Review

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Systemic therapies for hepatocellular carcinoma

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Summary **Hepatocellular carcinoma (HCC) is a common cancer with high incidence and mortality worldwide. The main treatments for HCC include radical hepatectomy, liver transplant, locoregional therapies, and systemic therapies. Systemic treatments include targeted agent treatment, chemotherapies, antiviral therapies, and nutritional treatments. According to the results of SHARP and ORIENTAL study, sorafenib became the standard first-line therapy since 2008 because of nearly three months of survival improvement in patients with advanced HCC. Subsequent studies on targeted agents found that neither sunitinib nor brivanib were superior to sorafenib as first-line therapy. After progression or intolerance of sorafenib, brivanib did not improve the overall survival (OS) compared with placebo as second-line therapy. Randomized controlled EACH study and retrospective AGEO study for systemic chemotherapy showed that oxaliplatin-based or gemcitabine-based regimen was effective for advanced HCC patients. Randomized controlled trial for adjuvant chemotherapy in China showed that capecitabine could reduce the risk of recurrence and improve postoperative survival of HCC. Comparing sorafenib with other treatments, several retrospective studies found that other treatments were not inferior to sorafenib in terms of OS. In the systemic treatment of HCC, antiviral treatment can decrease the recurrence of HBV-related HCC postoperation and prolong the survival of patients. Based on the etiology, symptoms, complications, and treatment-related side effects, nutritional treatment is also very important for HCC patients. Systemic chemotherapy, newer targeted agents, and immune therapy are the new directions in future research.**

Keywords: Hepatocellular carcinoma, systemic therapy, targeted agent, antiviral therapy, nutritional therapy

1. Introduction

Hepatocellular carcinoma (HCC) is common cancer with high incidence and high mortality worldwide, especially in less developed regions. GLOBOCAN showed that the estimated incidence of liver cancer (including cancers from intrahepatic bile ducts) in both sexes was 782,451 and the estimated mortality was 745,533 in 2012 (*http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx*). Liver cancer is the fifth most common cancer in men and ninth in women. Although it is the seventh most common solid tumor in terms of incidence, liver cancer is the second leading cause of cancer-related death. The main risk factors of HCC include hepatitis virus infection, alcoholic cirrhosis, and non-alcoholicsteatohepatitis (NASH). Without obvious symptoms in its early stage, most of the HCCs are advanced diseases without the opportunity of radical operations upon diagnosis. A percentage of the patients with advanced HCC present abnormal liver functions. With the development of cancer progression, aggravation of liver dysfunction makes systemic drug therapy unavailable. All these factors result in worse prognosis of advanced HCC.

Radical resection or liver transplantation is an important treatment for patients with resectable and transplantable HCC. Meanwhile, locoregional therapy, such as ablation, arterially directed therapies, and

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external-beam radiation therapy, as well as systemic therapy, are available for cases with unresectable HCC or those who are not transplant candidates. Systemic therapy includes targeted agent therapy, chemotherapy, antiviral treatment and nutritional support treatment, and so on. According to the results of Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP), the targeted agent sorafenib has become the standard systemic therapy drug for patients with inoperable HCC (*1*). Systemic chemotherapy has also been considered as palliative treatment for advanced HCC, especially with extrahepatic spread. The response rates of traditional cytotoxic chemotherapy agents, such as adriamycin, fluorouracil, cisplatin, and mitomycin, are less than 10%. The EACH (*2*) and AGEO (*3*) study have shown the effectiveness of oxaliplatin-based or gemcitabine-based regimen in advanced HCC. Randomized controlled studies have also been carried out for adjuvant chemotherapy after radical resection and liver transplantation. Systemic nutrition is also one of the most important palliative treatments for advanced HCC. To date, more studies have focused on systemic therapies for HCC. Thus, the systemic treatments for HCC are reviewed in this study.

2. Targeted agents

In 2008, the SHARP study demonstrated an overall survival (OS) improvement of nearly three months for sorafenib compared with the best supportive care in patients with advanced HCC (*1*). Thereafter, studies on targeted agents for HCC treatments have increased. The ORIENTAL study in Asia-Pacific also obtained similar OS improvement (*4*). To explore more targeted agents for advanced HCC, sunitinib and brivanib have been investigated and compared with sorafenib as first-line therapy in phase III trials. Results showed that sunitinib and brivanib were not superior in terms of OS. Thus, the European Society for Medical Oncology (ESMO) 2012 and the latest National Comprehensive Cancer Network (NCCN) guideline recommended sorafenib as the standard first-line therapy for advanced HCC with liver function of Child-Pugh A (CPA) (*5,6*). The phase III clinical trials on targeted agents are summarized in Table 1.

2.1. *Sorafenib*

Sorafenib is a small molecule tyrosine kinase inhibitor of multitargets, such as VEGFR-1, VEGFR -2, VEGFR -3, PDGFR-β, Raf, RET, and FLT-3 (*7*). Thus, it has the double antitumor effect of antiproliferation and antiangiogenesis. First, sorafenib can inhibit the growth of cancer cells through the RAF/MEK/ERK pathway (*8*). Second, it can inhibit the angiogenesis of the tumor, which leads indirect antitumor effect (*9*). The 2010 ESMO clinical practice guidelines recommended

Table 1. Summary of phase III clinical trials in targeted agents in HCC

Year	Author (*Ref.*)	Phase	Total No. cases	Treatments	ORR	DCR	Median TTP (months)	Median PFS (months)	Median OS (months)
2008	Llovet (*1*)	III	602	Sorafenib *vs.* placebo	2.0% *vs.* 1%	43.0% *vs.* 32%	5.5 *vs.* 2.8	-	10.7 *vs.* 7.9
2009	Cheng (*4*)	III	271	Sorafenib *vs.* placebo	3.3% *vs.* 1.3%	35.3% *vs.* 15.8%	2.8 *vs.* 1.4	-	6.5 *vs.* 4.2
2013	Cheng (*24*)	III	1074	Sunitinib *vs.* sorafenib	-	-	4.1 *vs.* 3.8	3.6 *vs.* 3.0	7.9 *vs.* 10.2
2013	Johnson (*25*)	III	1155	Brivanib *vs.* sorafenib	12% *vs.* 9%	66% *vs.* 65%	4.2 *vs.* 4.1	-	9.5 *vs.* 9.9
2013	Llovet (*26*)	III, second-line	395	Brivanib + BSC *vs.* placebo + BSC	10% *vs.* 2%	61% *vs.* 40%	4.2 *vs.* 2.7	-	9.4 *vs.* 8.2
2014	Kudo (*27*)	III, adjuvant therapy after TACE	502	Brivanib + TACE *vs.* placebo+TACE	48% *vs.* 42%	79% *vs.* 79%	8.4 *vs.* 4.9	-	26.4 *vs.* 26.1

TACE: transarterial chemoembolization; BSC: best supportive care.

sorafenib as the standard first-line therapy option for advanced HCC in grade IA (*10*). Other studies on second-line and adjuvant therapy with sorafenib have also been reported.

