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Chinese Expert Consensus on the Whole-Course Management of Hepatocellular Carcinoma (2023 Edition)

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Keywords
Hepatocellular carcinoma · Surgery · Surveillance · Systemic chemotherapy · Treatment

Abstract
Background: Hepatocellular carcinoma (HCC) is one of the most common malignant tumors in China. Most HCC patients have the complications of chronic liver disease and need overall consideration and whole-course management, including diagnosis, treatment, and follow-up. To develop a reasonable, long-term, and complete management plan, multiple factors need to be considered, including the patient's general condition, basic liver diseases, tumor stage, tumor biological characteristics, treatment requirements, and economic cost. ***Summary:*** To better guide the whole-course management of HCC patients, the Chinese Association of Liver Cancer and the Chinese Medical Doctor Association has gathered multidisciplinary experts and scholars in relevant fields to formulate the "Chinese Expert Consensus on The Whole-Course Management of Hepatocellular Carcinoma (2023)." ***Key Messages:*** This expert consensus, based on the current clinical evidence and experience, proposes surgical and nonsurgical HCC management pathways and involves 18 recommendations, including perioperative treatment, systematic treatment combined with local treatment, conversion treatment, special population management, symptomatic support treatment, and follow-up management.

Introduction

Primary liver cancer, which includes hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma, and combined hepatocellular-cholangiocarcinoma, is one of the most common malignant tumors worldwide [1]. HCC accounts for 75–85% of total liver cancer cases. In 2020, the liver cancer incidence and mortality were 410,038 and 391,152, respectively, in China, accounting for nearly half of the global incidence (45.3%) and mortality (47.1%) of liver cancer [2]. In China, approximately 70% of HCC patients are first diagnosed at an intermediate or advanced stage, and nearly 70% of HCC patients develop tumor recurrence within 5 years after surgery [3, 4]. The question of how to effectively ease the burden and improve the overall prognosis of HCC patients has become a major public health issue in China. HCC generally occurs in patients with baseline liver diseases, such as chronic liver disease or/and cirrhosis, and must be managed in a holistic manner beginning at disease diagnosis. Multiple factors need to be considered concerning patient management, including the patient's general condition, baseline liver disease, tumor condition, tumor biological characteristics, treatment requirements, and economic cost. All the characteristics need to be taken into account to meet the treatment goal. The patient's responses to tumor treatment, changes in physical fitness, serological and imaging examinations, etc., need to be observed dynamically, and the treatment needs to be adjusted in a timely manner. Moreover, attention must be given to baseline liver disease status, symptom relief and nutritional support. It is highly important to develop comprehensive long-term treatment and follow-up programs. The core of the whole-course management of HCC is to aim at key points in the treatment process to propose a scientific management plan through multidisciplinary diagnosis and treatment models based on the existing clinical evidence and integrate treatment and follow-up management to avoid single-disciplinary or ineffective multidisciplinary treatment models.

To better guide the whole-course management of HCC patients, the Chinese Association of Liver Cancer and Chinese Medical Doctor Association has gathered multidisciplinary experts and scholars in relevant fields to formulate the "Chinese Expert Consensus on The Whole-Course Management of Hepatocellular Carcinoma (2023)," providing theoretical and practical references for colleagues engaged in HCC-related clinical work. This expert consensus, based on the current clinical evidence and experience, proposes surgical and nonsurgical HCC management pathways and involves 18 recommendations, sequentially including neoadjuvant and adjuvant therapy (Recommendation 1, 2), first-line and second-line treatment (Recommendation 3–6), management of adverse reactions to systemic therapy (Recommendation 7), Systemic therapy combined with transcatheter arterial chemoembolization (TACE), hepatic arterial infusion chemotherapy (HAIC), radiotherapy and ablation (Recommendation 8–11), conversion therapy (Recommendation 12), management in specific groups (Recommendation 13–16), symptomatic support treatment (Recommendation 17), and follow-up management (Recommendation18) (online suppl. Table 1; for all online suppl. material, see https://doi.org/10.1159/000541622). The medicines recommended by this consensus have been approved by the National Medical

