Chapter 6 Chemotherapy

- Introduction

In the same way as other types of cancers, molecular targeted drugs are now available to HCC. In the field 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 the 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. Although 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 sorafenib 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) (LF120541) Level 1b, L3F003532) 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 (LF120541 Level 1b, L3F003532 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 (L024403 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 (L3F000604 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 (L3F003185 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 (L3F004186 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


**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 (LF020891) 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 (LF102442) 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 circulation 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 rationale 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 arterial infusion chemotherapy may improve prognosis because the study compared with
historical controls reported improvement of prognosis in hepatic arterial infusion chemotherapy
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.

therapy of intraarterial 5-fluorouracil and systemic interferon-alpha for advanced

CO43  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 (L3F003209) Level 1b, L3F004204 Level 4, L3F002282 Level 4, L3F005601 Level 4, L3F005671 Level 4, L3F042734 Level 4, L3F004591 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**


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


**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 (LF023441 Level 1b, LF106472 Level 1b, LF071433 Level 1b). At high doses, survival time was not extended, mortality rate was increased, and quality of life (QOL) was not improved (LF071433 Level 1b). Two meta-analyses disallowed the efficacy of tamoxifen for HCC (LF103434 Level 1a, LF101935 Level 1a).

Two RCTs of anti-androgen therapy conducted in more than 200 HCC patients also found that this
treatment was ineffective (LF02322\textsuperscript{6} Level 1b, LF10551\textsuperscript{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**

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 (L3F006251Level 2a) and low alpha fetoprotein (AFP) levels (L3F006582Level 3, L3F042793Level 3) are suggested to be predictors of outcome. Prediction of treatment outcome using combinations of multiple serum markers has also been reported (L3F008344Level 2a). On the other hand, lung metastasis is suggested to be an indicator of poor prognosis (L3F006545Level 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


**CO46  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), 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, L3F04278, L3H000444).

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) (L3F004875), the Liver Cancer Study Group of Japan’s RECICL 2009 (L3H000286), and the EASL criteria (L3F008127) 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


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, erythopenia, 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 associated 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


## Appendix table

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>No. of patients</th>
<th>Response rate (%)</th>
<th>Median survival time (months)</th>
<th>Reference ID</th>
<th>Study design</th>
<th>Evidence Level</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monotherapy</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Doxorubicin (hepatic arterial infusion) Doxorubicin (systemic)</td>
<td>72</td>
<td>60</td>
<td>7</td>
<td>LF02215&lt;sup&gt;1&lt;/sup&gt;</td>
<td>RCT</td>
<td>1b</td>
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<td>CDDP</td>
<td>67</td>
<td>37</td>
<td>10.7</td>
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<td>DDP-H</td>
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<td>33.8</td>
<td>ND</td>
<td>L3F00666&lt;sup&gt;3&lt;/sup&gt;</td>
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<tr>
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<td>3.6</td>
<td>7.0</td>
<td>L3F00178&lt;sup&gt;4&lt;/sup&gt;</td>
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<td><strong>Combination therapy</strong></td>
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<td>CDDP, 5-FU (low FP)</td>
<td>52</td>
<td>71</td>
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<td>LF00319&lt;sup&gt;5&lt;/sup&gt;</td>
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<td>CDDP, 5-FU (low FP) CDDP, 5-FU</td>
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<td>0</td>
<td>16.7</td>
<td>5.0</td>
<td>L3F00639&lt;sup&gt;8&lt;/sup&gt;</td>
<td>RCT</td>
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<td>13.2</td>
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<td>L3H00022&lt;sup&gt;14&lt;/sup&gt;</td>
<td>RCT</td>
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### References

1) LF02215  Tzoracoleftherakis EE, Spiliotis JD, Kyriakopoulou T, Kakkos SK. Intra-arterial versus systemic chemotherapy for non-operable hepatocellular carcinoma.


9) LF12076 Lin CP, Yu HC, Cheng JS, Lai KH, Lo GH, Hsu PI, et al. Clinical effects of