2.1.1. *Sorafenib in treatment of advanced HCC*

The first phase III, randomized, placebo-controlled trial is the SHARP study, which involved 602 patients with advanced HCC or progression after surgical or locoregional therapies. All eligible patients were randomly assigned in a 1:1 ratio to receive either 400 mg of sorafenib twice a day or a placebo. The primary endpoints are OS and the time to symptomatic progression. The results showed that the OS of the sorafenib and placebo groups was 10.7 and 7.9 months, respectively ($p < 0.001$). Although the difference in time to symptomatic progression was not statistically significant (4.1 months *vs*. 4.9 months, $p = 0.77$), the time to radiologic progression was obviously longer in the sorafenib group, with 5.5 months (2.8 months in the placebo group; $p < 0.001$). The disease control rate (DCR) was significantly higher in the sorafenib group (43% *vs*. 32%, $p = 0.002$). The common adverse events (AEs) include diarrhea, weight loss, hand-foot skin reaction, and hypophosphatemia. This experiment is the first trial with great significance in proving that systemic therapy is effective in advanced HCC.

The second trial is the ORIENTAL study carried out in 23 sites of the Asia-Pacific region where chronic hepatitis B infection and virus-related HCC was prevailing. The design of the ORIENTAL study was similar to that of the SHARP study, except for the 2:1 ratio. A total of 226 patients were randomized in the study. The results showed that sorafenib treatment could also prolong the OS and time to progression (TTP) of patients in the Asia-Pacific region. The OS of the sorafenib and placebo groups were 6.5 and 4.2 months ($p = 0.014$), respectively. The TTP in the sorafenib and placebo groups were 2.8 and 1.4 months ($p = 0.0005$), respectively. In 2012, a subset analysis of the ORIENTAL study suggested that sorafenib was effective for patients from the Asia-Pacific region with advanced HCC, irrespective of the baseline status (*11*). Comparing the ORIENTAL study with the SHARP study, the OS of the patients significantly varied. The OS of the patients in the Asia-Pacific region was much worse than that in the SHARP study. This difference may be attributed to the following reasons: The patients in the Asia-Pacific region have more Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 2, Barcelona Clinic Liver Cancer (BCLC) stage C, hepatitis B virus infection, tumor burden, and lung metastasis.

Sorafenib is also effective as a second-line therapy. A retrospective study in Korea showed the DCR was 58.3% in the second-line therapy after failure of the

Table 2. Response assessment by modified RECIST (mRECIST) in ESMO 2012 (*5*)

Target lesions	
Complete response (CR)	Disappearance of any intratumoral arterial enhancement in all target lesions
Partial response (PR)	At least a 30% decrease in the sum of the diameters of viable (enhancement in the arterial phase) target lesions, taking the baseline sum of the diameters of target lesions as reference
Stable disease (SD)	Any cases that do not qualify for either PR or PD
Progressive disease (PD)	An increase in at least 20% in the sum of the diameters of viable (enhancement in the arterial phase) target lesions recorded since treatment started
Non-target lesions	
Complete response (CR)	Disappearance of any intratumoral arterial enhancement in all non-target lesions
Stable disease (SD) or incomplete response (IR)	Persistence of intratumoral arterial enhancement in one or more non-target lesions
Progressive disease (PD)	Appearance of one or more new lesions and/ or unequivocal progression of existing non-target lesions
Additional recommendations	
New lesion	A new lesion can be classified as HCC if its longest diameter is at least 1 cm and the enhancement pattern is typical for HCC. A lesion with atypical radiological pattern can be diagnosed as HCC by evidence of at least 1 cm interval growth.
Pleural effusion or ascites	Cytopathological confirmation of the neoplastic nature of any effusion that appears or worsens during treatment is required to declare PD.
Lymph nodes in the porta hepatis	Lymph nodes detected at the porta hepatis can be considered malignant if the lymph-node short axis is at least 2 cm
Portal vein thrombosis	Malignant portal vein thrombosis should be considered as a non-measurable lesion and thus included in the non-target lesion group

first-line chemotherapy with fluorouracil plus cisplatin (*12*). The OS and progression-free survival (PFS) was 7.1 and 2.3 months, respectively. The effectiveness of sorafenib in second-line therapy was not inferior to that of the first-line therapy. Second-line therapy with sorafenib after the systemic chemotherapy did not augment the incidence of AEs. Phase III randomized clinic trials are still needed to confirm the results of this retrospective study involving 24 patients.

2.1.2. *Sorafenib in adjuvant treatment*

In 2014, the American Society of Clinical Oncology (ASCO) presented the results of sorafenib as adjuvant treatment after resection or ablation. Sorafenib as Adjuvant Treatment in the Prevention of Recurrence of Hepatocellular Carcinoma (STORM) is a phase III randomized, double-blind, placebo-controlled trial with 1114 patients. The primary endpoint is the recurrence-free survival (RFS) by independent review. The secondary endpoints included time to recurrence (TTR) and OS. However, the trial did not meet the primary endpoint of the study. No differences in RFS and TTR were observed between the sorafenib and placebo groups, with an RFS of 33.4 and 33.8 months and a TTR of 38.6 and 35.8 months, respectively. The OS was not yet reached (*13*). The results of the STORM study did not meet the primary endpoint either.