Table 1. Levels of evidence in evidence-based medicine

Level of evidence	Description
Ia	The evidence comes from a meta-analysis of multiple randomized controlled trials
Ib	The evidence comes from at least one well-designed randomized controlled study
IIa	The evidence comes from at least one well-designed prospective non-randomized controlled study
IIb	The evidence comes from at least one other type of well-designed interventional clinical study
III	The evidence comes from well-designed non-interventional studies, such as descriptive studies, correlation studies, etc.
IV	The evidence comes from the reports of the expert committee or the clinical experience reports of authoritative experts

Products Administration (NMPA) or the US Food and Drug Administration (FDA) for HCC indications or well-designed phase II-III clinical research. This consensus has been registered on the International Practice Guidelines Registration and Transparency Platform with the registration number PREPARE-2023CN365. The recommendations in the consensus are divided into 5 levels, which are based on 6 levels of evidence, as shown in Tables 1 and 2.

HCC Whole-Course Management Pathway

By combining the Barcelona Clinic Liver Cancer (BCLC) staging system and the China Liver Cancer Staging (CNLC) system [5, 6], surgical and nonsurgical HCC management pathways were proposed based on whether the goal was to perform radical surgical treatment as a consensus (Fig. 1). The consensus recommends the best treatment options according to the different tumor stages and treatment stages of HCC patients.

HCC Whole-Course Management with Radical Surgical Treatment as the Goal

The treatment plan for these patients should be oriented toward improving the curative effect of surgery, emphasizing the use of multidisciplinary comprehensive treatment based on tumor conditions to reduce the recurrence rate and prolong the survival time (Fig. 1).

Neoadjuvant Therapy

Neoadjuvant therapy, including systemic therapy, radiotherapy, and interventional therapy, refers to preoperative treatment for patients with technically resectable HCC (R0 resection, sufficient future liver remnant) and a high risk of recurrence. Its main purpose is to reduce recurrence after surgery and prolong overall survival (OS). Current research on neoadjuvant therapy for HCC can be divided into two stages. (1) Preoperative treatment for patients with resectable HCC classified as intermediate or advanced stage (CNLC stage IIb/IIIa). Some experts believe that the prognosis of direct surgery in these patients is poor, and preoperative treatment should be called transformation therapy (in the sense of oncology) [7]. The ultimate goal of oncological transformation therapy and neoadjuvant therapy is to further improve the survival rate after surgery. (2) Preoperative treatment was administered for patients in the early stage (CNLC stage I/IIa) with resectable tumors. For these patients, direct surgery is recommended, and neoadjuvant therapy is only recommended for the preliminary explorative stage.

A randomized controlled study showed that in resectable HCC patients with type II/III portal vein tumor thrombus (PVTT) (referred to Cheng's Classification [8]), neoadjuvant radiotherapy (18 Gy/6f) significantly improved the 2-year OS (27.4% vs. 9.4%, $p < 0.01$) and disease-free survival (DFS) (13.3% vs. 3.3%, $p = 0.009$) [8]. A prospective study showed that preoperative TACE treatment in patients with type I/II/III PVTT could significantly improve OS (19.2 vs. 11.2 months, $p = 0.001$), but there was no significant survival benefit in the type III PVTT subgroup [9]. A multicenter retrospective study showed that after lenvatinib plus anti-PD-1 monoclonal antibody plus TACE neoadjuvant therapy and postoperative adjuvant therapy, the 1-year and 2-year survival rates of patients with high risks of postoperative recurrence (type II PVTT, solitary tumor >10 cm and

