC should pay close attention to the development of therapeutic agents not only for HCC but also for other cancers, and be aware of the use of molecular-targeted agents for treating cancers in clinical and basic research settings, and understand approaches to limit or control adverse effects associated with these drugs.

Although sorafenib was recently approved, many issues remain to be addressed, including:

1 how to determine and define refractoriness; and
2 whether to continue TACE or hepatic arterial infusion chemotherapy (a de facto standard in Japan) in patients with TACE-refractory tumors or portal tumor thrombi before starting sorafenib therapy.

For oncology, in particular, the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan has approved several drugs based on results from global clinical trials and on Japanese phase I study data alone. We strongly recommend that, on the basis of the molecular-targeted agents currently under development, clinical studies (including IITs) should be conducted aggressively, and therapeutic strategies should be devised to resolve the limitations of currently used therapeutic approaches and to improve therapeutic outcomes.

The introduction of sorafenib to treat HCC in 2007 in Western countries and in 2009 in Japan was undoubtedly the beginning of a change of emphasis, representing a significant breakthrough for HCC treatment not previously experienced for this unique tumor.

Conflict of interest statement M. Kudo has received honoraria for the lecture from Bayer HealthCare, Pfizer, and Bristol-Meyers.

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Management of Hepatocellular Carcinoma: From Prevention to Molecular Targeted Therapy

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Key Words
Hepatocellular carcinoma, prevention · Molecular targeted therapy · Sorafenib · Treatment algorithm

Abstract
Hepatocellular carcinoma is a malignant tumor responsible for approximately 600,000–700,000 deaths worldwide, and is becoming more prevalent not only in South-East 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 3rd International Kobe Liver Symposium on Hepatocellular Carcinoma (HCC) was held on June 6–7, 2009, in conjunction with the 45th Annual Meeting of the Japan Society of Hepatology on June 4–5 (Congress President: Prof. Masatoshi Kudo). To this symposium, a total of 20 oversea guests, all globally recognized HCC specialists, were invited (table 1). Numerous topics were presented followed by extensive discussions with Japanese HCC specialists.

This supplement issue focuses on these topics, from the prevention 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.

Table 1. Invited overseas speakers at the 3rd IKLS 2009 in Kobe

Luigi Bolondi (Italy)	Joong-Won Park (Korea)
Jordi Bruix (Spain)	Ronnie T. Poon (Hong Kong)
Pei-Jer Chen (Taiwan)	Tania Roskams (Belgium)
Byung Ihn Choi (Korea)	Myron Schwartz (USA)
Michel Claudon (France)	Morris Sherman (Canada)
Kwang Hyub Han (Korea)	Mitchell L. Shiffman (USA)
Riccardo Lencioni (Italy)	Hui Chuan Sun (China)
Shi-Ming Lin (Taiwan)	S. Thorgeirsson (USA)
Joseph M. Llovet (Spain	Swan N. Thung (USA)
Jorge Marrero (USA)	J. Zucman-Rossi (France)
Vincenzo Mazzaferro (Italy)	

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Prevention

Prevention of Hepatitis B Virus (HBV)-Related HCC

Primary Prevention of HCC by HBV Vaccination

About 350 million people are chronic carriers of the HBV worldwide. The efficacy of universal immunization has been shown in many countries, with striking reductions of the prevalence of HBV carriage in children. A nationwide vaccination program against HBV launched in Taiwan [1–3] has drastically reduced the HBsAg carrier rate in younger populations [4]. More importantly, follow-up results from the Taiwan vaccination programs have shown 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 between 1986 and 1990, and further to 0.36/100,000 between 1990 and 1994 ($p < 0.01$) [5].

Secondary Prevention of HCC by Interferon (IFN) Therapy

There was one randomized controlled trial [6] which involved 101 Taiwanese men with chronic hepatitis B, 67 of whom received 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 treated patients ($p = 0.013$).

A meta-analysis of randomized studies comparing IFN-treated versus untreated patients with HBV-related cirrhosis showed that IFN seemingly decreased the rate of HCC [7].