2.1.3. *Other questions about sorafenib usage*

The first question is about the safety and effectiveness of sorafenib in advanced patients with worse liver function. The SHARP and ORIENTAL phase III trials did not answer these questions because all patients involved had CPA liver function. All the current data are from retrospective studies with liver function of CPB, data about sorafenib in patients with CPC are limited. A retrospective study observed the effectiveness and safety of sorafenib in 41 advanced HCC with CPA (n = 25) and B (n = 16) liver functions (*14*). The results showed that toxicities led to treatment interruption in 7 patients with CPA and 3 with patients with CPB, as well as dose reduction in 10 patients with CPA and 6 patients with CPB. The incidence of toxicities was not higher in patients with CPB compared with that in patients with CPA. In terms of survival, TTP and OS were better in patients with CPA than those with CPB. TTP was 4 and 2 months (p = 0.0045), while OS was 8.4 and 3.2 months (p = 0.0007) in patients with CPA and CPB, respectively. Another retrospective study by Chiu *et al*. explored the efficacy, tolerability, and survival benefits of sorafenib in 64 patients with CPB liver function (*15*). The patients with CPB were divided into CPB7 (with a CPB score of 7) and CPB8-9 (with a CPB score of 8 and 9) subgroups and compared with those with CPA. The clinical benefit rate and PFS were similar in CPA, CPB7, and CPB8-9. However, the OS of patients with CPB8-9 was much worse because of advanced diseases. The incidence of grade 3/4 hand-foot syndrome, diarrhea, rash, leukopenia, thrombocytopenia, and anemia was similar. However, patients with CPB experienced more anemia, gastrointestinal bleeding, and hepatic encephalopathy partially because more patients had higher total bilirubin and alanine aminotransferase in the CPB subgroup. The third and largest study of the Global Investigation of therapeutic Decisions in hepatocellular carcinoma and its treatment with sorafenib (GIDEON) provided more data about the safety of sorafenib in HCC patients with CPB liver function (*16,17,18*). The GIDEON study is a global, non-interventional, prospective surveillance study with two interim analysis and one final analysis in 2012 and 2013 when approximately 500, 1,500, and 3,200 treated patients were followed up for ≥ 4 months. A total of 3,202 patients were evaluable for safety. In the second interim analysis with 1,571 patients, 61% of the patients had CPA status and 23% had CPB (*17*). In the final analysis, 61.5% had CPA status and 20.8% had CPB (*18*). The GIDEON study showed that the incidence rates of AEs were comparable between the Child-Pugh subgroups at 60% to 70%. Drug related serious AEs were more common in 14.1% of CPB than 8.8% of CPA patients. The Child-Pugh status did not affect the starting dose of sorafenib, and the average of daily dose of sorafenib in patients with CPB was not less than that with CPA. Survival analysis showed that the median OS was longer in patients with CPA at 13.6 months than those with CPB at 5.2 months. In patients with CPB, the median OS was 6.2, 4.8, and 3.7 months in patients with CPB7, CPB8, and CPB9 (*18*). Based on these data, the latest NCCN guideline of 2015 suggested sorafenib should be used with caution for HCC patients with CPB liver function.

The second question is about the safety and effectiveness of sorafenib in older HCC patients. In a retrospective study by Wong *et al*., the patients were divided into older (age ≥ 70 years, n = 35) and younger (age < 70 years, n = 172) groups. The PFS, OS, and Grade 3/4 AEs were similar in the older and younger groups. The median PFS was 2.99 months in the older group, while 3.09 months in younger group (p = 0.275), and the OS was 5.32 months versus 5.16 months (p = 0.310). Grade 3/4 AEs were observed in 68.6% of the older group and 62.7% of the younger group (p = 0.560). However, neutropenia, malaise, and mucositis were more frequent in the older cohort (*19*). The use of sorafenib in older patients was not mentioned in the NCCN or ESMO guidelines, caution should be included when sorafenib is used in older advanced HCC patients.

The third question is how to measure the tumor response of the targeted agents. The response evaluation of targeted therapy in advanced HCC is controversial. The Response Evaluation Criteria in Solid Tumors

(RECIST) is used to measure tumor response based on tumor size changes of target lesions and nontarget lesions. RECIST is an important and valuable method to evaluate the antitumor activity of cytotoxic drugs. In the SHARP and ORIENTAL studies, the evaluation method both applied the RECIST standard. Given that the targeted agents are often used solely in HCC with slow action, RECIST assessment is limited in response evaluation of targeted therapies. In 2010, the modified RECIST assessment (mRECIST) was proposed for response assessment of targeted agents and mentioned in detail in the 2012 ESMO guideline (Figure 1) (*5,20*). The mRECIST assessment is still not used as the standard evaluation method for targeted agents. Further studies are still needed to confirm the accuracy of this method. In some studies, symptoms from targeted agent treatment were reported to be related to antitumor response, such as diarrhea (*21*), hypertension (*14*), early skin toxicity (*22*), and early decrease in AFP (*23*). Given that the symptoms in some extent are subjective, they were not be used as routine assessment of antitumor response.

2.2. *Sunitinib*

Sunitinib is also an oral multitargeted tyrosine kinase inhibitor and effective in HCC. In 2013, an open-label, phase III trial comparing sunitinib and sorafenib was carried out by Cheng *et al*., in Taipei (*24*). A total of 1,074 patients were randomized for the study (530 patients in the sunitinib and 544 patients in the sorafenib groups). The median OS was 7.9 and 10.2 months in the sunitinib and sorafenib groups (p = 0.0014), respectively. The median PFS and TTP were not significantly different in the two groups. In terms of safety, more sAEs were observed in the sunitinib group, especially thrombocytopenia (29.7%) and neutropenia (25.7%). Meanwhile, more hand-foot syndrome (21.2%) was observed in the sorafenib group. The subgroup analysis showed that the median OS was similar in hepatitis B-infected patients in the two groups, but shorter in hepatitis C-infected patients with sunitinib (9.2 *vs*. 17.6 months; p = 0.9835). Sunitinib is significantly inferior to sorafenib in terms of OS. Therefore, sorafenib is still the standard systemic therapy for advanced or inoperable HCC patients.

2.3. *Brivanib*

Brivanib is a selective dual inhibitor of vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) signaling. It is the third targeted agent that has been proven to be effective in advanced HCC. Most frequent grade 3/4 AEs are hyponatremia, AST elevation, fatigue, hand-foot-skin reaction, and hypertension. Several phase III trials have investigated brivanib for first-line, second-line, and adjuvant therapies for advanced HCC. However, the results showed that brivanib totally failed in advanced HCC. In the first-line therapy, brivanib exhibited similar survival and DCR with sorafenib (*25*). In the second-line therapy, the combination of brivanib with the best supportive care (BSC) was superior to BSC in terms of OS (*26*). As an adjuvant therapy, brivanib did not improve the OS after transarterial chemoembolization (TACE) (*27*).

In first-line therapy of the BRISK-FL study, advanced HCC patients were randomly assigned (1:1) to the sorafenib group (400 mg twice daily, n = 578) and brivanib group (800 mg once daily, n = 577) (*25*). Tumor response was assessed with the mRECIST standard. Results showed that the primary end point of OS noninferiority for brivanib was not met. The median OS was 9.9 and 9.5 months in the sorafenib and brivanib groups (p = 0.3116), respectively. The secondary end points of TTP, ORR, and DCR were also similar between two groups.

In the second-line therapy of the BRISK-PS study, brivanib was used after progression or intolerance to sorafenib in patients with advanced HCC (*26*). A total of 395 patients were randomly assigned (2:1) to brivanib (800 mg orally once daily) or placebo groups. Although TTP and ORR were better in brivanib, the OS was not significantly different between brivanib plus BSC and placebo plus BSC. TTP was 4.2 months in the brivanib group and 2.7 months in the placebo group (p = 0.001). ORR was 10% and 2% in the brivanib and the placebo groups by mRECIST standard. The median OS was 9.4 and 8.2 months in the brivanib and placebo groups (p = 0.3307), respectively. Therefore, patients with advanced HCC after progression or intolerance to sorafenib did not seem to benefit from brivanib in terms of OS.

