Chapter 6　Chemotherapy

- **Introduction**

In same way as other types of cancers, molecular targeted drugs are now available to HCC. In the filed of chemotherapy, molecular targeted drugs are sometimes handled separately from conventional cytotoxic anticancer drugs; however, both types of drugs will be discussed in this chapter.

Until second edition, most reports pertaining to chemotherapy for HCC have presented the results of phase I or phase II clinical trials without control groups, and no large-scale RCTs have been conducted. In this revised edition, two double-blinded RCTs that compared sorafenib with placebo in patients with advanced HCC have been reported, and their results showed that prognosis was improved in the sorafenib group. These reports were the first studies providing high-grade evidence that chemotherapy improves prognosis in patients with advanced HCC because the reports compared treatment outcomes in the chemotherapy group with that in a placebo group. On the basis of this evidence, sorafenib has become the standard chemotherapy for advanced HCC.

On the other hand, in Japan, hepatic arterial infusion chemotherapy has been proactively administered to patients with intrahepatic advanced HCC until now. Althought the evidence level of hepatic arterial infusion chemotherapy is not high because of no comparisons with placebo, a higher response rate has been reported with hepatic arterial infusion chemotherapy than with sorafenib, and also overall survival is comparable to sarafenib in nearly all reports.

Although sorafenib became available in Japan in May 2009, there are some issues pertaining to its position in treatment of advanced HCC, inclusion criteria (e.g., degree of tumor progression, degree of hepatic reserve), initial dose, and timing for evaluating treatment response and treatment completion.

This is a very active area of research at present, leading to developments of new molecular targeted drugs using sorafenib as control drug, second-line chemotherapy after sorafenib failure,

adjuvant chemotherapy to follow curative therapy or transcatheter arterial embolization (TAE), and combination chemotherapy with other treatments. Therefore, the appearance of useful drugs other than sorafenib is expected in the future.

- **Document Selection**

In this revised edition, search formulae for each clinical question (CQ) were applied to detect articles written in English that had been published through December 2011. The abstracts of relevant articles were evaluated, and articles were selected on the basis of purpose, patient number, and study design. We excluded studies that used drugs in development, old discontinued drugs, treatments that included embolization, and chemotherapy before and/or after surgery, as well as studies that reported about the drugs which have no significant antitumor effects.

CQ41　Who are eligible candidates for systemic chemotherapy?

Recommendation

Systemic chemotherapy is indicated for patients contraindicated for liver resection, liver transplantation, percutaneous ablation therapy, and TACE. Sorafenib treatment, in particular, is indicated for patients with preserved hepatic reserve (Child–Pugh class A) and a good performance status (PS) **(Grade A)**

- **Scientific Statement**

RCTs that proved the efficacy of sorafenib against HCC involved the treatment of patients contraindicated for liver resection, liver transplantation, percutaneous ablation therapy, or transcatheter arterial chemoembolization (TACE) (LF12054[1)] Level 1b, L3F00353[2)] Level 1b). In addition, systemic chemotherapy was administered to patients contraindicated for treatments such as liver resection, TACE, and radiofrequency ablation (RFA) in reports of other chemotherapy for

HCCs.

These reports included patients with portal vein tumor thrombus in the portal vein main trunk or first order branches, multiple tumors in the liver and distant metastases as tumor progression degree.

With regard to hepatic reserve, in RCTs demonstrating the efficacy of sorafenib compared with that of placebo, patients with a good PS and Child–Pugh class A hepatic reserve were investigated. Therefore, the usefulness of sorafenib has currently been proven only in patients with Child–Pugh class A hepatic reserve (LF12054[1)] Level 1b, L3F00353[2)] Level 1b).

A study examining predictive factors of systemic chemotherapy reported no response in patients with a PS of 2–3, ascites, tumors occupying 50% or more of the liver, tumor thrombus in the portal vein main trunk, and serum bilirubin levels of 2.0 mg/dL or higher. Therefore, it was concluded that systemic chemotherapy is usually not recommended for patients with severely advanced HCC or severely impaired liver function (LF02440[3)] Level 4).

