Treatment strategies for advanced hepatocellular carcinoma: Sorafenib vs hepatic arterial infusion chemotherapy

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Abstract

Sorafenib is used worldwide as a first-line standard...
systemic agent for advanced hepatocellular carcinoma (HCC) on the basis of the results of two large-scale Phase III trials. Conversely, hepatic arterial infusion chemotherapy (HAIC) is one of the most recommended treatments in Japan. Although there have been no randomized controlled trials comparing sorafenib with HAIC, several retrospective analyses have shown no significant differences in survival between the two therapies. Outcomes are favorable for HCC patients exhibiting macroscopic vascular invasion when treated with HAIC rather than sorafenib, whereas in HCC patients exhibiting extrahepatic spread or resistance to transcatheter arterial chemomobilization, good outcomes are achieved by treatment with sorafenib rather than HAIC. Additionally, sorafenib is generally used to treat patients with Child-Pugh A, whereas HAIC is indicated for those with either Child-Pugh A or B. Based on these findings, we reviewed treatment strategies for advanced HCC. We propose that sorafenib might be used as a first-line treatment for advanced HCC patients without macroscopic vascular invasion or Child-Pugh A, while HAIC is recommended for those with macroscopic vascular invasion or Child-Pugh A or B. Additional research is required to determine the best second-line treatment for HAIC non-responders with Child-Pugh B through future clinical trials.

Key words: Treatment strategy; Hepatic arterial infusion chemotherapy; Sorafenib; Hepatocellular carcinoma

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GUIDELINES FOR ADVANCED HCC

The results of the global investigation of therapeutic decisions in HCC and of its treatment with sorafenib (GIDEON) study show differences in the management of HCC, including diagnosis, treatment, and monitoring, among several regions. In consequence, there have been regional differences in patient outcomes[3,4]. Although several guidelines for the clinical management of HCC have been established worldwide, there are some differences in the treatment algorithms among these guidelines. Table 1 shows the major recent guidelines from Asia, Europe and the United States[6-13]. The Barcelona clinic liver cancer (BCLC) staging system, which stratifies patients by tumor stage and underlying liver disease, is widely accepted in clinical practice[14]. Among the five HCC stages (BCLC 0, A, B, C and D), the advanced BCLC C stage includes symptomatic patients with performance status (PS) 1-2, vascular invasion, extrahepatic spread, or a combination thereof[15]. For patients with BCLC C and good liver function (Child-Pugh A), sorafenib is the preferred first-line treatment according to guidelines from Europe and the United States[11-13]. According to guidelines from Asia[7-9], systemic therapy (molecular-targeted drugs) or transcatheter arterial chemoembolization (TACE) is recommended as standard treatment for such patients. However, HAIC is not generally recommended as a standard of care in the above-mentioned guidelines.

Whereas sorafenib and HAIC are indicated for the patients with minor portal vein invasion (so-called Vp1, 2) or portal invasion at the first portal branch (so-called Vp3) in the Japan Society of Hepatology and Liver Cancer Study Group of Japan (JSH-LCSGJ) Consensus-based Treatment Algorithm for HCC revised in 2014, HAIC, but not sorafenib, is recommended for portal invasion at the main trunk of the portal vein (so-called Vp4)[9]. Fur-
Currently, according to the most recent version (2017) of the Clinical Practice Guidelines for HCC proposed by JSH, TACE, resection, HAIC, and molecular-targeted agents are equally recommended for HCC patients with portal invasion. It has also been argued that the treatment should be selected after considering all of the patient's conditions as a whole[10].

Finally, the 2017 version of the National Comprehensive Cancer Network (NCCN) Guidelines supports HAIC for unresectable HCC; however, its use in the context of a clinical trial is preferred[15].