Secondary Prevention of HCC by Nucleoside Analog

To date, only one randomized controlled trial 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; $p = 0.047$) [8]. A multicenter retrospective study of 2,795 patients (657 treated with LAM, 2,138 not treated with LAM) was reported from Japan [9]. 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 about HIV, and this trend should be further encouraged considering the absence of an effective vaccination for either HCV or HIV.

Secondary Prevention by Treatment of Chronic Hepatitis C

The effect of IFN therapy on HCC incidence in non-cirrhotic patients has been evaluated in non-randomized studies. All studies agree that the risk is reduced in patients who show sustained virologic response or persistent normalization of serum ALT levels [10–13]. Although documentation is rather scarce, the combination with ribavirin will produce a stronger effect on HCC prevention among overall treated patients [14].

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. Since carcinogenesis occurs in some cases of liver cirrhosis associated with non-alcoholic steatohepatitis, alcoholic liver disease, primary biliary cirrhosis and autoimmune hepatitis, the course of the disease should be followed with 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, patients with chronic hepatitis B and C and non-viral liver cirrhosis are defined as high-risk populations for HCC in both the Evidence-Based Practice Guidelines [15] proposed by the Japan Society of Hepatology and the Consensus-Based Clinical Practice Manual [16] in Japan and Practice Guidelines published by the American Association of Study of the Liver (AASLD) [17]. Patients with liver cirrhosis types B and C are defined as a super-high-risk population [15, 16].

Surveillance Protocol for Early Detection of HCC

No clear evidence is available to determine the optimal interval for periodic screening, but HCCs detected in pe-

riodic 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, as compared to those detected in symptomatic patients. Thus, the Japanese Evidence-Based Clinical Practice Guidelines [15] and Consensus-Based Clinical Practice Manual [16] propose ultrasonography and tumor marker measurements every 3–4 months in the super-high-risk population and every 6 months in high-risk populations.

Result of Early Detection of HCC in Japan

In Japan, approximately 65% of the patients are detected in an early stage, for which curative treatment intervention is possible according to the nationwide survey in 198,000 patients [18]. This can be attributed to the establishment of a nationwide surveillance system all over the Japan.

Newly Introduced Diagnostic Techniques

Contrast-Enhanced US (CEUS) with a New Contrast Agent, Sonazoid

Clinical Significance of CEUS

Sonazoid is a newly introduced second-generation ultrasound 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 low acoustic power and stable Kupffer phase imaging, tolerable for multiple scanning from 10 to 120 min after its injection [19], which resulted 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.

Development of Defect Reperfusion Imaging (Dual-Phase Fusion Imaging)

We recently developed defect reperfusion imaging [20–22] 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 [21]. Until recently, diagnosis in dynamic studies is usually based on enhancing patterns according to a time sequence or phase; however, by introducing the novel idea of dual-phase imaging with the re-injection 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: re-injection of Sonazoid is performed into areas that show defects in the post-vascular phase [19–22]. The introduction of this method has led to dramatic solutions of many limitations in the diagnosis and treatment of HCC, such as detection of small HCCs [23], evaluation of treatment response [24], or needle insertion guidance [25]. The detection rate of small HCCs by Sonazoid-enhanced US is even more sensitive than that by MDCT [23].

MRI Using a New Contrast Agent, Gd-EOB-DTPA, 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 to diagnose cases which would have been difficult using previous techniques such as dynamic MRI or SPIO-MRI.

In well-differentiated early HCC, some nodules may not be completely shown as a defective area on CTAP, but 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 hypointense nodule using Gd-EOB-DTPA MRI in many early HCC cases due to differences in the biological characteristics, indicating that this contrast agent may lead to a breakthrough in the diagnosis of early HCC [26, 27], which has been clinically difficult and difficult even by pathological diagnosis when 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.

Therefore, diagnostic algorithm will be changed by introducing Gd-EOB-DTPA MRI in hyper- and hypovascular liver nodules [28, 29].