Adjuvant therapy with brivanib after TACE did not prolong the survival time of the patients in a multinational, randomized, double-blind, placebo-controlled, phase III study. Patients with TACE-eligible HCC were assigned (1:1) to receive either brivanib (800 mg) or placebo orally every day after the first TACE. A total of 870 patients were planned to be randomized. However, the therapy was terminated after randomization of 502 patients (brivanib n = 249; placebo n = 253) when BRISK-FL and BRISK-PS studies failed to meet the OS objectives. The median OS was 19.1 months with brivanib versus 26.1 months with placebo (p = 0.5280). The most frequent grade 3-4 AEs included hyponatremia (18% with brivanib *vs*. 5% with placebo) and hypertension (13% *vs*. 3%). Thus, brivanib did not improve the OS of HCC as adjuvant therapy after TACE (*27*).

3. Chemotherapy drugs

Studies about traditional chemotherapy agents in

advanced HCC, especially after progression or failure of locoregional therapy, are limited because the OS time was short, with low ORR and obvious side effects. Newer chemotherapy agents, such as oxaliplatin, gemcitabine, irinotecan, taxus, and orally administered fluorouracil are widely used in digestive tract cancers to prolong the survival of patients. Oxaliplatin is one of the third generation platinum drugs with higher efficiency and good tolerance. It is also effective in advanced HCC in some phase II studies, and increasingly used in advanced HCC. Capecitabine and S-1 are oral anticancer drugs that are as effective as venous fluoropyrimidine in gastric and colorectal cancers. Gemcitabine is a standard chemotherapy drug for inoperable pancreatic cancer. Meanwhile, liver is tissue homologous with the gallbladder and pancreas. Thus, systemic chemotherapy in advanced or inoperable HCC has drawn lessons from the chemotherapy of other digestive tract cancers. Single agents are often used in patients with high PS score or worse tolerance. Combination of two or more drugs is used in patients with better conditions. Oxaliplatin-based or gemcitabine-based chemotherapy regimens are currently used in advanced HCC.

3.1. *Single-drug regimen*

Single-agent chemotherapy is frequently used in patients postoperation or those with high PS. At present, the investigated newer drugs include gemcitabine, oxaliplatin, capecitabine, and so on. Capecitabine is an orally administered anticancer drug that can be easily accepted by patients. Capecitabine is used in gastric, colorectal, and breast cancers, and has been proven effective by phase III trials. At present, capecitabine is used in advanced HCC, as well as adjuvant therapy postoperation. A retrospective study conducted by Patt *et al*. investigated the anticancer effect of capcitabine on 63 liver patients with 37 HCC, 18 cholangiocarcinoma, and 8 gallbladder cancer (*28*). The ORR of capecitabine in the HCC group was 1%, and one patient obtained radiological complete response; the OS was 10.1 months. The main side effects include hand-foot syndrome with 37% and grade 3 thrombocytopenia with 8%.

A randomized, controlled trial conducted by Xia *et al*. provided evidence on capecitabine in adjuvant chemotherapy after HCC operation (*29*). In two years, 60 postoperative HCC patients were randomized into the capecitabine group (n = 30) or control group (n = 30). The recurrence rate was lower in the capecitabine group (53.3% *vs*. 76.7%). The median TTR in capecitabine was twice that of the control group (40.0 months *vs*. 20.0 months, p = 0.046). The 5-year OS rate was also higher in the capecitabine group (62.5% *vs*. 39.8%, p = 0.216). Adverse reactions, such as nausea, vomiting, diarrhea, and decreased white blood cell and/or platelet counts, were all tolerable. Postoperative adjuvant chemotherapy with capecitabine can reduce the risk of recurrence and tends to improve postoperative survival of HCC.

3.2. *Two-drug regimen*

Combination of two drugs is an often used regimen in chemotherapy. Platinum plus fluoropyrimidine is one of the most frequently used combination regimen. A phase III trial, named EACH study, with systemic chemotherapy was sponsored by Chinese researchers in 2007 (*2*). This study is a multicenter, open-label, randomized trial comparing FOLFOX4 (infusional fluorouracil, leucovorin, and oxaliplatin, n = 184) and doxorubicin (n = 187). A total of 371 patients with advanced or metastatic HCC were included in the study. The primary end point was OS, and response rate was assessed by RECIST. The results showed that FOLFOX4 was superior in terms of PFS, ORR, and DCR. The median PFS was 2.93 months for FOLFOX4 and 1.77 months for doxorubicin (p = 0 .001; HR = 0.62). The ORR was higher in patients with FOLFOX4 than that with doxorubicin (8.15% *vs*. 2.67%, p = 0.02). The DCR was 52.17% and 31.55% (p < 0.001), respectively. Final analysis after 266 events showed that FOLFOX4 had a trend to improve the OS of advanced HCC compared with adriamycin. The median OS of patients with FOLFOX4 or adriamycin were 6.40 and 4.97 months (HR = 0.80; p = 0.07), respectively. Additional analysis was carried out after 305 events had occurred, approximately 7 months after the final analysis. The survival benefit was maintained for FOLFOX, and the median OS was 6.47 months for FOLFOX4 and 4.90 months for DOX (p = 0.04; HR = 0.79). According the results of the EACH study, oxaliplatin-based regimen was approved by the State Food & Drug Administration (SFDA) to be used in locally advanced or metastatic HCC ineligible for curative resection or local treatment. Several factors affect the final results, making it a negative study in terms of OS. The high proportion of hepatitis B virus (HBV) infection (approximately 90%) and Barcelona Clinic Liver Cancer (BCLC) stage C disease (approximately 80%) may result in worse tolerance of the patients. Subsequent therapies, including sorafenib or others, were not mentioned. Given that the EACH study started before the publication of the SHARP study, ADM was chosen as control. The evidence for ADM benefit in advanced HCC was marginal based on the two studies that showed ADM was superior to no antitumor therapy (*30*) or nolatrexed (*31*). An imbalance was noted between the two groups, such as more cycles of prior transarterial chemoembolization (3.46 *vs*. 2.77 cycles) and greater proportion with prior systemic therapy (30% *vs*. 21%). The lack of blinding and imbalance also resulted in more patients withdrawing

after randomization, but before treatment (13patients *vs*. 1 patient) (*32*). As a result, reaching significance in unplanned analysis did not make the EACH study positive. Given that EACH study is a negative study in terms of OS, it was not been recommended as category I evidence in the ESMO and NCCN guidelines.