**SORAFENIB FOR ADVANCED HCC**

**Current status of sorafenib**

Sorafenib is an oral multi-targeted kinase inhibitor that suppresses tumor growth, and it was the first drug to demonstrate a survival benefit in patients with advanced HCC. In two large-scale Phase III trials, although the response rate of sorafenib was only 2%-3.3% according to the Response Evaluation Criteria in Solid Tumors (RECIST), sorafenib treatment significantly improved overall survival (OS) [sorafenib vs placebo median survival time (MST): 10.7 mo vs 7.9 mo, hazard ratio (HR): 0.69, P < 0.001 in the SHARP trial; and MST: 6.5 mo vs 4.2 mo, HR: 0.68, P = 0.014 in the Asia-Pacific trial] and the time-to-progression (TTP) (sorafenib vs placebo TTP: 5.5 mo vs 2.8 mo, HR: 0.58, P < 0.001 in the SHARP trial; and TTP: 2.8 mo vs 1.4 mo, HR: 0.57, P = 0.0005 in the Asia-Pacific trial) in patients with advanced HCC[16,17]. Therefore, sorafenib is utilized as a standard first line agent for the treatment of advanced HCC worldwide[6-13]. Recently, Rimola et al[18] reported that 1% of patients treated with sorafenib (12/119) exhibited complete response (CR), according to RECIST, and the MST for those patients was 85.8 mo.

For several years, antiangiogenic tyrosine-kinase inhibitors other than sorafenib have failed in Phase III clinical trials[19,20]. However, recent studies have demonstrated the efficacy of two oral multi-kinase inhibitors, the second-line agent regorafenib, which is used for sorafenib-resistant HCC, and the first-line agent lenvatinib, which has been shown to be non-inferior to sorafenib for OS[21,22].

Regorafenib has been reported as a second-line agent following sorafenib because of improvement in OS (regorafenib vs placebo MST: 10.6 mo vs 7.8 mo, HR: 0.63, P < 0.0001) (RESORCE trial)[21]. According to the results of this study, regorafenib was approved in the United States and Japan in 2017.

Lenvatinib is an oral multi-target inhibitor of vascular endothelial growth factor (VEGF) receptors 1-3, fibroblast growth factor receptors 1-4, platelet-derived growth factor receptor alpha, KIT, and RET[23]. A comparative global Phase III trial of lenvatinib in the first-line setting (REFLECT trial) demonstrated non-inferiority to sorafenib in advanced HCC patients (lenvatinib vs sorafenib MST: 13.6 mo vs 12.3 mo, HR: 0.92)[22]. In addition, the progression-free survival (PFS), TTP, and overall response rate (ORR) were significantly better in patients treated with lenvatinib than in those treated with sorafenib (lenvatinib vs sorafenib, median PFS: 7.4 mo vs 3.7 mo, HR: 0.66, P < 0.0001; median TTP: 8.9 mo vs 3.7 mo, HR 0.63, P < 0.0001; ORR: 24.1% vs 9.2%, P < 0.0001). Lenvatinib is approved for unresectable thyroid cancer and has been usable for HCC in Japan prior to it being approved in the rest of the world. However, HCC patients with 50% or higher liver occupation, bile duct invasion, or main portal invasion met the exclusion criteria of the REFLECT trial. Such HCC patients may be candidates for general usage of sorafenib.

**Predictive factors for response and survival**

Bruix et al[24] conducted analyses of two large trials...
(827 patients, SHARP and Asia-Pacific trials) and reported prognostic factors. According to this report, vascular invasion, high alpha-fetoprotein (AFP), and high neutrophil-lymphocyte ratio (NLR) were prognostic factors for poorer OS, while lack of extrahepatic spread, HCV, and low NLR were predictive factors for greater sorafenib benefit. Among serum and plasma factors, VEGF [25-27], angioptiogen-2 (Ang-2) [25,26], AFP [25,26,28-31], NLR [32,33], TIE-2 expressing monocytes (TEMs) [34], microRNA [35-37], and circulating tumor cells (CTCs) [38] have been identified as potential biomarkers (Table 2). The expression of phospho-ERK [39-41], phospho-c-Jun [42], and VEGFR-2 [43], and amplification of FGF3/FGF4 [43], have been identified as possible predictive biomarkers in tissues (Table 3). In studies of imaging biomarkers, it has been reported that decreased blood flow after sorafenib treatment [44] and low pretreatment standardized uptake values of 18F-Fluorodeoxyglucose (FDG) in positron emission tomography (PET) [45] are associated with prolonged OS. Although there have been several reports of a correlation between adverse effects (hypertension, skin toxicity, diarrhea, etc.) and sorafenib efficacy, it has been difficult to establish conclusions because of difference in the frequencies of these adverse effects among patients of different races. However, Howell et al. [46] reported that patients with sorafenib-related toxicity such as diarrhea, hypertension, and hand-foot syndrome, had good prognoses in a large, multicenter prospective cohort study. Furthermore, the potential of other biomarkers has been explored [47]. Although several studies have investigated predictive biomarkers for response and survival associated with sorafenib, no such biomarkers have been established.