The efficacy of sorafenib as adjuvant chemotherapy or in combination with other therapies has not been demonstrated. However, the results of an RCT studying sorafenib administration after TACE have been reported, although the efficacy has not been demonstrated (L3F00060[4)] Level 1b).

- **Explanation**

When patients with Child–Pugh class B are treated with sorafenib, there is no difference in pharmacokinetics comparing to patients with Child-Pugh class A. However, hepatic function often worsens with elevated bilirubin levels, ascites, and encephalopathy. Furthermore, the median time to progression and median overall survival are shorter than those for patients with Child–Pugh class A (L3F00318[5)] Level 2a). In addition, although the Child–Pugh score did not affect the frequency of adverse effects or treatment discontinuation, the time to progression and overall survival were very short. Therefore, sorafenib must be administered with care in patients with Child-Pugh class B (L3F00418[6)] Level 2b).

Two RCTs proving the usefulness of sorafenib were performed in patients with Child–Pugh class

A. Because the safety and efficacy of sorafenib have yet to be verified in patients with Child–Pugh class B, this treatment cannot be recommended for these patients.

- **References**

1) LF12054 Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al; SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359(4):378-90.

2) L3F00353 Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma:a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009;10(1):25-34.

3) LF02440 Nagahama H, Okada S, Okusaka T, Ishii H, Ikeda M, Nakasuka H, et al. Predictive factors for tumor response to systemic chemotherapy in patients with hepatocellular carcinoma. Jpn J Clin Oncol 1997;27(5):321-4.

4) L3F00060 Kudo M, Imanaka K, Chida N, Nakachi K, Tak WY, Takayama T, et al. Phase III study of sorafenib after transarterial chemoembolisation in Japanese and Korean patients with unresectable hepatocellular carcinoma. Eur J Cancer 2011;47(14):2117-27.

5) L3F00318 Abou-Alfa GK, Amadori D, Santoro A, Figer A, De Greve J, Lathia C, et al. Safety and efficacy of sorafenib in patients with hepatocellular carcinoma (HCC) and Child-Pugh A versus B cirrhosis. Gastrointest Cancer Res 2011;4(2):40-4.

6) L3F00418 Hollebecque A, Cattan S, Romano O, Sergent G, Mourad A, Louvet A, et al. Safety and efficacy of sorafenib in hepatocellular carcinoma:the impact of the Child-Pugh score. Aliment Pharmacol Ther 2011;34(10):1193-201.

CQ42　Does hepatic arterial infusion chemotherapy improve prognosis?

Recommendation

Hepatic arterial infusion chemotherapy may improve prognosis, but there is insufficient evidence to support this speculation **(Grade C1)**.

- **Scientific Statement**

In a small-scale RCT, systemic administration of interferon was combined with hepatic arterial infusion of cisplatin (combined interferon plus cisplatin infusion group), and this treatment was compared with the infusion of cisplatin alone or with best supportive care (BSC). The median survival time was significantly longer in the combined interferon plus cisplatin infusion group than in the cisplatin alone infusion o BSC groups (LF02089[1] Level 1b).

Hepatic arterial infusion chemotherapy using a combination of interferon and 5-flurouracil (5-FU) was compared with a historical control, and the survival rate in the combination therapy was significantly improved compared with that in the historical control (LF10244[2] Level 2b).

In addition, there were no large-scale comparative studies reporting prognostic improvement comparing hepatic arterial infusion chemotherapy and BSC in HCC patients.

- **Explanation**

Hepatic arterial infusion chemotherapy needs special procedures; however, it has been conducted to treat many patients in Japan. In this treatment, HCC can be treated directly with high-concentration of anticancer drugs through hepatic artery, and the concentration of anticancer agents for systemic criculation can also be kept low, thereby decreasing the incidence of adverse effects.