Gemcitabine with oxaliplatin is another frequently used two-drug combination regimen. A retrospective AGEO study reported in 2011 ASCO meeting shed more light on the systemic treatment of advanced HCC (*3*). In 10 years, the trial involved 204 patients, wherein 38.2% had extra-hepatic metastasis. For liver function assessment, 51.0% of the patients had CPA, 20.6% had CPB, and 4.4% had CPC. The analysis of effectiveness showed that the ORR was 22% and the DCR was 66%. The survival analysis proved that the PFS, TTP, and OS were 4.5, 8, and 11 months, comparable with those of sorafenib. More importantly, the patients with an objective response obtained more than twice of OS than those without an objective response (19.9 months *vs*. 8.5 months). About 8.5% of the patients were eligible for curative-intent therapies. In terms of safety, in a total of 1522 cycles of chemotherapy, grade 3/4 toxicity occurred in 90 patients (44.1%) and 32 patients (16%) discontinued the treatment because of limiting toxicities or patient refusal. The main severe toxicities include thrombocytopenia, 24%; neutropenia, 18.1%; diarrhea, 13.7%, and neurotoxicity, 11.7%.

Based on the results of the EACH and AGEO studies, oxaliplatin- or gemcitabine-based chemotherapy is effective and tolerant in patients with advanced or metastatic HCC. Some phase II trials also investigated the effectiveness of oxaliplatin plus capcitabine (XELOX), cisplatin plus capcitabine, or gemcitabine plus cisplatin (GP). Phase III trials to compare FOLFOX or GEMOX in advanced HCC have not been conducted. Given the limited data, no obvious recommendations for systemic chemotherapy were given in the 2012 ESMO or 2015 ASCO guidelines.

3.3. *Comparison of sorafenib and other treatments*

Sorafenib is a standard therapy for advanced inoperable HCC, but it is expensive, especially for developing countries. To find inexpensive treatments that are not inferior in efficiency, sorafenib was compared with other treatments. Several studies showed that the OS of patients was similar between sorafenib and other treatments. Kim *et al*. investigated sorafenib (n = 123) versus other treatments (TACE, radiotherapy and chemotherapy, n = 253) (*33*), and found no obvious difference in the OS of sorafenib (8.4 months) and the other treatments (8.2 months) (p = 0.601). Prognostic factors include high alpha-fetoprotein, massive/infiltrative intrahepatic tumors, macrovascular invasion, extrahepatic spread, and higher tumor-node-metastasis stage. According to these factors, a subgroup analysis found that patients with extrahepatic spread and massive/infiltrative tumors treated with sorafenib had longer survival time. Meanwhile, other treatments were superior to sorafenib without these prognostic factors. A retrospective study by Pinter *et al*. obtained similar results. The OS was similar in patients with sorafenib (7.4 months, n = 63) and TACE (9.2 months, n = 34) (*34*). In 2011, a single center retrospective study by Lee *et al*. compared the effect of sorafenib (n = 44) and traditional chemotherapy (n = 129) in patients with inoperable HCC (*35*). The OS of patients with sorafenib and chemotherapy were 23 and 43.6 weeks (p = 0.105) and the median PFS was 11.1 and 12.4 weeks (p = 0.496), respectively. The ORR was 2.3% and 6.2% and DCR was 52.3% and 43.4%, respectively. In terms of side effects, grade 3/4 neutropenia and skin toxicity are more common in the chemotherapy and sorafenib groups, respectively. No randomized clinical trials for comparing the targeted agents with other treatments have been conducted. According to the results of the retrospective studies, chemotherapy and other treatments are at least not inferior to sorafenib. Thus, identifying which one could benefit more from targeted agents or other treatments is difficult.

4. Anti-virus therapy

HBV infection is associated with the incidence of HCC and has unfavorable influence on anticancer therapies of HCC (*36,37*). During the course of chemotherapy and other immunosuppressive treatment, HBV will be reactivated in HCC patients with chronic virus carriers. Thus, anti-viral therapy is very important, especially in patients with HCC. Anti-viral therapy can reduce the risk of developing HCC, as well as decrease the risk of HBV reactivation, reduce the recurrence, and improve OS and DFS of HCC patients.

First, antiviral therapy can reduce the risk of developing HCC. Retrospective analysis showed that HBV-infection resulted in 17-fold higher risk of HCC through a follow up time of 8.0 years (*38*). A US study involving 2,671 adult participants with chronic HBV infection (49% Asian) showed that antiviral therapy for chronic HBV can reduce the risk of HCC (*39*). With a median follow up of 5.2 years, 3% developed HCC: 20 among the 820 patients had a history of antiviral therapy and 47 among the 1,851 patients did not undergo antiviral treatment. In propensity-adjusted Cox regression, patients with antiviral therapy had lower risk of HCC (HR = 0.39; $p < 0.001$). When viral loads > 20,000 IU/mL, patents with antiviral treatment had a significantly lower risk of HCC than that without antiviral treatment.

Second, antiviral therapy can reduce the risk of recurrence and improve the survival of HCC patients postoperation, or treatment with sorafenib. Retrospective analysis showed that antiviral therapy improved the DFS

and OS of HBV-related HCC patients after hepatectomy (*40*). In 2015, a Japanese study reported similar results in 162 HBV-related HCC patients (*41*). Several meta-analysis showed that antiviral therapy was associated with reduced risk of recurrence, as well as significant reductions in liver-related overall mortality (*42,43*). In 2014, a meta-analysis including 20 studies with a total of 8,204 participants showed that nucleoside analogs (NAs) antiviral therapy improved the prognosis of HBV-related HCC postoperation. The analysis also found that high viral load was significantly related to the risk of recurrence (RR = 1.85; $p < 0.001$) and poorer OS (RR = 1.47; $p < 0.001$) of HBV-related HCC postoperation. NA antiviral therapy significantly decreased the risk of HCC recurrence (RR = 0.69; $p < 0.001$) and improved both DFS (RR = 0.70; $p < 0.001$) and OS (RR = 0.46; $p < 0.001$) (*44*). In 2015, a randomized controlled trial on antiviral therapy showed that adefovir (10 mg/d) antiviral therapy improved the long-term survival after hepatic resection in patients with HBV-related HCC. The RFS and OS of the antiviral group were significantly better than those of the control group ($p = 0.026$, $p = 0.001$). In the Cox analysis, the antiviral therapy was an independent protective factor of late tumor recurrence (HR = 0.348; $p = 0.002$) (*45*). When combined with sorafenib, antiviral treatment also improved the prognosis of HBV-related HCC patients. A retrospective from China also showed that the antiviral therapy with NAs improved the OS of HBV-related HCC patients treated with sorafenib, especially with higher HBV-DNA level. The OS was 17.47 months and 13.10 months in patients with NA treatment and without antiviral treatment (HR = 0.67; $p = 0.03$) (*46*).