HAIC FOR ADVANCED HCC

Current status of HAIC

In HAIC, as it is theoretically possible to accumulate local concentrations of anti-cancer drugs in the liver and to reduce their systemic distribution, it is believed to have a stronger antitumor effect and lower incidence of adverse reactions compared with systemic chemotherapy. On the other hand, one disadvantage is the need to master the HAIC procedure, and several adverse effects are associated with HAIC including inflammation of blood vessels, arterial obstructions, peptic ulcers due to drug leakage, and infections or obstructions of reservoir catheters.

According to the 2017 version of the treatment algorithm for HCC produced by JSH [10], HAIC is recommended as a second-line treatment for patients with ≥4 HCCs and an absence of portal invasion, while HAIC is considered a first-line treatment for those with portal invasion.

HAIC has become widely used in Asia, especially Japan, where the main HAIC regimens are low-dose cisplatin (CDDP) combined with 5-fluorouracil (5-FU) (low-dose FP) [48-51], interferon (IFN) in combination with 5-FU (FAIT) [50,52,53], and CDDP alone [51,54-56] (Table 4). In both low-dose FP and FAIT regimens, the key drug is 5-FU. In addition, CDDP or IFN exert their own effects to amplify the effect of 5-FU, and they are therefore considered biochemical modulators of 5-FU. Moreover, one benefit of the CDDP alone regimen is that a catheter is inserted each time, making the troublesome implantation of a reservoir catheter unnecessary. The regimens using low-dose FP or FAIT have response rates of approximately 30%-40%, while the CDDP alone regimen has rates of approximately 20%-30% (Table 4) [58-51,55-57]. Survival is significantly better in patients with radiological response (CR or partial response (PR)) (so-called responders) than in patients with radiological no-response (stable or progressive disease) (so-called non-responders).

The principal reasons for low clinical recognition of HAIC are the small sample size of almost all studies and the lack of large randomized trials. However, effective results have been demonstrated by previous studies. In a report comparing the FAIT regimen of HAIC with historical controls, HAIC was shown to significantly improve survival [62]. A Japanese nationwide survey supported the efficacy of the low-dose FP regimen of HAIC for treating advanced HCC [69]. After adjusting for known risk factors, survival benefits of this therapy were evident (HR: 0.48, 95%CI: 0.41-0.56, P < 0.0001). In a propensity score-matched analysis, the MST was longer in patients who received HAIC (n = 341, 14.0 mo) than in those who did not receive active treatment (n = 341, 5.2 mo) (HR: 0.60, 95%CI: 0.49-0.73, P < 0.0001). In cases of Child-Pugh A or B disease with more than three tumors (370 propensity score-matched patients), the MST was longer in patients treated with HAIC (13.9 mo) than in those with no therapy (3.7 mo) (P < 0.0001). In cases of Child-Pugh A or B disease with portal vein tumor thrombus (378 propensity score-matched patients), the MST was also longer in patients treated with HAIC (7.9 mo) than in those with no therapy (3.1 mo) (P < 0.0001).

Predictive factors for response and survival

As HAIC is selected for advanced HCC patients with poor prognoses, it is important to identify predictive factors for response and survival (Table 5) [48,49,53,58-61].