Table 2. Levels of expert recommendations

Level of recommendation	Description
A	Good scientific evidence suggests that the medical behavior confers clear benefits; it is recommended that physicians perform the medical behavior on patients
B	Existing evidence shows that the medical behavior can confer moderate benefits, outweighing its potential risks; physicians can recommend or perform the medical behavior on patients
C	Existing evidence shows that the medical behavior may have less benefit, or the benefit is equal to the risk; physicians can selectively recommend and perform the medical behavior to patients according to the individual conditions
D	Existing evidence shows that the medical behavior has no benefit, or its potential risks outweigh the benefits; physicians should not perform the medical behavior on patients
I	Lack of scientific evidence or the existing evidence cannot evaluate the benefits and risks of the medical behavior; physicians should help patients understand the uncertainty of the medical behavior

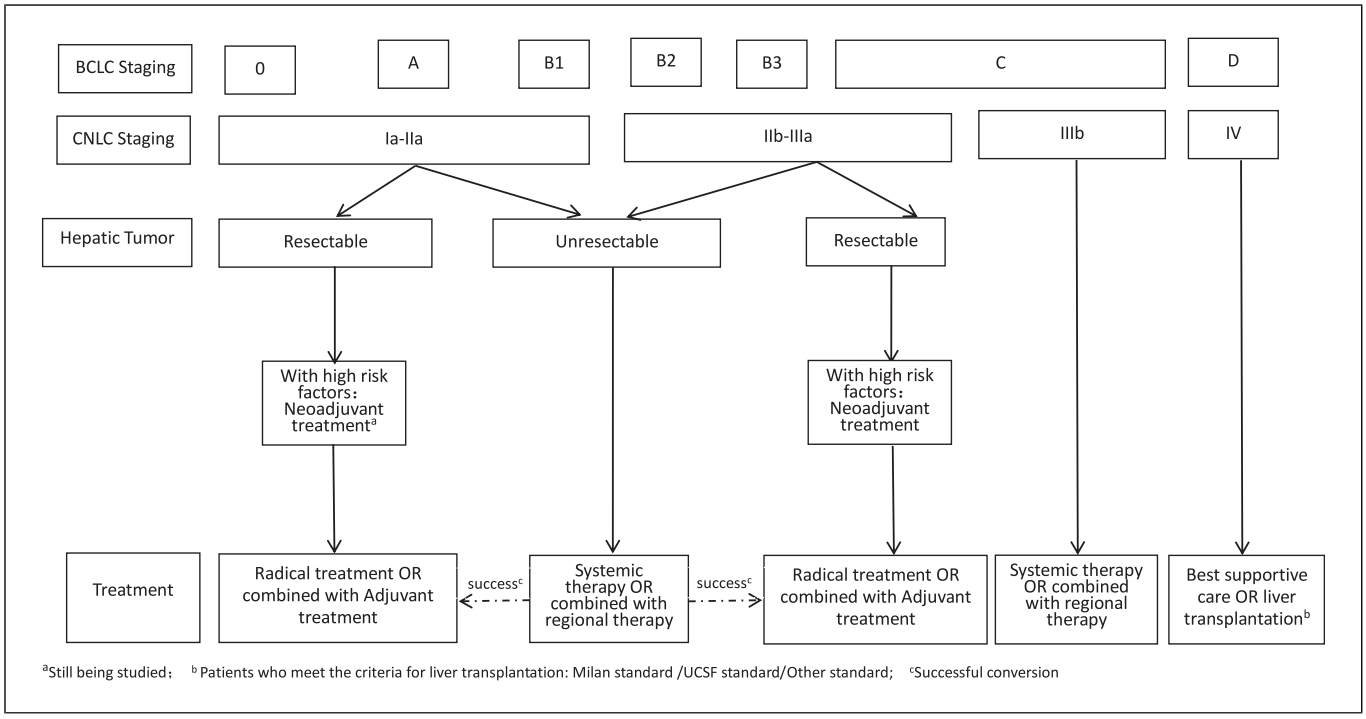

Fig. 1. Whole-course management path for HCC.