Third, antiviral therapy can reduce the risk of reactivation and liver failure. A retrospective study involving 590 HCC patients who were HBV surface antigen-positive and accepted either surgical resection or TACE showed that the HBV-reactivation rate in TACE treatment was 1.5% with antiviral therapy and 17.5% without anti-HBV therapy. The rate of deterioration of liver function was much lower in the anti-HBV therapy (1.5% *vs*. 8.1%) (*47*). In 2014, a prospective-retrospective study of 404 HBV-related HCC patients with hepatectomy showed that antiviral therapy improved the survival and liver function reserved at the time of recurrence. With a mean follow-up time of 52.4 months, patients in the antiviral group had higher 5-year OS rate (66.7% *vs*. 56.0%, $p = 0.001$). Meanwhile, the 5-year DFS was significant different in the two groups (44.7% *vs*. 38.1%, $p = 0.166$). With disease recurrence, the patients who received antiviral therapy had better liver function reserve, and more patients can receive curative treatment (38.5% *vs*. 24.3%, $p = 0.041$) (*48*).

In 2015, the American Gastroenterological Association (AGA) presented a guideline on the prevention and treatment of HBV reactivation during immunosuppressive drug therapy. Antiviral prophylaxis in hepatitis B surface antigen (HBsAg)-positive or antibody to hepatitis B core antigen (anti-HBc)-positive patients was associated with a reduction of 87% relative risk of reactivation, as well as 84% relative risk of HBV-related hepatitis flared. The HBV reactivation was obviously associated with the types of immunosuppressive drugs, such as B cell-depleting agents, anthracycline derivatives, tumor necrosis factor alpha inhibitors, cytokine or integrin inhibitors, tyrosine kinase inhibitors, and traditional immunosuppressive agents. However, newer anticancer agents have not been mentioned in the guideline. According to the estimated reactivation with available evidence, the drugs are divided into high-, moderate- and low-risk groups. HBV screening (HBsAg and anti-HBc, followed by a sensitive HBV DNA test if positive) is recommended for patients with moderate- or high- risk, who will undergo immunosuppressive drug therapy (Strong recommendation; Moderate-quality evidence). In patients with high risk, such as HBsAg-positive/anti-HBc-positive patients treated with anthracycline derivatives, AGA recommended antiviral treatment for at least 6 months after discontinuation of immunosuppressive therapy (Strong recommendation, Moderate-quality evidence). In patients with moderate risk, such as HBsAg-positive/anti-HBc-positive or HBsAg-negative/anti-HBc-positive patients treated with tyrosine kinase inhibitors, AGA suggested antiviral prophylaxis over monitoring for patients (Weak recommendation; Moderate-quality evidence). In patients with low-risk, AGA did not suggest routine administration of antiviral prophylaxis for patients undergoing immunosuppressive drug therapy (Weak recommendation; Moderate-quality evidence) (*49*).

5. Nutritional therapy

Liver is an important organ for digestion and related to nutrition metabolism absorption and detoxification. Liver cancer affects the nutrition of the patients, especially with other liver illness. The effect of liver cancer on the nutrition of the patients can be divided into etiology, symptoms, complications, and treatments. First, the main etiology of HCC includes viral hepatitis, heavy alcohol intake, nonalcoholic steatohepatitis (NASH), and aflatoxins intake. In hepatitis and NASH, the structures and functions of the liver change, which in turn change the metabolism of foods and energies. Thus, the incidence of malnutrition is high. Second, nontypical symptoms in patients with HCC have unfavorable effect on digestion. Nausea, vomiting, dyspepsia, abdominal distension, and loss of appetite aggravate malnutrition of advanced HCC patients. Third, complications of hypoalbuminemia, portal hypertension, ascites, gastrointestinal hemorrhage, hepatic encephalopathy, and electrolyte disorder in advanced disease also affect the nutrition of advanced

HCC patients. Fourth, anticancer treatment of operation, TACE, targeted agents, and chemotherapy prolong the survival of HCC patients, as well as lead to several side effects. Reduced remnant liver volume, diarrhea of targeted agents, and digestive tract reaction of systemic chemotherapy all result in negative effect to the nutrition of HCC patients. As a result, nutritional therapy is also very important in advanced HCC patients, as well as in postoperation patients.

Based on nutrition screening and assessment, nutrition therapy is administered according to the individual situations of the patients. No guidelines on nutritional treatments of primary HCC have been reported. However, several guidelines have been provided as references: ESPEN guidelines on enteral nutrition: hepatology (*50*), surgery (*51*), and non-surgical oncology (*52*). Detailed recommendations for energy, lipid, and special substance have been provided in the guideline (*52*). Diet and nutrition directions are also provided by the experts (*53*).

6. Conclusion

With the development of systemic therapies in HCC, prognosis in HCC patients has been improved. Given the inadequacy of evidence, more phase III randomized clinical trials are needed to support the utility of systemic chemotherapy. Owing to the development of newer chemotherapy agents and immune therapy, systemic chemotherapy or targeted agents and immune therapy are the future therapeutic directions. China has high HCC prevalence, especially HBV-related advanced HCC. Thus, multicenter, randomized, and controlled clinical trials must be conducted. The EACH study and the capecitabine adjuvant therapy in Shanghai were a good start. Immune regulator thymalfasin had been proven effective by several pilot studies as an adjuvant therapy. A large-scale, multicenter, randomized, controlled study has been planned in China to investigate the effect of thymalfasin (1.6 mg twice a week for 12 months) on the 2-year RFS rate and tumor immune microenvironment (ClinialTrials.gov Identifier: NCT02281266). Results of the proposed study are worth expecting.