The predictive factors for poor response to HAIC include the presence of vascular invasion [59], the presence of extrahepatic metastasis [58], NLR ≥ 2.87 [58], a concentration of serum VEGF ≥ 100 pg/mL [60], a negative HCV antibody test result [61], and a platelet count ≥ 15 × 10^9/μL [61], and a negative des-gamma-carboxy prothrombin (DCP) response (defined as a reduction of < 20% or an increase from baseline after a half course of HAIC (2 wks)) [60].

Survival benefits for HAIC have been reported in HAIC responders [53,60,61]. However, therapeutic effect is not an effective prognostic predictor. The poor prognostic predictors include not only tumor-associated factors,
such as more than three tumors, large tumors (> 3 cm), the presence of vascular invasion, the presence of extrahepatic metastasis and high AFP levels, but also those associated with the patient, including dysfunction of the liver reserve, ECOG PS 1-2, and a positive HBs antigen test result.

Additionally, poor prognostic predictors include negative responses of AFP or DCP, high levels of inflammation-related markers such as NLR and CRP, low transferrin levels (< 190 mg/dL) and high VEGF levels (≥ 100 pg/mL).

A new assessment score: Assessment for continuous treatment with HAIC

It is important to identify the effective benefit of early HAIC treatment in HCC patients. Therefore, we developed a new therapeutic assessment score to guide decisions regarding HAIC treatment, the Assessment for Continuous Treatment with HAIC (ACTH). The ACTH score (range, 0-3) is calculated from simple three parameters: Child-Pugh score before HAIC (A = 0, B = 1), AFP response (yes = 0, no = 1), and DCP response (yes = 0, no = 1). The tumor markers’ responses are

Table 2  Serum and plasma biomarkers of sorafenib response and survival

| Biomarkers | Ref. | Publishing year | Case number | Predictive factors for response | Predictive factors for survival | Others |
|------------|------|----------------|-------------|---------------------------------|--------------------------------|--------|
| VEGF      | Llovet et al[25] | 2012       | 299         | No predictive value             | Not prognostic value           |        |
|           | Miyahara et al[26] | 2013       | 120         | No predictive value             | Not prognostic value           |        |
|           | Tsuchya et al[27] | 2014       | 63          | No predictive value             | VEGF response (a > 5% decrease during 8 wk of treatment): Better OS |        |
| Ang-2     | Llovet et al[25] | 2012       | 299         | No predictive value             | Low Ang-2: Better OS           |        |
|           | Miyahara et al[26] | 2013       | 120         | High Ang2: PD                   | Low Ang-2: Better OS           |        |
| Changes of AFP | Personeni et al[28] | 2012       | 85          | AFP response (a > 20% decrease during 8 wk of treatment): Better ORR, DCR | AFP response: Better OS |        |
|           | Yau et al[29] | 2011       | 94          | AFP response (a > 20% decrease during 6 wk of treatment): Better DCR | AFP response: Better PFS |        |
|           | Kuzuya et al[30] | 2015       | 47          | High AFP ratio (a > 1.2 at 2 wk relative to baseline): Poor OS | High poor prognostic score (the absence of disappearance of arterial tumor enhancement on CE-CT, AFP ratio of > 1.2, and two or more increments in CP score after 2 wk of Treatment): Poor OS and DCR |        |
|           | Nakazawa et al[31] | 2013       | 59          | AFP increase (more than 20% from baseline during 4 wk of treatment): PD | AFP increase: Better OS and PFS |        |
|           | Llovet et al[25] | 2012       | 299         | -                               | AFP > 200 ng/mL: Poor OS       |        |
|           | Miyahara et al[26] | 2013       | 120         | -                               | Not prognostic value           |        |
|           | Kuzuya et al[30] | 2015       | 47          | -                               | Not prognostic value           |        |
| NLR       | Zheng et al[32] | 2013       | 65          | -                               | High NLR (> 4): Poor OS and TTP |        |
| Howell et al[33] | 2017       | 175         | -           | High NLR (> 2.5): Poor OS       |        |
| TEMs      | Shoji et al[34] | 2017       | 25          | High ΔTEMs (changes in TEMs before and at 1 mo after therapy): PD | High ΔTEMs (changes in TEMs before and at 1 mo after therapy): Poor OS |        |
|           | Howell et al[34] | 2017       | 175         | -                               | High ΔTEMs (changes in TEMs before and at 1 mo after therapy): Poor OS |        |
| MicroRNA  | Stiuso et al[35] | 2015       | 39          | Upregulation of miR-423-5p after treatment: SD or PR | -                               |        |
|           | Yoon et al[36] | 2017       | 24          | Low miR-10b-3p: Poor OS         |        |
|           | Nishida et al[37] | 2017       | 53          | High miR-181a-5p: PR + SD       | High miR-181a-5p: Better OS    |        |
| CTCs      | Li et al[38] | 2016       | 59          | pERK+/pAkt- CTCs: Better DCR    | pERK+/pAkt- CTCs: Better DCR   |        |