The response rate for hepatic arterial infusion chemotherapy is 14%–71%, and tumor shrinkage can be observed with this treatment. However, there is insufficient evidence that this treatment extends survival time (appended table, p. 157). The aforementioned study investigating interferon

plus cisplatin combination chemotherapy was an RCT. However, there are issues with the study design because basic information about the trial, such as setting retionale for the number of patients, has not been documented. The median survival time for hepatic arterial infusion chemotherapy reportedly ranges from 2.6–17.6 months, with some variation (appended table) that results from differences in tumor progression and hepatic reserve among included patients. Hepatic arteral infusion chemotherapy may improve prognosis because the study compared with historical controls reported improvement of prognosis in hepatic arterial infusion chmoetherapy group, however, evidence level is not high. Therefore, comparative studies with sorafenib will be required in the future to demonstrate an improvement in prognosis with hepatic arterial infusion chemotherapy.

- **References**

1) LF02089 Chung YH, Song IH, Song BC, Lee GC, Koh MS, Yoon HK, et al. Combined therapy consisting of intraarterial cisplatin infusion and systemic interferon-alpha for hepatocellular carcinoma patients with major portal vein thrombosis or distant metastasis. Cancer 2000;88(9):1986-91.
2) LF10244 Obi S, Yoshida H, Toune R, Unuma T, Kanda M, Sato S, et al. Combination therapy of intraarterial 5-fluorouracil and systemic interferon-alpha for advanced hepatocellular carcinoma with portal venous invasion. Cancer 2006;106(9):1990-7.

CQ43 Which chemotherapy regimens (drug regimens) are effective?

Recommendation

Sorafenib is recommended for systemic chemotherapy in patients with unresectable HCC and Child–Pugh class A **(Grade A)**.

- **Scientific Statement**

The only drug that has been proven to improve the prognosis of HCC is sorafenib. Sorafenib is a multikinase inhibitor drug that inhibits tumor growth by blocking Raf in the MAP kinase proliferation signaling pathway of HCC and by inhibiting vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR) kinase activities in vascular endothelial cells and pericytes. It has been approved by the National Health Insurance in Japan since May 2009.

Two RCTs have verified the effects of sorafenib monotherapy against advanced HCC (LF12054[1] Level 1b, L3F00353[2] Level 1b). Both were large-scale RCTs that treated patients with Child–Pugh class A and unresectable HCC with no history of previous treatment with chemotherapy, and the results demonstrated that the overall survival and time to progression were significantly prolonged compared with those in the placebo group. In Korea and Japan, an RCT was conducted to examine the preventive effects on recurrence after TACE (L3F00060[3] Level 1b); however, there was no evidence that sorafenib treatment effectively prevented recurrence. Nevertheless, subgroup analysis of the results by country showed that recurrence was prevented in the Korean group, in which sorafenib was administered at higher average daily dosage and for a longer period than those in Japan. Therefore, if long-term, continuous oral administration of sorafenib is possible, it may be effective in preventing recurrence.

Sorafenib has been proven to be safe and effective only in patients with preserved hepatic reserve, Child–Pugh class A. The safety and efficacy of this drug in patients with impaired hepatic reserve, Child–Pugh class B or C, has been reported in only a few scattered retrospective cohort studies (L3F00418[4] Level 2a, L3F00426[5] Level 2b, L3F00554[6] Level 2b, L3F00642[7] Level 4, L3F00318[8] Level 2b); therefore, sorafenib treatment should be administered only to patients with preserved hepatic reserve, Child–Pugh class A.

There are a few reports related to the combination of sorafenib with other anticancer drugs, as well as reports related to its adjuvant use after curative therapy or TAE. All studies were at the phase I

or phase II level, however, and there were no reports of large-scale phase III studies. Therefore, the efficacy and safety of sorafenib combined with other anticancer drugs or local therapy have not been proven; therefore, it is recommended for use as monotherapy (L3F00320[9] Level 1b, L3F00420[10] Level 4, L3F00228[11] Level 4, L3F00560[12] Level 4, L3F00567[13] Level 4, L3F04273[14] Level 4, L3F00459[15] Level 4).