References

1. Llovet JM, Ricci S, Mazzaferro V, *et al*. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008; 359:378-390.
2. Qin S, Bai Y, Lim HY, Thongprasert S, Chao Y, Fan J, Yang TS, Bhudhisawasdi V, Kang WK, Zhou Y, Lee JH, Sun Y. Randomized, multicenter, open-label study of oxaliplatin plus fluorouracil/leucovorin versus doxorubicin as palliative chemotherapy in patients with advanced hepatocellular carcinoma from Asia. J Clin Oncol. 2013; 31:3501-3508.
3. Zaanan A, Williet N, Hebbar M, Dabakuyo TS, Fartoux L, Mansourbakht T, Dubreuil O, Rosmorduc O, Cattan S, Bonnetain F, Boige V, Taieb J. Gemcitabine plus oxaliplatin in advanced hepatocellular carcinoma: A large multicenter AGEO study. J Hepatol. 2012; 58:81-88.
4. Cheng AL, Kang YK, Chen Z, *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; 10:25-34.
5. Verslype C, Rosmorduc O, Rougier P. Hepatocellular carcinoma: ESMO-ESDO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2012; 23 (Suppl 7):vii41-48.
6. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Hepatobiliary cancers. *http://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf* (accessed version 2, 2015).
7. McDermott U, Sharma SV, Dowell L, *et al*. Identification of genotype-correlated sensitivity to selective kinase inhibitors by using high-throughput tumor cell line profiling. Proc Natl Acad Sci U S A. 2007; 104:19936-19941.
8. Wilhelm SM, Carter C, Tang L, *et al*. BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. Cancer Res. 2004; 64:7099-7109.
9. Wilhelm SM, Adnane L, Newell P, Villanueva A, Llovet JM, Lynch M. Preclinical overview of sorafenib, a multikinase inhibitor that targets both Raf and VEGF and PDGF receptor tyrosine kinase signaling. Mol Cancer Ther. 2008; 7:3129-3140.
10. Jelic S, Sotiropoulos GC. Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2010; 21 (Suppl 5):v59-64.
11. Cheng AL, Guan Z, Chen Z, *et al*. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma according to baseline status: Subset analyses of the phase III Sorafenib Asia-Pacific trial. Eur J Cancer. 2012; 48:1452-1465.
12. Kim JW, Lee JO, Han SW, Oh DY, Im SA, Kim TY, Bang YJ. Clinical outcomes of sorafenib treatment in patients with metastatic hepatocellular carcinoma who had been previously treated with fluoropyrimidine plus platinum-based chemotherapy. Am J Clin Oncol. 2010; 34:125-129.
13. Bruix JTT, Mazzaferro V, *et al*. STORM: A phase III randomized,double-blind,placebo-controlled trial of adjuvant sorafenib after resection or ablation to prevent recurrence of hepatocellular carcinoma (HCC). (Abstracts4006). *http://meetinglibrary.asco.org/content/133873-144*. 2014.
14. Estfan B, Byrne M, Kim R. Sorafenib in advanced hepatocellular carcinoma: Hypertension as a potential surrogate marker for efficacy. Am J Clin Oncol. 2012; 36:319-324.
15. Chiu J, Tang YF, Yao TJ, Wong A, Wong H, Leung R, Chan P, Cheung TT, Chan AC, Pang R, Fan ST, Poon R, Yau T. The use of single-agent sorafenib in the treatment of advanced hepatocellular carcinoma patients with underlying Child-Pugh B liver cirrhosis: A retrospective analysis of efficacy, safety, and survival benefits. Cancer. 2012; 118:5293-5301.
16. Lencioni R, Kudo M, Ye SL, *et al*. First interim analysis

of the GIDEON (Global Investigation of therapeutic decisions in hepatocellular carcinoma and of its treatment with sorafeNib) non-interventional study. Int J Clin Pract. 2012; 66:675-683.
17. Lencioni R, Kudo M, Ye SL, *et al*. GIDEON (Global Investigation of therapeutic DEcisions in hepatocellular carcinoma and Of its treatment with sorafeNib): Second interim analysis. Int J Clin Pract. 2013; 68:609-617.
18. Marrero JA LR, Ye S-L, *et al*. Final analysis of GIDEON (Global Investigation of Therapeutic Decisions in Hepatocellular Carcinoma [HCC] and of Its Treatment with Sorafenib [Sor]) in >3000 Sor-treated patients (pts): Clinical findings in pts with liver dysfunction. Journal of Clinical Oncology. 2013; 31(15, suppl): 4126.
19. Wong H, Tang YF, Yao TJ, Chiu J, Leung R, Chan P, Cheung TT, Chan AC, Pang RW, Poon R, Fan ST, Yau T. The outcomes and safety of single-agent sorafenib in the treatment of elderly patients with advanced hepatocellular carcinoma (HCC). Oncologist. 2011; 16:1721-1728.
20. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis. 2010; 30:52-60.
21. Bettinger D, Schultheiss M, Knuppel E, Thimme R, Blum HE, Spangenberg HC. Diarrhea predicts a positive response to sorafenib in patients with advanced hepatocellular carcinoma. Hepatology. 2012; 56:789-790.
22. Vincenzi B, Santini D, Russo A, Addeo R, Giuliani F, Montella L, Rizzo S, Venditti O, Frezza AM, Caraglia M, Colucci G, Del Prete S, Tonini G. Early skin toxicity as a predictive factor for tumor control in hepatocellular carcinoma patients treated with sorafenib. Oncologist. 2010; 15:85-92.
23. Kuzuya T, Asahina Y, Tsuchiya K, *et al*. Early decrease in alpha-fetoprotein, but not des-gamma-carboxy prothrombin, predicts sorafenib efficacy in patients with advanced hepatocellular carcinoma. Oncology. 2011; 81:251-258.
24. Cheng AL, Kang YK, Lin DY, *et al*. Sunitinib versus sorafenib in advanced hepatocellular cancer: Results of a randomized phase III trial. J Clin Oncol. 2013; 31:4067-4075.
25. Johnson PJ, Qin S, Park JW, *et al*. Brivanib versus sorafenib as first-line therapy in patients with unresectable, advanced hepatocellular carcinoma: Results from the randomized phase III BRISK-FL study. J Clin Oncol. 2013; 31:3517-3524.
26. Llovet JM, Decaens T, Raoul JL, *et al*. Brivanib in patients with advanced hepatocellular carcinoma who were intolerant to sorafenib or for whom sorafenib failed: Results from the randomized phase III BRISK-PS study. J Clin Oncol. 2013; 31:3509-3516.
27. Kudo M, Han G, Finn RS, *et al*. Brivanib as adjuvant therapy to transarterial chemoembolization in patients with hepatocellular carcinoma: A randomized phase III trial. Hepatology. 2014; 60:1697-1707.
28. Patt YZ, Hassan MM, Aguayo A, Nooka AK, Lozano RD, Curley SA, Vauthey JN, Ellis LM, Schnirer, II, Wolff RA, Charnsangavej C, Brown TD. Oral capecitabine for the treatment of hepatocellular carcinoma, cholangiocarcinoma, and gallbladder carcinoma. Cancer. 2004; 101:578-586.
29. Xia Y, Qiu Y, Li J, Shi L, Wang K, Xi T, Shen F, Yan Z, Wu M. Adjuvant therapy with capecitabine postpones recurrence of hepatocellular carcinoma after curative resection: A randomized controlled trial. Ann Surg Oncol. 2010; 17:3137-3144.
30. Lai CL, Wu PC, Chan GC, Lok AS, Lin HJ. Doxorubicin versus no antitumor therapy in inoperable hepatocellular carcinoma. A prospective randomized trial. Cancer. 1988; 62:479-483.
31. Gish RG, Porta C, Lazar L, Ruff P, Feld R, Croitoru A, Feun L, Jeziorski K, Leighton J, Gallo J, Kennealey GT. Phase III randomized controlled trial comparing the survival of patients with unresectable hepatocellular carcinoma treated with nolatrexed or doxorubicin. J Clin Oncol. 2007; 25:3069-3075.
32. Kelley RK. Brivanib and FOLFOX in hepatocellular carcinoma: Finding the common themes among negative trials. J Clin Oncol. 2013; 31:3483-3486.
33. Kim HY, Park JW, Nam BH, Kim HK, Choi JI, Kim TH, Kim HB, Kim CM. Survival of patients with advanced hepatocellular carcinoma: Sorafenib versus other treatments. J Gastroenterol Hepatol. 2011; 26:1612-1618.
34. Pinter M, Hucke F, Graziadei I, Vogel W, Maieron A, Konigsberg R, Stauber R, Grunberger B, Muller C, Kolblinger C, Peck-Radosavljevic M, Sieghart W. Advanced-stage hepatocellular carcinoma: Transarterial chemoembolization versus sorafenib. Radiology. 2012; 263:590-599.
35. Lee S, Yoon SH, Park JY, Kim do Y, Ahn SH, Han KH, Choi HJ. Sorafenib versus cytotoxic chemotherapy for patients with advanced hepatocellular carcinoma: A retrospective, single-institution study. Invest New Drugs. 2011; 30:1150-1157.
36. Lim S, Han J, Kim GM, Han KH, Choi HJ. Hepatitis B viral load predicts survival in hepatocellular carcinoma patients treated with sorafenib. J Gastroenterol Hepatol. 2015; 30:1024-1031.
37. Zhang XD, Wang Y, Ye LH. Hepatitis B virus X protein accelerates the development of hepatoma. Cancer Biol Med. 2014; 11:182-190.
38. Andersen ES, Omland LH, Jepsen P, Krarup H, Christensen PB, Obel N, Weis N; DANVIR Cohort Study. Risk of all-type cancer, hepatocellular carcinoma, non-Hodgkin lymphoma and pancreatic cancer in patients infected with hepatitis B virus. J Viral Hepat. 2015; 22:828-834.
39. Gordon SC, Lamerato LE, Rupp LB, Li J, Holmberg SD, Moorman AC, Spradling PR, Teshale EH, Vijayadeva V, Boscarino JA, Henkle EM, Oja-Tebbe N, Lu M. Antiviral therapy for chronic hepatitis B virus infection and development of hepatocellular carcinoma in a US population. Clin Gastroenterol Hepatol. 2013; 12:885-893.
40. Chan AC, Chok KS, Yuen WK, Chan SC, Poon RT, Lo CM, Fan ST. Impact of antiviral therapy on the survival of patients after major hepatectomy for hepatitis B virus-related hepatocellular carcinoma. Arch Surg. 2011; 146:675-681.
41. Sakamoto K, Beppu T, Hayashi H, Nakagawa S, Okabe H, Nitta H, Imai K, Hashimoto D, Chikamoto A, Isiko T, Kikuchi K, Baba H. Antiviral therapy and long-term outcome for hepatitis B virus-related hepatocellular carcinoma after curative liver resection in a Japanese cohort. Anticancer Res. 2015; 35:1647-1655.
42. Singal AK, Salameh H, Kuo YF, Fontana RJ. Meta-analysis: The impact of oral anti-viral agents on the