close proximity to large blood vessels resulting in narrow resection margins, single-lobe lesions >3 and one >5 cm) were 100% and 85.7%, respectively. These results were significantly better than those of direct surgery and postoperative TACE treatment, which have 1-year and 2-year survival rates of 73.3% and 48.7%, respectively ($p < 0.001$). After propensity score matching, the DFS and OS of patients in the neoadjuvant therapy group still improved significantly [10]. In a phase II study, 18 patients with resectable HCC (BCLC B/C stage) received apatinib combined with camrelizumab for 3 cycles of neoadjuvant therapy and 8 cycles of postoperative adjuvant therapy, and the annual recurrence-free survival (RFS) rate was 53.8% [11].

To date, only a small number of exploratory studies have been conducted on neoadjuvant systemic therapy for early HCC, including targeted therapy combined with immunotherapy and dual-immune therapy. Preliminary results show that the major pathological response of patients after short-term treatment (6–8 weeks) before surgery is approximately 20–33%, and the pathological complete response can reach approximately 6–22%. The safety of neoadjuvant systemic therapy for early HCC is acceptable, but its impact on postoperative tumor recurrence and long-term survival is still unclear [12–14] (online suppl. Table 2).

Recommendation 1

Surgical resection is the first choice for CNLC I/IIa or BCLC 0/A/B1 patients. Radical surgery after neoadjuvant therapy is recommended for technically resectable CNLC IIb/IIIa or BCLC B/C patients with a high risk of recurrence. Development of a neoadjuvant treatment plan according to the characteristics of the tumor is recommended, including first-line targeted therapy plus immunotherapy or systemic therapy plus TACE (IIb, B) or type II/III PVTT radiotherapy (Ib, A).

Adjuvant Therapy

Adjuvant therapy refers to postoperative treatment for HCC patients at high risk of recurrence after radical surgery to reduce recurrence and metastasis. The recurrence rate of HCC within 5 years after surgery is 40–70% or above [6], but currently, there is no globally recognized adjuvant therapy. Antiviral treatment can reduce postoperative recurrence in patients with HBV-related HCC. Adjuvant TACE therapy for patients at high risk of postoperative recurrence can reduce recurrence and prolong postoperative survival [15, 16]. Studies [17–19] have shown that postoperative adjuvant radiotherapy for patients with PVTT (especially type I/II PVTT) or microvascular invasion with boundary resection or narrow margins (cutting edge<1 cm) can improve survival. Although sorafenib adjuvant therapy did not reduce postoperative recurrence or improve survival in the Storm study, many new antitumor drugs have been investigated for adjuvant therapy (online suppl. Table 3). A prospective multicenter study showed that the 1-year RFS rate after surgery in patients with CNLC IIb/IIIa or BCLC B/C treated with lenvatinib adjuvant monotherapy was 50.5% [20]. The results of the LANCE study, which was carried out in China, showed that, compared with TACE alone, TACE combined with lenvatinib for postoperative adjuvant therapy could significantly prolong the median DFS in HCC patients with high recurrence risk (17.0 vs. 9.0 months, HR = 0.6, p = 0.0228) [21]. A prospective randomized controlled study [22] containing 198 HCC patients with microvascular invasion in China showed that sintilimab significantly prolonged DFS compared with active surveillance (27.7 months vs. 15.5 months, $p < 0.001$), but further follow-up is needed to confirm the difference in OS, and also some phase III clinical studies comprising immunotherapy alone or in combination with targeted therapy are in progress [23]. A recent interim analysis of the global phase III study IMbrave050 showed that, compared with active surveillance, atezolizumab combined with bevacizumab (T+A) adjuvant therapy can significantly improve tumor RFS in patients with a high risk of recurrence after radical resection or ablation (HR 0.72, 95% CI = 0.56–0.93; p = 0.0120) [24]. The final RFS and OS data need to be followed up, and this program is expected to fill the gap in the field of drug-adjuvant therapy. A randomized controlled study in China showed that the Chinese medicinal preparation Huaier granule significantly prolonged RFS and reduced the occurrence of extrahepatic metastases after HCC surgery [25].