- **Explanation**

At present, sorafenib is the standard drug used to treat advanced HCC in the world. Sorafenib is approved by National Health Insurance in Japan for the treatment of unresectable HCC. However, many local therapies such as RFA, TACE, and hepatic arterial infusion chemotherapy are widely used in Japan, and these therapies are performed first. In fact, there is a consensus that sorafenib is indicated for patients with Child–Pugh class A who are unresponsive to TACE or unable to treat by TACE, have vascular invasion, or have distant metastases. The safety and efficacy of sorafenib administered as adjuvant therapy with local therapies or in combination with other anticancer drugs have not been confirmed; therefore, such usages of sorafenib should not be performed.

- **References**

1) LF12054 Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al; SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359(4):378-90.

2) L3F00353 Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009;10(1):25-34.

3) L3F00060 Kudo M, Imanaka K, Chida N, Nakachi K, Tak WY, Takayama T, et al. Phase III study of sorafenib after transarterial chemoembolisation in Japanese and Korean patients with unresectable hepatocellular carcinoma. Eur J Cancer 2011;47(14):2117-27.

4) L3F00418 Hollebecque A, Cattan S, Romano O, Sergent G, Mourad A, Louvet A, et al.

Safety and efficacy of sorafenib in hepatocellular carcinoma:the impact of the Child-Pugh score. Aliment Pharmacol Ther 2011;34(10):1193-201.

5) L3F00426 Iavarone M, Cabibbo G, Piscaglia F, Zavaglia C, Grieco A, Villa E, et al; SOFIA(SOraFenib Italian Assessment)study group. Field-practice study of sorafenib therapy for hepatocellular carcinoma:a prospective multicenter study in Italy. Hepatology 2011;54(6):2055-63.

6) L3F00554 Pinter M, Sieghart W, Graziadei I, Vogel W, Maieron A, Konigsberg R, et al. Sorafenib in unresectable hepatocellular carcinoma from mild to advanced stage liver cirrhosis. Oncologist 2009;14(1):70-6.

7) L3F00642 Wörns MA, Weinmann A, Pfingst K, Schulte-Sasse C, Messow CM, Schulze-Bergkamen H, et al. Safety and efficacy of sorafenib in patients with advanced hepatocellular carcinoma in consideration of concomitant stage of liver cirrhosis. J Clin Gastroenterol 2009;43(5):489-95.

8) L3F00318 Abou-Alfa GK, Amadori D, Santoro A, Figer A, De Greve J, Lathia C, et al. Safety and Efficacy of Sorafenib in Patients with Hepatocellular Carcinoma(HCC)and Child-Pugh A versus B Cirrhosis. Gastrointest Cancer Res 2011;4(2):40-4.

9) L3F00320 Abou-Alfa GK, Johnson P, Knox JJ, Capanu M, Davidenko I, Lacava J, et al. Doxorubicin plus sorafenib vs doxorubicin alone in patients with advanced hepatocellular carcinoma:a randomized trial. JAMA 2010;304(19):2154-60.

10) L3F00420 Hsu CH, Shen YC, Lin ZZ, Chen PJ, Shao YY, Ding YH, et al. Phase II study of combining sorafenib with metronomic tegafur/uracil for advanced hepatocellular carcinoma. J Hepatol 2010;53(1):126-31.

11) L3F00228 Pawlik TM, Reyes DK, Cosgrove D, Kamel IR, Bhagat N, Geschwind JF. Phase II trial of sorafenib combined with concurrent transarterial chemoembolization with drug-eluting beads for hepatocellular carcinoma. J Clin Oncol 2011;29(30):3960-7.

12) L3F00560 Prete SD, Montella L, Caraglia M, Maiorino L, Cennamo G, Montesarchio V,

et al. Sorafenib plus octreotide is an effective and safe treatment in advanced hepatocellular carcinoma:multicenter phase II So. LAR. study. Cancer Chemother Pharmacol 2010;66(5):837-44.

13) L3F00567 Richly H, Schultheis B, Adamietz IA, Kupsch P, Grubert M, Hilger RA, et al. Combination of sorafenib and doxorubicin in patients with advanced hepatocellular carcinoma:results from a phase I extension trial. Eur J Cancer 2009;45(4):579-87.

14) L3F04273 Gomez-Martin C, Bustamante J, Castroagudin JF, Salcedo M, Garralda E, Testillano M, et al. Efficacy and safety of sorafenib in combination with mammalian target of rapamycin inhibitors for recurrent hepatocellular carcinoma after liver transplantation. Liver Transpl 2012;18(1):45-52.