incidence of hepatocellular carcinoma in chronic hepatitis B. Aliment Pharmacol Ther. 2013; 38:98-106.
43. Miyake Y, Takaki A, Iwasaki Y, Yamamoto K. Meta-analysis: Interferon-alpha prevents the recurrence after curative treatment of hepatitis C virus-related hepatocellular carcinoma. J Viral Hepat. 2010; 17:287-292.
44. Zhou Y, Zhang Z, Zhao Y, Wu L, Li B. Antiviral therapy decreases recurrence of hepatitis B virus-related hepatocellular carcinoma after curative resection: A meta-analysis. World J Surg. 2014; 38:2395-2402.
45. Huang G, Lau WY, Wang ZG, Pan ZY, Yuan SX, Shen F, Zhou WP, Wu MC. Antiviral therapy improves postoperative survival in patients with hepatocellular carcinoma: A randomized controlled trial. Ann Surg. 2015; 261:56-66.
46. Xu L, Gao H, Huang J, Wang H, Zhou Z, Zhang Y, Li S, Chen M. Antiviral therapy in the improvement of survival of patients with hepatitis B virus-related hepatocellular carcinoma treated with sorafenib. J Gastroenterol Hepatol. 2015; 30:1032-1039.
47. Lao XM, Luo G, Ye LT, Luo C, Shi M, Wang D, Guo R, Chen M, Li S, Lin X, Yuan Y. Effects of antiviral therapy on hepatitis B virus reactivation and liver function after resection or chemoembolization for hepatocellular carcinoma. Liver Int. 2013; 33:595-604.
48. Chong CC, Wong GL, Wong VW, Ip PC, Cheung YS, Wong J, Lee KF, Lai PB, Chan HL. Antiviral therapy improves post-hepatectomy survival in patients with hepatitis B virus-related hepatocellular carcinoma: A prospective-retrospective study. Aliment Pharmacol Ther. 2014; 41:199-208.
49. Reddy KR, Beavers KL, Hammond SP, Lim JK, Falck-Ytter YT. American Gastroenterological Association Institute guideline on the prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. Gastroenterology. 2015; 148:215-219; quiz e216-217.
50. Plauth M, Cabre E, Campillo B, Kondrup J, Marchesini G, Schutz T, Shenkin A, Wendon J. ESPEN Guidelines on Parenteral Nutrition: Hepatology. Clin Nutr. 2009; 28:436-444.
51. Braga M, Ljungqvist O, Soeters P, Fearon K, Weimann A, Bozzetti F. ESPEN Guidelines on parenteral nutrition: Surgery. Clin Nutr. 2009; 28:378-386.
52. Bozzetti F, Arends J, Lundholm K, Micklewright A, Zurcher G, Muscaritoli M. ESPEN Guidelines on Parenteral Nutrition: Non-surgical oncology. Clin Nutr. 2009; 28:445-454.
53. Mandair DS, Rossi RE, Pericleous M, Whyand T, Caplin M. The impact of diet and nutrition in the prevention and progression of hepatocellular carcinoma. Expert Rev Gastroenterol Hepatol. 2014; 8:369-382.

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