Chapter 7:

Drug Therapy

● Introduction

Molecular-targeted therapy has been incorporated into treatment for HCC, as in other types of cancers, and many studies are currently being carried out to investigate the efficacy of immune checkpoint inhibitors. This chapter was previously entitled “Chemotherapy”, but we use “Drug Therapy” in the current Guidelines. Drug therapy for HCC essentially began in 2008 when a double-blind RCT, the SHARP study, showed that sorafenib significantly improved prognosis in patients with advanced HCC over placebo. Until then, studies that investigated prognosis after drug therapy for HCC were not large-scale double-blind RCTs, so the SHARP study was the first such study to show, with high-quality evidence, the beneficial effects of drug therapy on HCC. Sorafenib subsequently became the standard drug for HCC. Since then, many studies have been carried out to develop drug therapies for advanced HCC.

Various drugs, including molecular-targeted drugs, have been compared with sorafenib as first-line therapy, but none showed superiority or non-inferiority over sorafenib until the first report of the non-inferiority of lenvatinib to sorafenib was made at the ASCO Annual Meeting in June 2017. A phase III clinical study is currently underway to compare sorafenib with the immune checkpoint inhibitor nivolumab.

The utility of various other drugs as second-line therapy after sorafenib therapy was also investigated in many placebo-controlled studies, but none of them have shown superiority. However, in January 2017, regorafenib was reported to improve survival in patients with disease progression during sorafenib therapy, marking for the first time the superiority of second-line therapy after sorafenib failure. Consequently, in June 2017, regorafenib was approved for HCC in Japan. A placebo-controlled phase III clinical study is also currently underway to investigate the utility of the immune checkpoint inhibitor pembrolizumab as second-line therapy after sorafenib.

In Japan, intrahepatic progression is conventionally treated with hepatic arterial infusion chemotherapy (HAIC), even after sorafenib became available. HAIC is performed especially in patients with HCC accompanied by vascular invasion in the major vessels.

This fourth edition of the Guidelines excludes CQ44 “Is hormone therapy effective?” in the third edition because hormone therapy is not used to treat HCC in Japan. Also, by integrating CQ41 “Which cases are indicated for systemic chemotherapy?” and CQ43 “What chemotherapy regimens (drug regimens) are effective?”, the current edition newly includes CQ43 “Is molecular-targeted therapy recommended for unresectable advanced HCC?”

In the current revision process, 2 committee members independently performed a literature search of English articles published before June 2016, using the search query developed for each CQ. After carefully reading each abstract, they extracted articles in the first screening based on article type, number of cases, and study design. Disagreements were resolved by discussion. As in previous editions, studies were excluded that reported treatment involving embolization or perioperative drug

therapy and studies equivalent to a phase I or II clinical study that used drugs still in development or no longer in use. Also excluded were studies that described indeterminate antitumor effects and systematic reviews with insufficient or redundant data. Articles and conference reports published after June 2016 that described the results of a large-scale RCT were included as far as possible.

Recommendations for individual CQs were decided in the meeting for finalizing recommendations, and among the 2 committee members who performed the literature search, one prepared the abstracts and the other reviewed them.

Currently, many studies to establish drug therapies for HCC are ongoing. These studies are expected to produce new evidence and may lead to the approval of certain drugs before the next revision of these Guidelines. Newly developed drugs with high-quality scientific evidence are announced and officially recommended on the JSH webpage when they are approved for National Health Insurance coverage, without waiting for publication of the next edition of the Guidelines.

CQ43 Is molecular-targeted therapy recommended for unresectable advanced HCC?

Recommendation

Strong recommendation: Sorafenib or lenvatinib therapy is recommended as first-line therapy for unresectable advanced HCCs that are not indications for surgical resection, liver transplantation, locoregional therapy, or TACE in patients with Child-Pugh A liver function, good hepatic functional reserve, and good PS.

Strong recommendation: Regorafenib therapy is recommended as second-line therapy for patients with Child-Pugh A liver function who, during sorafenib therapy, show HCC disease progression on imaging study and tolerancy for sorafenib.