Ang-2: Angiopoietin-2; CE-CT: Contrast-enhanced computed tomography; NLR: Neutrophil-to lymphocyte ratio; AFP: Alpha-fetoprotein; CTC: Circulating tumor cells; TEMs: TIE-2-expression monocytes; VEGF: Vascular endothelial growth factor; PD: Progressive disease; OS: Overall survival; DCR: Disease control rate; ORR: Overall response rate; PFS: Progression-free survival; CP: Child-Pugh; pERK: Phosphorylated extracellular signal-regulated kinase; PR: Partial response; SD: Stable disease; TTP: Time to progression.

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assessed as the difference between the baseline and 2 wk after HAIC induction (positive response: A reduction of ≥ 20% from the baseline). ACTH score could stratify patients’ survival (score ≤ 1 vs score ≥ 2, 15.1 mo vs 8.7 mo; P = 0.003)\(^\text{[48]}\). A validation study similarity showed that this score is useful for therapeutic assessment\(^{[62]}\). Therefore, the ACTH score makes it possible to provide an early prediction of the prognosis of advanced HCC patients receiving HAIC, and can improve treatment efficiency by switching to other treatments, such as sorafenib or an experimental treatment in a clinical trial, for patients with a score ≥ 2 (Figure 1).

**Modified HAIC and the combination approach**

Nagamatsu et al\(^{[63]}\) developed a modified procedure for administering a low-dose FP regimen: HAIC using 5-FU after lipiodol-transcatheter arterial infusion chemotherapy (Lip-TAI) with CDDP; a multicenter phase II study showed that the MST and response rate were 27.0 mo and 75% for advanced HCC patients with portal vein thrombosis, respectively\(^{[64]}\). Although this regimen produced a favorable outcome, it has not become widespread owing to the high level of proficiency needed for the procedure.

A multicenter open-labeled randomized Phase II trial was conducted to evaluate the effect of combining the CDDP regimen of HAIC with sorafenib for treating advanced HCC. The results showed that survival was significantly better for patients receiving sorafenib plus HAIC (MST, 10.6 mo) than those receiving sorafenib alone (MST, 8.7 mo) (HR: 0.60, \(P = 0.031\))\(^{[65]}\); however, there was not a significant difference in survival between patients receiving sorafenib plus HAIC using low-dose FP and those receiving sorafenib alone\(^{[66]}\). Therefore, further investigation is required.

Radiotherapy (RT) has become recognized as an optional treatment for HCC in the APASL and NCCN guidelines\(^{[6,15]}\), but it is not recommended in the AASLD and EASL guidelines\(^{[11,13]}\). For advanced HCC patients with intravascular tumor thrombus, a combination of HAIC with RT is a reasonable approach. Compared to HAIC alone, a beneficial effect of 3-D conformal radiotherapy (3D-CRT) for major portal vein tumor thrombosis combined with HAIC has been demonstrated, although these results came from retrospective cohort studies\(^{[67,68]}\).