Recommendation 2

For hepatitis B-related HCC, antiviral therapy should be continued after surgery (Ia, A). In HCC patients with a high risk of postoperative recurrence, T+A (Ib, A), sintilimab (Ib, B), and TACE (Ib, A) can reduce recurrence and/or prolong survival. In postoperative HCC patients with type I/II PVTT and narrow resection margins, postoperative radiotherapy can improve DFS and OS (Ib, A). Huaier granule therapy as postoperative adjuvant therapy can reduce recurrence and extrahepatic metastasis (Ib, A). In postoperative patients with intermediate and advanced-stage HCC, the use of targeted drugs or an original neoadjuvant/transformation systemic treatment regimen ± TACE is recommended as adjuvant therapy (IIb, B).

Management of HCC Patients with Nonsurgical Treatment

The treatment regimen for these patients should be based on liver function. Primary treatment should be able to control HCC lesions as much as possible. Prolonging survival time and improving quality of life are

emphasized by combining multidisciplinary comprehensive treatment according to the outcome of the primary therapy.

Systematic Treatment

First-Line Treatment. With the development of new drugs and the progress of clinical research, first-line treatment strategies for unresectable or metastatic HCC have taken shape. Active systemic antitumor treatment can be considered for patients with liver function at Child-Pugh level A or level B less than 7 points. In terms of targeted monotherapy, sorafenib (approved by the FDA and NMPA) was the earliest treatment for HCC [26, 27]. Lenvatinib (approved by the FDA and NMPA) was non-inferior to sorafenib in mOS (13.6 vs. 12.3 months, HR = 0.92, 95% CI = 0.79–1.06) but improved the mPFS (7.3 vs. 3.6 months, $p < 0.0001$) and ORR (18.8% vs. 6.5%, $p < 0.0001$) (RECIST1.1) [28, 29]. Compared with sorafenib, donafenib (approved by NMPA) significantly improved the mOS (12.1 vs. 10.3 months, $p = 0.0245$) but not the mPFS (3.7 vs. 3.6 months, $p = 0.0570$) or ORR (4.6% vs. 2.7%) [30]. Several phase III trials have shown that targeted therapy combined with immunotherapy is superior to sorafenib monotherapy. The phase III global IMbrave150 study [31, 32] showed that atezolizumab combined with bevacizumab (approved by the FDA and NMPA) can significantly improve the mOS (19.2 vs. 13.4 months, $p < 0.001$), mPFS (6.8 vs. 4.3 months, $p < 0.001$), and ORR (30% vs. 11%, $p < 0.001$). The phase II/III ORIENT-32 study [33] in China showed that sintilimab combined with IBI305 (a bevacizumab analog) (approved by NMPA) can significantly improve the mOS (not reached vs. 10.4 months, $p < 0.0001$), mPFS (4.6 vs. 2.8 months, $p < 0.0001$) and ORR (21% vs. 4%, $p < 0.0001$). The global phase III SHR-1210-III-310 study [34] showed that apatinib combined with camrelizumab (approved by NMPA) can significantly improve the mOS (22.1 vs. 15.2 months, $p < 0.0001$), mPFS (5.6 vs. 3.7 months, $p < 0.0001$) and ORR (25.4 vs. 5.9%, $p < 0.0001$). The phase III global study