■ Background

HCC tends to recur repeatedly at high rates and often progresses to advanced disease that has no clear indications for surgical resection, liver transplantation, locoregional therapy, or TACE. The efficacy of the molecular-targeted drug sorafenib for this type of unresectable HCC was first reported by a placebo-controlled study in 2008. Several other molecular-targeted drugs have been developed since then. Here, we investigated the utility of molecular-targeted therapy for advanced HCC to decide the level of recommendation.

■ Scientific Statement

This CQ was established by integrating CQ41 “Which cases are indicated for systemic chemotherapy?” and CQ43 “What chemotherapy regimens (drug regimens) are effective?” in the third edition. A literature search conducted with a modified version of the search query used in the third edition and a publication date between January 1, 2012 and June 30, 2016 extracted 95 articles. This was narrowed down to 18 articles about RCTs, subgroup analyses, and systematic reviews in the first screening. Eleven articles were extracted in the second screening. In addition to these 11 articles, 2 articles published after July 2017 and 2 conference reports are cited as important articles. After extracting 2 articles that comply with the above selection criteria from the 16 articles cited in the third edition, a total of 17 articles are cited here for Q43.

Compared with placebo, sorafenib significantly extended survival periods in patients with Child-Pugh A liver function and good PS who were not eligible for surgical resection, liver transplantation, locoregional therapy, or TACE[1,2]. The efficacy of sorafenib has also been verified in different subgroups[3-5]. A systematic review showed that sorafenib is effective and safe[6].

Sunitinib, brivanib, and linifanib failed to show superiority or non-inferiority over sorafenib as first-line therapy in RCTs[7-9]. Lenvatinib was not inferior to sorafenib in overall survival in another RCT[10].

Brivanib, everolimus, ramucirumab, S-1, and tivantinib all failed to improve overall survival as second-line therapy after sorafenib in placebo-controlled RCTs[11-15]. In the placebo-controlled RESORCE (Regorafenib after Sorafenib in Patients with Hepatocellular Carcinoma) study, regorafenib significantly improved overall survival in Child-Pugh A patients with disease progression on image study during sorafenib therapy and tolerancy for sorafenib (it is possible to administer ≥ 400 mg for ≥ 20 days during the 28-day period before the end of treatment)[16].

An RCT of sorafenib and erlotinib found that the addition of erlotinib to sorafenib conferred no survival benefit[17].

■ Explanation

Many RCTs related to CQ43 were extracted in the literature search. Therefore, the current edition excludes articles about the predictive factors for the efficacy of systemic chemotherapy that were cited in the third edition because their content does not fit the intent of CQ43. Also excluded are articles that report outcomes of sorafenib therapy in Child-Pugh B patients because of low levels of evidence compared with the RCTs, as well as articles on post-TACE therapy, adjuvant TACE therapy, and combination therapy with anticancer drugs and locoregional therapy because they did not involve RCTs.

Sorafenib had better overall survival than placebo in the SHARP study in 2008[1] and the Asia-Pacific study in 2009[2]. In both studies, sorafenib was administered for unresectable advanced HCCs that were not indications for surgical resection, liver transplantation, locoregional therapy, or

TACE in Child-Pugh A patients with good PS and favorable hepatic functional reserve. Therefore, the same indications are used as indications for sorafenib. The efficacy of sorafenib was also verified in both studies' subgroup analyses as well as by a systematic review[3-6]. Therefore, based on sufficient evidence for the beneficial effect on unresectable HCC, sorafenib is strongly recommended. In Japan, many patients have been treated with sorafenib in the last 8 years following its approval for public health insurance in May 2009.

After reports of the efficacy of sorafenib for advanced HCC, many RCTs were performed to investigate the efficacy of other molecular-targeted drugs such as sunitinib, brivanib, and linifanib and of combination therapy with sorafenib and erlotinib, using sorafenib as a control; however, none of the drugs or the combination therapy showed superiority or non-inferiority over sorafenib in overall survival, the primary endpoint of the RCTs[7-9,17]. Lenvatinib was reported to be non-inferior to sorafenib at the 2017 Annual Meeting of the ASCO[10]. In March 2018, lenvatinib was approved for treatment of HCC in Japan and is expected to become the treatment of choice for first-line therapy.