Value of an Integrated Staging System

The staging system integrating the TNM and liver damage stage is very important. Various staging systems, such as (1) Okuda stage, (2) BCLC stage [30, 31], (3) CLIP

score [32], (4) JIS score [33, 34], and (5) Tokyo score [35] have been proposed and used in different regions of the world. The JIS score, utilizing both the LCSGJ TNM [36] and Child-Pugh stages, is considered to be the most useful for integrated staging of HCC in Japan. In contrast, the CLIP score has several disadvantages: specification of the tumor-spreading degree is rough, only AFP is used as a biological malignancy marker, and stratification ability is also poor in advanced cases (many cases cluster to a score of 0–2). By contrast, the JIS score is superior for score stratification.

Hepatic Arterial Infusion Chemotherapy for Advanced HCC

No effective anticancer drug for advanced liver cancer had been demonstrated before sorafenib was introduced [37]. '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 (5-FU and cisplatinum) [38] therapy and hepatic arterial infusion of 5-FU in combination with IFN treatment [39] were established as an effective treatment option in Japan. In fact, response rate (CR + PR) reaches 45.9% according to the Nationwide Survey by LCSGJ [18]. In addition, it is well established that overall survival of the responder is definitely better than the non-responder or best supportive care group. However, the intra-arterial infusion procedure is complex because establishment of a reservoir port for arterial infusion is necessary; therefore, this technique is not performed in Western countries.

Hepatic intra-arterial infusion chemotherapy is not recommended in the AASLD guidelines [17]; therefore, although the response rate is high, the efficacy of especially survival benefit of intra-arterial infusion chemotherapy and that using an intractable delivery port system should be confirmed by further randomized studies.

New Treatment Option: Molecular Targeted Agent, Sorafenib

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 c-Raf, the wild-type, and V600E mutant b-Raf, but also 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, Fms-related tyrosine kinase-3 (Flt-3), and c-Kit.

The positive results of a phase III study for HCC (SHARP trial) [40] gave a strong impact on 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 endpoints were overall survival. The secondary endpoints were 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 countries and Japan, respectively. The SILIUS trial using sorafenib in combination with hepatic arterial infusion chemotherapy is under investigation in Japan. Furthermore, head-to-head trials of sunitinib versus sorafenib and brivanib versus sorafenib for advanced HCC are ongoing globally. Finally, a second-line trial of brivanib for the sorafenib failure is also ongoing as a global clinical trial [29]. These trial results are awaited to bring better outcomes for different stages of HCC. If positive results are obtained by these clinical trials, the life expectancy in each stage is expected to be considerably prolonged if a theoretical calculation using the hazard ratio on overall survival is incorporated from the SHARP trial [29].

In Japan, although a phase III study in HCC patients following TACE was revealed to be a negative study [41], an investigator-sponsored trial of investigating efficacy and tolerability of a combination of TACE with sorafenib is underway. In addition, a phase III trial for HCC of acyclic retinoid, a vitamin A analog, after resection or RFA has been completed and will be presented at the American Society of Clinical Oncology Meeting, 2010.

A global phase III trial of sorafenib as an adjuvant therapy after surgery or ablation is now ongoing (STORM trial) and a global phase II trial of sorafenib as a maintenance therapy with a combination of TACE is also ongoing (SPACE trial). These results are awaited to

confirm its usefulness in daily clinical practice. A paradigm shift in HCC treatment may be induced if the positive results are obtained by these currently ongoing sorafenib trials.

Conclusion

Recent progress in the management of HCC, including issues from prevention to molecular targeted therapy for HCC, has been discussed at this symposium. It is strongly expected that this supplement issue will enhance the most up-to-date knowledge on HCC of the readers of *Oncology*.

Disclosure Statement

The author declares that he has no financial conflict of interest.