**SORAFENIB VS HAIC**

Sorafenib is recommended as a first-line treatment worldwide for advanced HCC patients (those with

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**Table 3** Tissue biomarkers of sorafenib response and survival

| Biomarkers                  | Ref.         | Publishing year | Case number | Predictive factors for response | Predictive factors for survival |
|-----------------------------|--------------|-----------------|-------------|---------------------------------|---------------------------------|
| Expression of p-ERK         | Aboou-Elfa et al\(^{[44]}\) | 2012            | 33          | -                               | High pERK: Longer TTP           |
|                            | Chen et al\(^{[44]}\)          | 2013            | 54          | -                               | High pERK: Longer TTP           |
|                            | Negri et al\(^{[41]}\)         | 2015            | 77          | -                               | High pERK: Shorter OS and PFS   |
| Expression of p-c-Jun      | Hagiwara et al\(^{[41]}\)      | 2012            | 39          | High p-c-jun; Poor response     | High p-c-jun; Shorter TTP and OS|
| Expression of VEGFR-2      | Negri et al\(^{[41]}\)         | 2015            | 54          | -                               | High VEGFR-2: Shorter OS and PFS|
| FGFR3/FGF4 amplification   | Arao et al\(^{[38]}\)          | 2013            | 48          | FGF3/FGF4 amplification: Responder| -                               |

**Table 4** Regimens of hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma

| Ref.                        | Publishing year | Case number | Vascular invasion (%) | Regimens                        | Response rate (%) | Median survival time (mo) |
|-----------------------------|-----------------|-------------|-----------------------|---------------------------------|-------------------|--------------------------|
| Saeki et al\(^{[64]}\)      | 2015            | 90          | ND                    | Low-dose FP, including the combination of LV/IV or IV plus IFN | 34.4              | 10.6                     |
| Nousu et al\(^{[40]}\)      | 2013            | 476         | 44.1                  | CDDP + 5-FU                      | 40.5              | 14.0 (341 patients)      |
| Mondon et al\(^{[40]}\)     | 2012            | 34          | 90                    | IFNa, 5-FU                       | 26.7              | 8.4                      |
| Yamashita et al\(^{[40]}\)  | 2011            | 35          | 90.3                  | Low-dose FP/CDDP                 | 25.8              | 11.8                     |
| Nagano et al\(^{[40]}\)     | 2011            | 102         | 100                   | IFNa, CDDP, 5-FU                 | 45.6              | 17.6                     |
| Obi et al\(^{[40]}\)        | 2006            | 116         | 100                   | IFNa, 5-FU                       | 24.6              | 10.5                     |
| Ikeda et al\(^{[40]}\)      | 2013            | 25          | 100                   | CDDP powder (IA call)           | 28                | 7.6                      |
| Iwasa et al\(^{[40]}\)      | 2011            | 84          | 31                    | CDDP powder (IA call)           | 3.6               | 7.1                      |
| Kim et al\(^{[40]}\)        | 2011            | 41          | 83.3                  | CDDP                            | 12.2              | 7.5                      |
| Yoshikawa et al\(^{[40]}\)  | 2008            | 97          | 27.5                  | CDDP powder (IA call)           | 33.8              | ND                       |

ND: Not described; Low-dose FP: Low-dose 5-FU plus Cisplatin; LV: Leucovorin; IV: Isovorin; IFN: Interferon; CDDP: Cisplatin.