LEAP-002 compared lenvatinib plus pembrolizumab with lenvatinib plus placebo, which used a double-blind design and lenvatinib as a control and was different from several other phase III studies [31, 33, 34]. The results showed that, compared with lenvatinib combined with placebo, the combination of lenvatinib and pembrolizumab did not significantly improve mOS (21.2 vs. 19.0 months, $p = 0.0227$; superiority threshold one-sided $a = 0.0185$) or mPFS (8.2 vs. 8.0 months, $p = 0.0466$; dominant threshold one-sided $a = 0.002$), and there is a certain improvement in ORR (26.1% vs. 17.5%) [35]. In the analysis of an Asian subgroup including more hepatitis B-related HCC (lenvatinib plus pembrolizumab group: 79% vs. 49%), the gap of survival between the lenvatinib combined with pembrolizumab group and lenvatinib combined with placebo group was further extended, with mOSs of 26.3 months and 22.4 months, respectively (HR = 0.727, 95% CI = 0.552–0.958), and mPFSs of 8.3 months and 6.5 months, respectively (HR = 0.710, 95% CI = 0.556–0.907) [36]. In clinical practice in China, the combination regimen of lenvatinib plus immunotherapy or combined with interventional therapy has also been actively explored. In terms of first-line immunotherapy alone, the phase III global study HIMALAYA [37] demonstrated that dual immunotherapy combined with durvalumab and ipilimumab (STRIDE regimen, approved by the FDA) was superior to sorafenib, with significantly improved mOS (16.43 vs. 13.77 months, $p = 0.0035$) and reduced ≥ grade 3 TRAEs (25.8% vs. 36.9%). However, the mPFS of STRIDE regimen group was not improved (3.78 vs. 4.07 months), which implied that immunotherapy alone did not reduce the risk of early disease progression compared to sorafenib. In terms of the absolute survival data of mOS or mPFS, the STRIDE regimen was at the end of the combined treatment regimens in the current phase III studies [31, 33–35]. The HIMALAYA study [37] also showed that durvalumab was non-inferior to sorafenib in terms of mOS (16.56 vs. 13.77 months, HR = 0.86; 96% CI = 0.73–1.03) with better safety (≥grade 3 TRAEs: 12.9% vs. 36.9%). However, the mPFS in the durvalumab group was also not improved (3.65 vs. 4.07 months). The early phase III CheckMate 459 study [38] did not prove that nivolumab was superior to sorafenib in terms of mOS (16.4 vs. 14.7 months, $p = 0.0752$). The phase III follow-up study RATIONALE-301 [39] showed that tislelizumab treatment was non-inferior to sorafenib in terms of mOS (15.9 vs. 14.1 months; HR = 0.85, 95% CI = 0.71–1.02), and the ORR was greater with tislelizumab treatment (14.3% vs. 5.4%). In terms of chemotherapy, the Asian phase III study EACH [40] showed that, compared with single-agent doxorubicin, the FOLFOX4 regimen (approved by NMPA) significantly improved mPFS (2.93 vs. 1.77 months, $p < 0.001$) and ORR (8.15% vs. 2.67%, $p = 0.02$). The analysis of extended follow-up time showed that mOS was beneficial (6.47 vs. 4.90 months, $p = 0.04$), and the OS, PFS and ORR of the