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Hepatic Arterial Infusion Chemotherapy Using Low-Dose 5-Fluorouracil and Cisplatin for Advanced Hepatocellular Carcinoma

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Key Words
Hepatocellular carcinoma · Hepatic arterial infusion chemotherapy · Cisplatin · 5-Fluorouracil · Low-dose FP

Abstract
Background: Although hepatic arterial infusion chemotherapy (HAIC) using low-dose 5-fluorouracil (5-FU) and cisplatin (low-dose FP) is commonly used for advanced hepatocellular carcinoma (HCC) with vascular invasion in Japan, few reports have investigated the efficacy and safety of this approach. We investigated the efficacy and toxicity of HAIC using low-dose FP for patients with advanced HCC as a phase II trial. ***Methods:*** Low-dose FP consisted of a continuous arterial infusion of 5-FU (250–500 mg/day, 5 days/week, for the first 2 weeks) and cisplatin (10 mg/day, 5 days/week, for the first 2 weeks). Then, 5-FU (1,000 mg/body for 5 h) and cisplatin (10 mg/body) were administered once weekly. ***Results:*** In these patients treated with low-dose FP, the response rate was 38.5%, the median time to progression was 4.1 months (95% CI 2.1–6.1 months) and the median survival time was 15.9 months (95% CI 9.8–22.0 months). The most frequent adverse events were myelosuppression such as neutropenia or thrombocytopenia. ***Conclusions:*** HAIC using low-dose FP is an effective treatment option for locally advanced HCC. However, it is not well tolerated hematologically because of potent pancytopenia and poor hepatic reserve. Therefore, this regimen should be performed carefully with regular monitoring of hematological function.

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies in Japan and the fifth most common cancer worldwide [1–3]. It was established in Japan that surveillance of high-risk groups, such as patients with hepatitis C virus (HCV) or hepatitis B virus (HBV), can enable the detection of HCC in the early stage. However, about 10% of patients with HCC are still detected in advanced stages [4]. In the early stage, HCC is treatable by standard therapies such as hepatic resection, radiofrequency ablation (RFA) and transcatheter arterial chemoembolization (TACE). Interferon therapy improves the prognosis of patients who are curatively treated by hepatic resection or RFA [5–9]. However, many patients require repeated treatment, and the standard therapies may not be effective in such patients. In the intermediate stage, TACE is considered to be the standard treatment, but TACE is often not curative and is commonly repeated. Moreover, TACE is contraindicated in patients with HCC

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that has progressed into the portal vein, particularly the main trunk. In such cases, hepatic arterial infusion chemotherapy (HAIC) using low-dose 5-fluorouracil (5-FU) and cisplatin (low-dose FP) is often selected. HAIC has been established as a treatment option in Japan. However, there is little evidence of the efficacy of this method. Therefore, we performed a phase II trial to investigate the efficacy and toxicity of low-dose FP for patients with advanced HCC.

Materials and Methods

Patients

Fifty-two patients with advanced HCC, who were admitted to the Department of Gastroenterology and Hepatology, Kinki University School of Medicine, were enrolled in the current study between April 2004 and August 2006. Advanced HCC was considered as the presence of a portal vein tumor thrombus or HCC refractory to TACE. Written informed consent was obtained from each participant after explaining the advantages and risks of HAIC using low-dose FP.

Eligibility Criteria

The eligibility criteria of this therapy were as follows: (1) advanced HCC, which was uncontrollable with standard treatment such as TACE, or HCC with vascular invasion; (2) age under 80 years; (3) Eastern Cooperative Group performance status of 0 or 1; (4) Child-Pugh grade A or B; (5) encephalopathy degree 0; (6) leukocyte count >2,000 cells/mm^3, hemoglobin level >10 g/dl, platelet count >75,000 cells/mm^3; (7) serum creatinine <1.5 mg/dl, and (8) serum total bilirubin level <3.0 mg/dl.

HAIC was performed in cases in which the intrahepatic tumor threatened the patient's life, even in the presence of extrahepatic spread.

Catheter Placement

Angiography was performed from the right femoral artery using the Seldinger technique. Arteriography of the celiac trunk and the superior mesenteric artery was performed to detect HCC and its feeding artery, and arterioportography via the superior mesenteric artery was performed to evaluate the portal vein patency. To avoid gastrointestinal mucosal injury due to anticancer agents, arteries supplying the gastrointestinal tract were embolized by the metallic coils. A 5-Fr heparin-coated catheter was placed and the tip of the catheter was located in the gastroduodenal artery and fixed by the metallic coils. The side hole of the catheter was located at the common hepatic artery (GDA-fixed method) [10]. Another tip of the catheter was connected to the injection port system and implanted in a subcutaneous pocket in the right inguinal part in front of the femoral region.