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ERK: Extracellular signal-regulated kinase; FGF: Fibroblast growth factor; TTP: Time to progression; OS: Overall survival; pERK: Phosphorylated extracellular signal-regulated kinase; PFS: Progressive-free survival; VEGFR: Vascular endothelial growth factor receptor.
Because of the low response rate to sorafenib, we suggest that maintaining the stability of HCC by suppressing tumor growth can significantly improve survival. Sorafenib therapy also worsens survival in patients with Child-Pugh B, unlike those with Child-Pugh A. Therefore, advanced HCC patients with Child-Pugh A are candidates for general usage of sorafenib.
Etiology

HCV

2970

62 mo

A (5)

HBV

233640

Hepatic

None

Tumor stage

III

Male

148 mo

IVA

A (5)

Cause of

γ

176 mo (dead)

120700

B (7)

None

7145

HCV

III

Male

CR

110

None

150

Low-dose FP

6.4

Vp4, Vv0

50

Vp3, Vv3

None

Therapeutic

260

151 mo (dead)

DCP (mAU/mL)

Low-dose FP

None

Larynx cancer

Male

Vp0, Vv0

Child-Pugh

Low-dose FP

68x781

Saeki I

Table 6  Clinical characteristics of three advanced hepatocellular carcinoma patients with complete response who have survived over 10 years

| Age diagnosed as HCC | Sex | Etiology | Child-Pugh | Tumor stage | Previous treatment | Maximum tumor size (mm) | Vascular invasion | Regimen | Therapeutic effect | AFP (ng/mL) | DCP (mAU/mL) | HCC recurrence | Prognosis | Cause of death |
|----------------------|-----|----------|------------|-------------|-------------------|------------------------|-----------------|---------|-------------------|--------------|---------------|----------------|-----------|----------------|
| 67                   | Male | HCV      | A (5)      | IVA         | None              | 110                    | Vp4, Vv0         | Low-dose FP+IV  | CR       | 120700            | 260          | 62 mo         | 151 mo (dead) | Hepatic failure |
| 66                   | Male | HCV      | A (5)      | III         | None              | 50                     | Vp0, Vv0         | Low-dose FP+IV  | CR       | 6.4               | 2970         | None          | 176 mo (dead) | Larynx cancer  |
| 44                   | Male | HBV      | B (7)      | III         | None              | 150                    | Vp3, Vv3         | Low-dose FP+IV+Peg IFN | CR       | 7.148             | 253640       | None          | 148 mo (alive) | -          |

1 According to the Liver Cancer Study Group of Japan; 2 The follow-up period ended on January 31, 2018. HCC: Hepatocellular carcinoma; AFP: Alpha-fetoprotein; DCP: Des-carboxyprothrombin; HCV: Hepatitis C virus; HBV: Hepatitis B virus; CR: Complete remission; Low-dose FP: Low-dose cisplatin combined with 5-FU; IV: Isovorin; Peg IFN: Pegylated interferon.

On the other hand, HAIC is not widely recommended as a standard of care for advanced HCC patients. As HAIC is thought to be one of the most effective treatment options for such patients, HAIC has become widely used in Asia, especially Japan. We propose that HAIC might be used as a treatment for achieving CR or PR. If patients with PR after HAIC receive additional therapies such as surgical resection, local ablation, or radiation, it is possible for those who show a disappearance of viable HCC to have a long survival time[64]. In addition, although liver reserve dysfunction is a poor prognostic factor[46,49,53,58-61], advanced HCC patients with Child-Pugh B are candidates for HAIC[6,10].

Currently, no criteria have been established for selecting advanced HCC patients to receive either sorafenib or HAIC. According to the results of two large-scale randomized controlled trials (RCTs), sorafenib indeed improved the survival of patients with macroscopic vascular invasion[16,17]. However, these HCC patients with macroscopic vascular invasion have poorer prognoses than those without such invasion[16,17,70,71]. Moreover, there have been no RCTs comparing sorafenib with HAIC. In a retrospective cohort study, while there was no significant difference in survival or disease progression between the two groups, while PFS was significantly longer in the HAIC group compared with the sorafenib group, particularly for patients with portal vein invasion and/or without extrahepatic spread[17,70]. On the other hand, survival was favorable in patients with HCC refractory to TACE treated with sorafenib rather than HAIC[24]. Furthermore, it is important to preserve liver function during and after chemotherapy in advanced HCC patients. It has been reported that liver function after therapy was not significantly reduced in patients treated with HAIC compared with those treated with sorafenib[78], and the Child-Pugh score of HAIC responders with deteriorated liver function was significantly improved after HAIC[79]. According to our report[82], most HAIC responders showed no deterioration of liver function. It was interesting to note that the Child-Pugh class of some responders with deteriorated liver function improved from B to A after HAIC, but this did not occur in non-responders. Therefore, we conclude that HAIC may be well tolerated by advanced HCC patients with deteriorated liver function.