Evaluation of the molecular targeted drugs brivanib, everolimus, ramucirumab, and cytotoxic anticancer drug S-1 as second-line chemotherapy after sorafenib revealed no superiority over placebo for overall survival, the primary endpoint of the studies[11-14]. In addition, tivantinib failed to improve overall survival in patients with HCC with high expression levels of MET in a placebo-controlled study[15]. Regorafenib was the first drug to improve overall survival as second-line chemotherapy after sorafenib, as reported by the RESORCE study which compared the efficacy of regorafenib versus placebo in Child-Pugh A patients with disease progression on image study during sorafenib therapy and tolerancy for sorafenib (it is possible to administer ≥ 400 mg for ≥ 20 days during the 28-day period before the end of treatment)[16]. Given the RESORCE study findings, regorafenib is now included in the Guidelines as a recommended second-line therapy after sorafenib failure. However, because of the characteristic inclusion criteria used in the RESORCE study compared with other studies of second-line chemotherapy drugs, regorafenib is strongly recommended only for Child-Pugh A patients who show disease progression on image study during sorafenib therapy and tolerancy for sorafenib. However, during the committee meeting, some members voiced concerns over the strong recommendation.

■ References

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CQ44 Is HAIC recommended for unresectable advanced HCC?

Recommendation

Weak recommendation: HAIC may be performed for advanced HCC accompanied by progressive intrahepatic lesions, which are not indications for surgical resection, liver transplantation, locoregional therapy, or TACE.

■ Background

Despite the need for specific skills, many patients have been treated by HAIC in Japan. It allows highly concentrated anticancer drugs to be adminstered directly into the HCCs, preventing the systemic administration of a high concentration of drugs and thus suppressing the incidence of adverse effects. Here, we reviewed the recommendation of TAI for unresectable advanced HCC.

■ Scientific Statement

A literature search conducted with a newly created search query and a publication date between January 1, 2012 and June 30, 2016 extracted 66 articles. This was narrowed down to 14 in the first screening. Ten articles that each reported ≥ 50 HAIC cases were extracted in the second screening. In addition, 2 articles were hand-searched from those published after July 2016. With the inclusion of 14 articles from the third edition, a total of 26 articles are cited here.

No large-scale studies have shown that HAIC has a beneficial effect on HCC compared with best supportive care (BSC) or sorafenib.

In a small-scale RCT, combination therapy with systemic administration of interferon and cisplatin arterial infusion significantly improved median overall survival compared with cisplatin arterial infusion chemotherapy or BSC alone[1]. Combination therapy with interferon and 5-FU arterial infusion also significantly improved overall survival compared with historical controls[2]. In a study using data from primary HCC cases recorded in the database of the Liver Cancer Study Group of Japan, treatment outcomes were compared between HAIC with 5-FU and cisplatin and BSC in two groups of patients matched by propensity score[3]. Compared with BSC, HAIC had a good treatment outcome (hazard ratio 0.60; $p < 0.0001$) even in patients with 4 or more nodules or portal vein tumor thrombus[3].

In a retrospective cohort study of HAIC and sorafenib in 2 groups of patients matched by propensity score, no difference in prognosis was observed between sorafenib therapy and HAIC with 5-FU and cisplatin[4,5].

In a phase II clinical study, combination therapy with sorafenib and cisplatin arterial infusion chemotherapy improved prognosis compared with sorafenib therapy alone[6].

When outcomes of HAIC using 5-FU as the main drug were stratified by hepatic functional reserve, response rate and prognosis were worse in patients with a Child-Pugh score of 8 or 9 than those in patients with a score of 5-7[7].