Treatment

Cisplatin and 5-FU were administered via the implanted port system. 5-FU was administered continuously using an ambulatory balloon infusion pump (LV2; Baxter, Chicago, Ill., USA) at a dose of 250–500 mg/day for 5 days/week for the first 2 weeks. Cisplatin was administered manually at the dose of 10 mg/day for 5 days/week for the first 2 weeks (fig. 1). The dose of these drugs was reduced according to hepatic reserve. To prevent emesis caused by cisplatin, 5-HT3 antagonists were given. After 2 weeks, the dose of cisplatin was changed to 10 mg/body and 5-FU was administered using an ambulatory balloon infusion pump (LV50; Baxter) at the dose of 1,000 mg/body for 5 h every week until HCC progressed (requiring a change in treatment) or an unacceptable adverse event occurred.

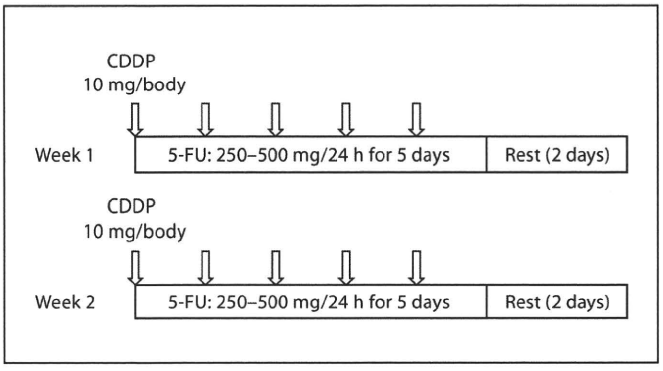

Fig. 1. Schedule of the low-dose FP during the first 2 weeks.

Evaluation and Statistical Analysis

Response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) [11] every 2 months on treatment. The overall survival time was calculated from the date of initiation of this therapy to the date of any cause or confirmed survival. The time to progression was calculated from the date of initiation of this therapy to the date of radiological progression. The overall survival and time to progression were analyzed using the Kaplan-Meier method. Statistical analysis was conducted using SPSS version 11.5.1 for Windows. Toxicity was assessed according to the Common Terminology Criteria for Adverse Events v3.0 (CTCAE) [12].

Results

Table 1 summarizes the clinical profiles of the 52 patients (46 males, 6 females) treated with low-dose FP. The mean age was 61.3 years (range 30–79; median age 63.5 years old). The numbers of patients at United International Consensus Committee (UICC) stages III, IVA and IVB were 10, 36 and 6, respectively. The number of patients at American Joint Committee of Cancer (AJCC) [13] stages II, IIIA, IIIB and IV were 9, 37, 2 and 4, respectively. Three patients were at an intermediate stage and 49 at an advanced stage based on Barcelona Clinic Liver Cancer (BCLC) [14] grading. Forty-two patients had macroscopic vascular invasion, including portal vein thrombosis. Four patients had extrahepatic spread including bone metasta-

Table 1. Patient characteristics

Age		61.3 (30–79)
Sex	male/female	46/6
Stage (UICC)	III/IVA/IVB	10/36/6
Stage (AJCC)	II/IIIA/IIIB/IV	9/37/2/4
Stage (BCLC)	B (intermediate)/ C (advanced)	3/49
MVI	yes/no	42/10
EHS	yes/no	4/48
Cause of disease	HBV/HCV/NBNC/ HBV+HCV	12/30/9/1
Child-Pugh class	A/B	38/14
ALB, g/dl	median (range)	3.5 (2.7–4.8)
BIL, mg/dl	median (range)	1.0 (0.3–2.5)
PT, %	median (range)	81.5 (48.3–120.0)

UICC = United International Consensus Committee; AJCC = American Joint Committee of Cancer; BCLC = Barcelona Clinic Liver Cancer; MVI = macroscopic vascular invasion; EHS = extrahepatic spread; NBNC = not infected with HBV and HCV.