As of 2017, only 10 years have passed since sorafenib was first shown to be efficacious against advanced HCC. As such, it is impossible to assess survival longer than 10 years. However, we can examine survival rates from shorter-duration studies. As previously mentioned, Rimola et al[18] reported a CR rate and MST for CR patients under sorafenib of 1% and 85.8 mo, respectively. Shiba et al[78] reported that the CR rate was below 0.6% (18/3047 patients) in a nationwide study from Japan. By contrast, the CR rate for HAIC was 4.0% (19/476 patients) in a nationwide survey in Japan[48]. According to our previous report[88], the CR rate under HAIC using a low-dose FP-based regimen was 5% (6/114 patients), and overall 1-, 3-, 5-, 7-, and 10-year cumulative survival rates were 43.9%, 10.0%, 5.6%, 2.8%, and 2.8%, respectively (MST: 10.2 mo). Three of six CR patients from our study survived over 10 years, though 2 patients have since died and only one is still alive (Table 6 and Figure 2). Further investigations are...
required to compare long-term survival rates between sorafenib and HAIC.

Finally, we present a draft proposal of a treatment strategy for advanced HCC (Figure 3): (1) For advanced HCC patients without macroscopic vascular invasion and Child-Pugh A, the first-line treatment should be sorafenib, and second-line treatments should be either regorafenib or HAIC; (2) For advanced HCC patients with macroscopic vascular invasion and Child-Pugh A, the first-line treatment should be HAIC, and the second-line treatments should be either sorafenib or experimental treatment in clinical trials; (3) For advanced HCC patients with Child-Pugh B, the first-line treatment should be HAIC, and the second-line treatment should be clinical trials. Miyaki et al. reported that additional therapy with sorafenib improved the prognosis of HAIC refractory patients compared with that of patients not treated with sorafenib therapy in a retrospective cohort study. Nonetheless, there have been no effective treatments for HAIC non-responders with deteriorated liver function (Child-Pugh B). We have shown the efficacy of an intra-arterial infusion therapy using the iron chelator deferoxamine for advanced HCC patients with deteriorated liver function, and clinical trials are now ongoing. Because the best second-line treatment for HAIC non-responders with Child-Pugh B is to enroll in clinical trials, this remains an issue for future research.

CONCLUSION

We reviewed the current status and predictive biomarkers regarding the administration of sorafenib and HAIC for advanced HCC, and we have proposed a treatment strategy for patients with advanced HCC. The success
Figure 3 Draft proposal of a treatment strategy for advanced hepatocellular carcinoma. (1) For advanced hepatocellular carcinoma (HCC) patients without macroscopic vascular invasion and Child-Pugh A, the first-line treatment should be sorafenib, while second-line treatments should be either regorafenib or experimental treatment in clinical trials; (2) For advanced HCC patients with macroscopic vascular invasion and Child-Pugh A, the first-line treatment should be sorafenib, while second-line treatments should be either regorafenib or hepatic arterial infusion chemotherapy (HAIC); (3) For advanced HCC patients with Child-Pugh B, the first-line treatment should be HAIC, and the second-line treatment should be clinical trials.

of sorafenib, regorafenib, and lenvatinib in treating advanced HCC has shifted the treatment paradigm to molecular-targeted therapies. Furthermore, several immune-oncologic agents have been identified with potential for the treatment of advanced HCC\textsuperscript{[82,83]}. Thus, the chemotherapeutic interventions for advanced HCC have been kept up-to-date through several advances. However, alternative therapies will be required because of the high cost and ineffectiveness of these molecular agents for patients with deteriorated liver function.

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