■ Explanation

The response rate of HCC to HAIC ranges widely from 0-71%, indicating varying tumor shrinkage effects, and no studies have clearly shown that HAIC improved overall survival (see Supplemental Table, p227-228). Although the small-scale study that reported combination therapy with interferon and cisplatin arterial infusion was an RCT, there is a problem associated with the study design in that the number of patients and the rationale for the study are not specified[1]. The median survival period was reported to be 2.6-17.6 months, showing considerable variation (Supplemental Table), and this is thought to be attributable to differences in tumor stage and hepatic functional reserve. Although a comparative study using historical controls[2] and a retrospective study of HAIC and BSC in 2 groups of patients matched by propensity score[3] suggested the prognostic benefits of HAIC, the lack of a large-scale RCT means that the level of evidence is not high. However, even after the molecular-targeted drug sorafenib was introduced into clinical practice in Japan, HAIC has been performed in cases of advanced HCC (e.g., with invasion of the main portal vein and multiple intrahepatic lesions). This suggests that the procedure may be performed for the treatment of advanced HCC with intrahepatic lesions. Therefore, the Revision Committee has decided on a weak recommendation for HAIC.

To verify the prognostic benefits of HAIC, it is desirable to conduct high-quality comparative studies that use molecular-targeted drugs like sorafenib as a control, but the difficulty associated with this means that there have been no such studies carried out as yet. Also, despite promising outcomes in phase II clinical studies[6,8], the efficacy of combination therapy with HAIC and molecular-targeted drugs has not been reproduced in a phase III clinical study[9].

■ References

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CQ45 What factors predict treatment response to drug therapy?

Recommendation

No recommendation: There is insufficient scientific evidence that some factors effectively predict treatment response to drug therapy.

■ Background

Greater benefit is expected of drug therapy with proven efficacy. Therefore, to grade recommendations, we investigated the predictors of treatment response in drug therapy.

■ Scientific Statement

The third edition cited 5 studies that investigated factors predicting response and the outcome of drug therapy with sorafenib, the standard drug for HCC. For the current Guidelines, a literature search conducted with a newly created search query and a publication date between January 1, 2012 and June 30, 2016 extracted 69 articles about HCC, drug therapy, and treatment outcome prediction. This was narrowed down to 17 articles in the first screening. Nine of these articles with highly reliable data were extracted in the second screening after excluding articles that reported analysis of

predictors before sugery or after curative surgery. A total of 14 articles, including the 5 articles from the third edition, are cited for CQ45.

Many studies have reported skin toxicity[1], reduced AFP levels[2-4], and a combination of several tumor markers[5–10] as predictive factors for clinical response. Some studies suggested the association of prognosis with changes in hepatic functional reserve during treatment[4,11]. Long-term survival is expected in patients whose treatment was terminated due to adverse events, in those without extrahepatic metastasis or vascular invasion, and in those with good PS[12]. On the other hand, lung metastasis was a factor predicting poor prognosis[13]. Also, the assessment of peri-treatment intratumoral hemodynamic changes on CT images[4] and peri-treatment changes on MRI (changes in K^{trans} and increases in ADC)[14] are useful predictive factors for prognosis.

■ Explanation

The United States Food and Drug Administration classifies predictive markers into known valid, probable valid, and exploratory groups based on evidence levels of the predictive ability of the markers. There are currently no well-established factors that predict treatment response of HCC to sorafenib. Low AFP levels before and after treatment[2-4], pre-treatment IGF-1 levels[9], low levels of angiopoietin 2 or VEGF[7,10], and low Child- Pugh scores[4,11] have been proposed as factors predictive of good prognosis, but none were proposed based on the findings of a large prospective study. Therefore, the Revision Committee concludes there is insufficient scientific evidence to verify that some factors effectively predict treatment response to drug therapy and therefore proposes no recommendation in the present Guidelines.

■ References

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CQ46 How should treatment response to drug therapy be assessed?

Recommendation

Strong recommendation: Treatment response to drug therapy should be assessed using response evaluation criteria that reflect intratumoral blood flow, because accurate assessment of areas of necrosis and viable tumor is essential.

■ Background

RECIST and World Health Organization (WHO) criteria that evaluate tumor shrinkage have been used to evaluate treatment response to conventional chemotherapy. Typical HCC is hypervascular, and intratumoral blood flow changes have been attracting attention since sorafenib became available.

Here, we investigated the recommendation about the assessment of response of HCC to drug therapy.