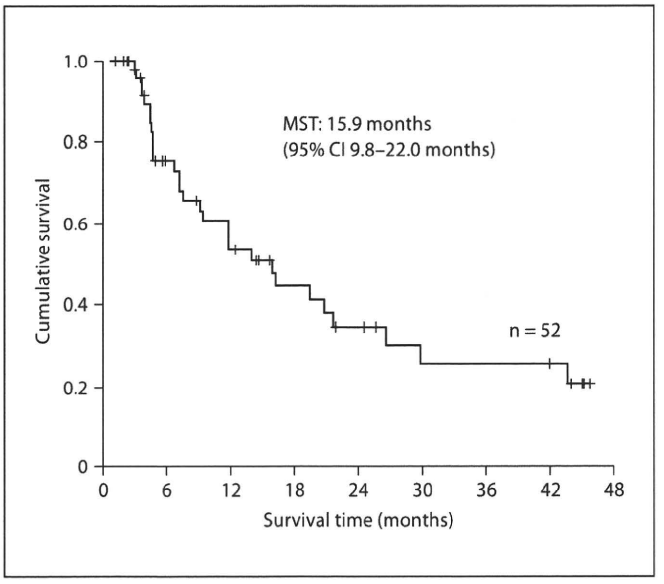

Fig. 2. Kaplan-Meier analysis of overall survival of 52 patients treated by HAIC with low-dose FP.

ses or lung metastases. Twelve patients were infected with HBV, 30 were infected with HCV, 9 were not infected with either HBV or HCV, and 1 was infected with HBV and HCV. Overall, 38 patients were at Child-Pugh grade A and 14 at Child-Pugh grade B.

Three patients (5.8%) withdrew during follow-up on their own accord and were not evaluated; therefore, tumor response could be assessed in 49 of 52 patients. In the intent-to-treat analysis (comprising all treated patients), 4 of 52 patients (7.7%) achieved complete response (CR) and 16 (30.8%) achieved partial response (PR). Stable disease (SD) was observed in 14 patients (26.9%) and progressive disease (PD) was observed in 15 patients (28.8%). Therefore, the objective response rate was 38.5%. The disease control rate (CR + PR + SD) was 65.4%.

The cumulative survival rate of the 52 patients is shown in figure 2. The 1-, 2- and 3-year cumulative survival rates were 53.3, 34.8, and 26.1%, respectively. The median survival time was 15.9 months (95% CI 9.8–22.0 months). The patients with PR or CR had a median survival of 40.7 months (95% CI 11.3–70.1), whereas the patients with SD or PD had a median survival of 6.8 months (95% CI 5.6–8.0 months). The overall survival (OS) of the patients with PR or CR was significantly longer than that of patients with SD or PD (median OS: 40.7 vs. 6.8 months; $p < 0.0001$) (fig. 3). The median time to progression was 4.1 months (95% CI 2.8–5.2 months) (fig. 4).

Adverse Effects

The treatment-related adverse effect was assessed in two categories: events potentially related to the anticancer agent and events potentially related to the implanted catheter system. The events related to the antitumor agent are summarized in table 2. Hematologic toxicities, including leukopenia, neutropenia, anemia, and thrombocytopenia, were relatively severe. Grade 3 leukocytopenia, neutropenia, anemia and thrombocytopenia were observed in 10 (19.2%), 12 (23.1%), 5 (9.6%), and 22 (42.3%) patients, respectively. Grade 4 thrombocytopenia without any associated bleeding event was observed in 2 patients (3.8%); 1 of these patients required thrombocyte transfusion. Grade 3 hyperbilirubinemia was observed in 7 patients (13.5%). These toxicities were improved by discontinuing the treatment or reducing the dose of anticancer agents. Non-hematological events were mild and well tolerated. Grade 1 anorexia, fatigue, mucositis and diarrhea were often observed. These events were managed by symptomatic therapy without discontinuing the treatment.

In terms of implanted catheter system-related complications, obstruction of the hepatic artery was observed in 1 patient. Anticoagulation therapy was performed but the obstruction did not improve. No infection of the catheter system was observed. No treatment-related deaths were observed.