15) L3F00459 Kim R, El-Gazzaz G, Tan A, Elson P, Byrne M, Chang YD, et al. Safety and feasibility of using sorafenib in recurrent hepatocellular carcinoma after orthotopic liver transplantation. Oncology 2010;79(1-2):62-6.

CQ44 Is hormone therapy effective?

Recommendation

Hormone therapy is not recommended because it is ineffective against advanced HCC **(Grade D)**.

- **Scientific Statement**

Three large-scale RCTs showed that treatment with tamoxifen did not improve prognosis in HCC patients (LF02344[1)] Level 1b, LF10647[2)] Level 1b, LF07143[3)] Level 1b). At high doses, survival time was not extended, mortality rate was increased, and quality of life (QOL) was not improved (LF07143[3)] Level 1b). Two meta-analyses disallowed the effecacy of tamoxifen for HCC (LF10343[4)] Level 1a, LF10193[5)] Level 1a).

Two RCTs of anti-androgen therapy conducted in more than 200 HCC patients also found that this

treatment was ineffective (LF02322[6] Level 1b, LF10551[7] Level 1b).

- **Explanation**

Large-scale RCTs of hormone therapy have been conducted, and there is enough evidence that such treatment is ineffective. Therefore, the recommendation level has been set as Grade D.

- **References**

1) LF02344 Tamoxifen in treatment of hepatocellular carcinoma:a randomised controlled trial. CLIP Group(Cancer of the Liver Italian Programme). Lancet 1998;352(9121):17-20.

2) LF10647 Barbare JC, Bouché O, Bonnetain F, Raoul JL, Rougier P, Abergel A, et al. Randomized controlled trial of tamoxifen in advanced hepatocellular carcinoma. J Clin Oncol 2005;23(19):4338-46.

3) LF07143 Chow PK, Tai BC, Tan CK, Machin D, Win KM, Johnson PJ, et al. High-dose tamoxifen in the treatment of inoperable hepatocellular carcinoma:A multicenter randomized controlled trial. Hepatology 2002;36(5):1221-6.

4) LF10343 Nowak A, Findlay M, Culjak G, Stockler M. Tamoxifen for hepatocellular carcinoma. Cochrane Database Syst Rev 2004;(3):CD001024.

5) LF10193 Gallo C, De Maio E, Di Maio M, Signoriello G, Daniele B, Pignata S, et al;CLIP(Cancer of the Liver Italian Programme)Investigators. Tamoxifen is not effective in good prognosis patients with hepatocellular carcinoma. BMC Cancer 2006;6:196.

6) LF02322 Grimaldi C, Bleiberg H, Gay F, Messner M, Rougier P, Kok TC, et al. Evaluation of antiandrogen therapy in unresectable hepatocellular carcinoma:results of a European Organization for Research and Treatment of Cancer multicentric double-blind trial. J Clin Oncol 1998;16(2):411-7.

7) LF10551 Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire. Randomized trial of leuprorelin and flutamide in male patients with hepatocellular carcinoma treated with tamoxifen. Hepatology 2004;40(6):1361-9.

CQ45　What are the predictive and prognostic factors for the treatment outcomes of chemotherapy?

Recommendation

There is no scientific evidence to support specific predictive or prognostic factors for the treatment outcome of chemotherapy **(Grade C1).**

- **Scientific Statement**

Sorafenib is the standard treatment for HCC, and five studies examined the predictive/prognostic factors for treatment outcome. Skin toxicity (L3F00625[1)] Level 2a) and low alpha fetoprotein (AFP) levels (L3F00658[2)] Level 3, L3F04279[3)] Level 3) are suggested to be predictors of outcome. Prediction of treatment outcome using combinations of multiple serum markers has also been reported (L3F00834[4)] Level 2a). On the other hand, lung metastasis is suggested to be an indicator of poor prognosis (L3F00654[5)] Level 2a).