■ Scientific Statement

A literature search conducted with a newly created search query and a publication date between January 1, 2012 and June 30, 2016 extracted 141 articles that assessed response to drug therapy in HCC. This was narrowed down to 24 in the first screening. This was narrowed further to 2 articles in the second screening after excluding review articles and clinical studies with a small number of patients. A study conducted by Lencioni et al. that investigated the validity of mRECIST using a large-scale database[1] was also included as an important article published after July 2016. With the addition of 7 articles from the third edition, a total of 10 articles are cited for CQ46.

The WHO criteria[2] and various other response evaluation criteria were established to share common criteria about how to assess clinical response to chemotherapy in trials. Among those criteria, RECIST1.1 is currently the most commonly used. However, the criteria used more often to determine the treatment response of HCC are the mRECIST, EASL RECICL, and Choi criteria[1,3-8], which evaluate decreases in intratumoral blood flow.

A comparison of RECIST1.1, mRECIST, and the Choi criteria showed that the Choi criteria most closely reflect treatment response to sorafenib[9]. The treatment response to sorafenib was assessed definitively with dual-energy CT to measure viable parts of tumors by changes in volumetric iodine uptake[10]. Analysis using cases from a placebo-controlled study of brivanib after sorafenib showed that objective response determined by mRECIST may become an alternative indicator of overall survival[11].

■ Explanation

In contrast to conventional chemotherapy with cytotoxic anticancer drugs, the therapies for HCC such as ablation and embolization do not necessarily lead to tumor shrinkage. Also, molecular-targeted drugs that suppress angiogenesis, such as sorafenib, often induce tumor necrosis without tumor shrinkage. For these reasons, response evaluation criteria for necrosis and viable tumor have been established for the evaluation of treatment response to HCC. Therefore, mRECIST[6], RECICL by the Liver Cancer Study Group of Japan[7], and the EASL criteria[8] are currently being used to assess the response of HCC. However, the problem associated with these evaluation criteria is difficulty objectively assessing necrotic areas. Regardless of this difficulty, because the accurate assessment of areas of necrosis and viable tumor is essential, the use of response evaluation criteria reflecting intratumoral blood flow changes is strongly recommended.

However, because existing response evaluation criteria rely on 2D imaging technology, accurate assessment may be limited when the tumor morphology is complicated. Recent advances in 3D

technology have allowed 3D imaging-based assessment of tumor volume response and an initial experience in patients with advanced hepatocellular carcinoma treated with sorafenib has been reported[10].

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CQ47 How should the side effects of drug therapy be managed?

Recommendation

Strong recommendation: When using cytotoxic anticancer drugs, attention must be paid to hematological toxicity because of a high incidence of pancytopenia in patients with HCC. Because

each drug used in molecular-targeted therapy is associated with specific severe side effects, it is important to follow up patients carefully and respond to adverse events properly, including reducing drug dosage and prescribing drug holidays.

■ Background

Because of the high prevalence of chronic liver disease in the background, HCC is often accompanied by pancytopenia or impaired liver function. Therefore, careful attention must be paid before instituting drug therapy. Here, we investigated drug therapy -related side effects and proper recommendations.

■ Scientific Statement

A literature search conducted with a newly created search query used in the third edition and a publication date between January 1, 2012 and June 30, 2016 extracted 153 articles related to the side effects of drug therapy for HCC, which were narrowed down to 140 in the first screening, from which 18 articles were selected after excluding review articles and clinical studies with a small number of patients in the second screening. A total of 25 articles, including the 7 from the third edition, are cited for CQ47.

■ Explanation

Because most patients with HCC have chronic liver disease such as chronic hepatitis and cirrhosis, there is a high prevalence of cytopenia such as neutropenia, erythropenia, and thrombocytopenia before treatment. Myelosuppression is a common side effect of cytotoxic anticancer drugs, so it is essential to be cognizant of the hematological toxicity[1]. Accordingly, the Revision Committee strongly recommends paying attention to hematological toxicity when using cytotoxic anticancer drugs.

Each molecular-targeted drug has specific side effects. For example, sorafenib causes some form of side effects in about 80% of patients. The most frequent are hand-foot syndrome, rash/desquamation, diarrhea, loss of appetite, hypertension, fatigue, alopecia, and nausea[2,3]. Side effects specific to individual molecular-targeted drugs have been reported in various large clinical studies[4-12].