- **Explanation**

Sorafenib is one of multikinase inhibitor drugs that act against a variety of target molecules. For this reason, it can be difficult to find specific treatment markers, unlike those for molecular targeted drugs that target a single molecule, such as epidermal growth factor receptor (EGFR) for gefitinib or human epidermal growth factor receptor 2 (HER2) for trastuzumab. Clinical indicators such as changes in tumor markers AFP and PIVKA-II and predictions based on tumor progression factors are under consideration. However, these may not necessarily become specific predictive factors.

Moreover, no prospective studies of the predictive/prognostic factors for the outcomes of sorafenib treatment have been reported. Therefore, we have determined that there are no factors supported by scientific evidence. For this reason, the recommendation level was set as Grade C1.

- **References**

1) L3F00625 Vincenzi B, Santini D, Russo A, Addeo R, Giuliani F, Montella L, et al. Early skin toxicity as a predictive factor for tumor control in hepatocellular carcinoma patients treated with sorafenib. Oncologist 2010;15(1):85-92.
2) L3F00658 Yau T, Yao TJ, Chan P, Wong H, Pang R, Fan ST, et al. The significance of early alpha-fetoprotein level changes in predicting clinical and survival benefits in advanced hepatocellular carcinoma patients receiving sorafenib. Oncologist 2011;16(9):1270-9.
3) L3F04279 Kuzuya T, Asahina Y, Tsuchiya K, Tanaka K, Suzuki Y, Hoshioka T, et al. Early decrease in alpha-fetoprotein, but not des-gamma-carboxy prothrombin, predicts sorafenib efficacy in patients with advanced hepatocellular carcinoma. Oncology 2011;81(3-4):251-8.
4) L3F00834 Miyahara K, Nouso K, Tomoda T, Kobayashi S, Hagihara H, Kuwaki K, et al. Predicting the treatment effect of sorafenib using serum angiogenesis markers in patients with hepatocellular carcinoma. J Gastroenterol Hepatol 2011;26(11):1604-11.
5) L3F00654 Yau T, Chan P, Ng KK, Chok SH, Cheung TT, Fan ST, et al. Phase 2 open-label study of single-agent sorafenib in treating advanced hepatocellular carcinoma in a hepatitis B-endemic Asian population:presence of lung metastasis predicts poor response. Cancer 2009;115(2):428-36.

CQ46 How should the treatment outcome of chemotherapy be determined?

Recommendation

In order to determine the outcome of HCC therapy, it is necessary to correctly evaluate areas with necrosis and surviving tumor tissue. Therefore, the modified Response Evaluation Criteria in Solid Tumors (RECIST), Response Evaluation Criteria in Cancer of the Liver (RECICL), and European Association for the Study of the Liver (EASL) criteria, evaluating the areas with necrosis and surviving tumor tissue, are useful **(Grade C1)**.

- **Scientific Statement**

Response evaluation criteria, beginning with the WHO criteria (L3H00045[1)]), were established to serve as a common criteria for clinical studies and trials. The RECIST has become the most common around the world, and RECIST version 1.1 is currently in use. RECIST have been validated by comparison with WHO criteria using various databases (LF10820[2)]. L3F04278[3)], L3H00044[4)]).

- **Explanation**

In HCC treatment, unlike chemotherapy with cytotoxic anticancer drugs, procedures that do not necessarily involve tumor shrinkage are conducted, such as ablation, embolization, and other treatments. In addition, even treatment with molecular targeted drugs that exert antiangiogenic effects, such as sorafenib, often results in tumor necrosis without tumor shrinkage. Therefore, response criteria that include areas with surviving tumors and areas with necrosis are being proposed as determining factors for treatment response. That is, the modified RECIST (mRECIST) (L3F00487[5)]), the Liver Cancer Study Group of Japan's RECICL 2009 (L3H00028[6)]), and the EASL criteria (L3F00812[7)]) may be useful as specialized response criteria for HCC.
One problem with the determination of treatment response is the difficulty in assessing necrotic areas using any of the abovementioned criteria. Furthermore, although treatment response in intrahepatic lesions can be determined more accurately with RECICL, the lack of criteria for extrahepatic metastasis is problematic. These criteria were created on the basis of consolidated opinions from specialists. Therefore, proper validation is needed, and the level of evidence is low. Therefore, the recommendation level was determined to be Grade C1.