In sorafenib therapy, the side effect of hand-foot syndrome influences continuation of therapy and often appears soon after its initiation[13], but administration of urea-based cream may prevent the worsening of this side effect[14].

Compared with Child-Pugh A, Child-Pugh B patients with impared hepatic functional reserve often develop hyperbilirubinemia, ascites, and hepatic encephalopathy during sorafenib therapy[15], although no significant differences in side effects were observed in a study that compared the 2

groups matched by age, sex, and tumor progression[16]. Other studies reported that sorafenib is safe and tolerated regardless of baseline liver function[17-20]. Furthermore, the side effects of sorafenib were not affected by different starting doses[21].

The incidence of hand-foot syndrome, rash, and liver failure is high in Japan compared with other countries, so proper management of drug side effects during therapy is required[22]. Survival tended to be longer in patients with skin toxicity, including hand-foot syndrome, than in patients without this condition, suggesting that the side effects may be an indicator of treatment response to sorafenib[23]. Even when therapy is terminated due to adverse side effects, patients with good hepatic functional reserve may move onto second-line therapy[24].

Accordingly, it is recommended that patients receiving molecular-targeted drugs be followed up carefully and adverse events be managed adequately by reducing drug dosage or prescribing drug holidays.

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Supplemental Table. Post-TAI response rate and survival period by drug (n = ≥ 50)

	Drug	Cases (n)	Response rate (%)	Median survival period (months)	PMID	Study design	Vascular invasion (%)
Single drug	Doxorubicin (intraarterial injection)	72	60	7	10370678[1]	RCT	
	Doxorubicin (systemic injection)	44.1	6.5				
	CDDP	67	37	10.7	12197216[2]	Cohort study	
	DDP-H	123	15.2	12.2			
	DDP-H	80	33.8	ND	18430093[3]	Cohort study	80
	DDP-H	84	3.6	7.0	21459893[4]	Cohort study	31
	DDP-H	123	15.2	12.2	24743198[5]	Cohort study	39.0
Multiple drugs	CDDP, 5-FU (low FP)	52	71	ND	10203596[6]	Cohort study	
	CDDP, 5-FU (low FP) ＋/－ LV	53	24.5	ND	18979100[7]	Cohort study	26.4
	CDDP, 5-FU (low FP)	52	38.5	15.9	20616598[8]	Cohort study	80.8
	CDDP, 5-FU (low FP)	90	34.4	10.6	25992784[9]	Cohort study	ND
	CDDP, 5-FU (low FP)	77	ND	10.9	26158136[10]	Cohort study	33.8
	CDDP, 5-FU (low FP)	54	22.2	5.1	24133667[11]	Cohort study	81.5
	CDDP, 5-FU (low FP)	68	0	5.0	19763572[12]	RCT	87.5
	CDDP, 5-FU		16.7	6.3			88.9
	CDDP, 5-FU	476	40.5	ND	24008659[13]	Cohort study	44.1
	CDDP, mitomycin C,	58	ND	9.5	24824520[14]	Cohort	55.2

5-FU					study	
CDDP, mitomycin C, 5-FU, LV	53	28.3	13.2	15779483[15]	Cohort study	
CDDP, mitomycin C, 5-FU	56	7.4	8.8	25663125[16]	RCT	88.8
CDDP, 5-FU		17.2	11.1			89.6
CDDP, Doxorubicin	50	22	8.3	24967421[17]	Cohort study	48
CDDP, Sorafenib	66	21.7	10.6	27573564[18]	Phase II	100
IFN, CDDP	68	33	4.4	10813709[19]	RCT	
CDDP		14	2.6			
BSC			1.2			
IFN, 5-FU	116	52	6.9	16565970[20]	Cohort study	100
BSC (historical control)			ND			
IFN, 5-FU	55	29.1	9.0	17940838[21]	Cohort study	63.6
IFN, 5-FU	102	39.2	9.0	21659784[22]	Cohort study	100
IFN, 5-FU	104	24.6	10.5	22133996[23]	RCT	50
IFN, 5-FU, CDDP		45.6	17.6			26.7

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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