- **References**

1) L3H00045 World Health Organization. WHO Handbook for Reporting Results of Cancer Treatment, Geneva, World Health Organization Offset Publication No. 48, 1979.
2) LF10820 Park JO, Lee SI, Song SY, Kim K, Kim WS, Jung CW, et al. Measuring response in solid tumors:comparison of RECIST and WHO response criteria. Jpn J Clin

Oncol 2003;33(10):533-7.

3) L3F04278 Jiang T, Kambadakone A, Kulkarni NM, Zhu AX, Sahani DV. Monitoring response to antiangiogenic treatment and predicting outcomes in advanced hepatocellular carcinoma using image biomarkers, CT perfusion, tumor density, and tumor size (RECIST). Invest Radiol 2012;47(1):11-7.

4) L3H00044 James K, Eisenhauer E, Christian M, Terenziani M, Vena D, Muldal A, et al. Measuring response in solid tumors:unidimensional versus bidimensional measurement. J Natl Cancer Inst 1999;91(6):523-8.

5) L3F00487 Lencioni R, Llovet JM. Modified RECIST (mRECIST)assessment for hepatocellular carcinoma. Semin Liver Dis 2010;30(1):52-60.

6) L3H00028 Kudo M, Kubo S, Takayasu K, Sakamoto M, Tanaka M, Ikai I, et al. Response Evaluation Criteria in Cancer of the Liver(RECICL)proposed by the Liver Cancer Study Group of Japan(2009 Revised Version). Hepatol Res 2010;40(7):686-92.

7) L3F00812 Forner A, Ayuso C, Varela M, Rimola J, Hessheimer AJ, de Lope CR, et al. Evaluation of tumor response after locoregional therapies in hepatocellular carcinoma:are response evaluation criteria in solid tumors reliable? Cancer 2009;115(3):616-23.

CQ47 What are the adverse effects of chemotherapy, and how should they be treated?

Recommendation

Caution with regard to hematotoxicity is required because pancytopenia is often observed prior to treatment because of coexisting liver cirrhosis **(Grade C1)**.

The characteristic adverse effects frequently associated with sorafenib treatment are hand-foot-skin reaction, rash, diarrhea, and hypertension. These effects often develop in the early stages of treatment; therefore, patients must be monitored carefully and treated accordingly **(Grade C1)**.

- **Scientific Statement**

Most HCC patients have a background of chronic liver disease, such as chronic hepatitis or cirrhosis, and hematocytopenia is often observed prior to treatment in the form of leukopenia, erythropenia, and thrombocytopenia. Great care must be exercised with regard to hematotoxicity because myelosuppression is developed with most of the anticancer drugs.

Some form of adverse effect is observed in approximately 80% patients treated with sorafenib, and the more commonly observed effects are hand-foot-skin reaction, rash/desquamation, diarrhea, anorexia, hypertension, fatigue, alopecia, and nausea (LF12054[1] Level 1b, L3F00353[2] Level 1b). Hand-foot-skin reaction, rash/desquamation, and hypertension are adverse effects that are not observed with conventional anticancer drugs (cytotoxic anticancer drugs). Hand-foot-skin reaction is a critical adverse effect that can affect the decision to continue treatment and is mostly observed in the early stages after therapy initiation (L3F00484[3] Level 2b).

- **Explanation**

When treated with sorafenib, patients with impaired hepatic reserve, Child–Pugh class B, reportedly developed hyperbilirubinemia, ascites, and hepatic encephalopathy more frequently than patients with Child–Pugh class A (L3F00318[4] Level 2a), and no significant differences in adverse effects between Child-Pugh class A and B were observed when patients were compared by matching with age, gender, and tumor progression (L3F00418[5] Level 2b).

Furthermore, compared with those in past reports, the adverse effects of hand-foot-skin reaction, rash, and hepatic failure are observed more commonly in Japan. Therefore, much attention must be paid to the management of adverse effects during treatment (L3F00836[6] Level 2b). Groups that developed skin toxicities, including hand-foot-skin reaction, tended to have a longer survival time compared with those without skin toxicity, and it was reported that adverse effects may also serve as an alternative indicator of treatment outcome (L3F00625[7] Level 2b).

The adverse effects of HCC chemotherapy are drug-specific, and those sassociated with certain anticancer drugs are described below.

- 5-FU drugs

Anorexia; digestive symptoms such as nausea/vomiting and diarrhea; general malaise; peptic ulcer and oral ulceration; myelosuppression such as neutropenia and thrombocytopenia; and hyperbilirubinemia

- Platinum-containing drugs (cisplatin, oxaliplatin)

Myelosuppression such as neutropenia and thrombocytopenia; anorexia; digestive symptoms such as nausea/vomiting; renal dysfunction; and hyperbilirubinemia

- Anthracycline drugs (doxorubicin, epirubicin, mitoxantrone)

Alopecia; myelosuppression such as neutropenia and thrombocytopenia; anorexia; digestive disorders such as nausea/vomiting; mucositis; sepsis; and cardiac dysfunction

- Etoposide

Alopecia; anorexia; digestive symptoms such as nausea/vomiting; myelosuppression such as neutropenia and thrombocytopenia

- Irinotecan

Anorexia; digestive symptoms such as nausea/vomiting; mucositis; myelosuppression such as neutropenia and thrombocytopenia; anemia; general malaise; and hyperbilirubinemia

- Gemcitabine

Myelosuppression such as neutropenia and thrombocytopenia; anemia; hepatic disorder; and rash

- Paclitaxel

Myelosuppression such as neutropenia and thrombocytopenia; infection; and allergies

- Sorafenib

Hand-foot-skin reaction, rash; anorexia; digestive symptoms such as nausea/vomiting; diarrhea; general malaise; alopecia; hypertension; and increased levels of pancreatic enzymes

- **References**

1) LF12054 Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al;SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359(4):378-90.

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Appendix table

Hepatic arterial infusion chemotherapy: response rate and survival duration for different regimens (studies that included at least 50 patients)

Drug		No. of patients	Response rate (%)	Median survival time (months)	Reference ID	Study design	Evi-dence Level
Monotherapy	Doxorubicin (hepatic arterial infusion) Doxorubicin (systemic)	72	60 44.1	7 6.5	LF02215[1)]	RCT	1b
	CDDP	67	37	10.7	LF01885[2)]	cohort study	4
	DDP-H	80	33.8	ND	L3F00666[3)]	cohort study	4
	DDP-H	84	3.6	7.0	L3F00178[4)]	cohort study	4
Combination therapy	CDDP, 5-FU (low FP)	52	71	ND	LF00319[5)]	cohort study	2b
	CDDP, 5-FU (low FP), +/-LV	53	24.5	ND	L3F00441[6)]	cohort study	3
	CDDP, 5-FU (low FP)	52	38.5	15.9	L3F00617[7)]	cohort study	4
	CDDP, 5-FU (low FP) CDDP, 5-FU	68	0 16.7	5.0 6.3	L3F00639[8)]	RCT	1b
	CDDP, mitomycin C, 5-FU, LV	53	28.3	13.2	LF12076[9)]	cohort study	4
	IFN, CDDP CDDP BSC	68	33 14	4.4 2.6 1.2	LF02089[10)]	RCT	1b
	IFN, 5-FU BSC (historical control)	116	52	6.9 ND	LF10244[11)]	cohort study	2b
	IFN, 5-FU	55	29.1	9.0	L3F00621[12)]	cohort study	4
	IFN, 5-FU	102	39.2	9.0	L3F00722[13)]	cohort study	4
	IFN, 5-FU IFN, 5-FU, CDDP	104	24.6 45.6	10.5 17.6	L3H00022[14)]	RCT	1b

CDDP: cisplatin, DDP-H: diamminedichloroplatinum (CDDP powder), 5-FU: fluorouracil, low FP: fluorouracil+cisplatin, LV: leucovorin, IFN: interferon, BSC: best supportive care, ND: not described

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