Table 3. First-line treatment of HCC

Research protocol	Name	Research design	Patients, *n*	mOS, months	mPFS, months	ORR, % (RECIST v1.1)	Level of TRAE ≥3, %	NMPA approval
Lenvatinib vs. sorafenib [28, 29]	REFLECT (global)	Stage III	478 vs. 476	13.6 vs. 12.3	7.3 vs. 3.6	18.8 vs. 6.5	57 vs. 49	Yes
	REFLECT (Chinese subgroup)		144 vs. 144	15.0 vs. 10.2	8.4 vs. 3.6	43.8% vs. 13.2% (mRECIST)	/	
Donafenib vs. sorafenib [30]	ZGDH3	Stage III	328 vs. 331	12.1 vs. 10.3	3.7 vs. 3.6	4.6 vs. 2.7	38 vs. 50	Yes
Sorafenib vs. placebo [26, 27]	SHARP	Stage III	299 vs. 303	10.7 vs. 7.9	5.5 vs. 2.8 (mTTP)	2 vs. 1	/	Yes
	ORIENTAL		150 vs. 76	6.5 vs. 4.2	2.8 vs. 1.4 (mTTP)	3.3 vs. 1.3	/	
Atezolizumab + bevacizumab vs. sorafenib [31, 32]	IMbrave150 (global)	Stage III	336 vs. 165	19.2 vs. 13.4	6.8 vs. 4.3	30 vs. 11	45 vs. 47	Yes
	IMbrave150 (Chinese subgroup)		133 vs. 61	24.0 vs. 11.4	5.7 vs. 3.2	25 vs. 7	46 vs. 40	
Sintilimab + IBI305 vs. sorafenib [33]	ORIENT-32	Stage III	380 vs. 190	NR vs. 10.4	4.6 vs. 2.8	21 vs. 4	36 vs. 34	Yes
Apatinib + camrelizumab vs. sorafenib [34]	SHR-1210-III-310	Stage III	272 vs. 271	22.1 vs. 15.2	5.6 vs. 3.7	25.4 vs. 5.9	80.9 vs. 52.4	Yes
Tremelimumab + durvalumab vs. sorafenib [37]	HIMALAYA	Stage III	393 vs. 389	16.4 vs. 13.8	3.8 vs. 4.1	20.1 vs. 5.1	25.8 vs. 36.9	No
FOLFOX4 vs. doxorubicin [40, 41]	EACH (Asian)	Stage III	184 vs. 187	6.47 vs. 4.90	2.93 vs. 1.77	8.15 vs. 2.67 (RR)	/	Yes
	EACH (Chinese subgroup)	Stage III	140 vs. 139	5.9 vs. 4.3	2.4 vs. 1.7	8.6 vs. 1.4 (RR)	41.0 vs. 26.9	
Lenvatinib + pembrolizumab vs. lenvatinib [35, 36]	LEAP-002 (global)	Stage III	395 vs. 399	21.2 vs. 19.0	8.2 vs. 8.0	26.1 vs. 17.5	62.5 vs. 57.5	No
	LEAP-002 (Asian subgroup)	Stage III	160 vs. 164	26.3 vs. 22.4	8.3 vs. 6.5	28.1 vs. 18.9	59.4 vs. 53.6	
Durvalumab vs. sorafenib [37]	HIMALAYA	Stage III	389 vs. 389	16.6 vs. 13.8	3.65 vs. 4.07	17.0 vs. 5.1	12.9 vs. 36.9	NO
Tislelizumab vs. sorafenib [39]	RATIONALE-301	Stage III	342 vs. 332	15.9 vs. 14.1	2.1 vs. 3.4	14.3 vs. 5.4	22.2 vs. 53.4	NO
Acradine [42]	/	Stage III	/	13.54 vs. 6.87	2.79 vs. 1.84	/	15.2 vs. 31.6	Yes

Chinese population subgroup also significantly benefited in the FOLFOX4 group. In addition, one study [41] showed that all-trans retinoic acid (ATRA) could further enhance the efficacy of FOLFOX4 in advanced HCC patients with distant metastasis, and the ORR of the ATRA combined with FOLFOX4 treatment group reached 24.5%. The Chinese phase III study compared acoladin (Icaritin soft capsule) (approved by NMPA) and cinobufacin as first-line treatments, and the study showed that it was effective for the enriched population (with ≥2 of the following characteristics: alpha-fetoprotein (AFP) ≥400 ng/mL, TNF-α <2.5 pg/mL, IFN-γ ≥7.0 pg/mL); the mOS of the alcoradine group was significantly prolonged (13.54 vs. 6.87 months, $p = 0.0092$) [42] (see Table 3 for details).

Recommendation 3

First-line systemic therapy for HCC includes atezolizumab combined with bevacizumab, sintilimab combined with bevacizumab analogs, sorafenib, lenvatinib, donafenib, apatinib combined with camrelizumab (Ib, A), and lenvatinib combined with pembrolizumab (Ib, C). If antiangiogenic targeted therapy is contraindicated, then durvalumab combined with tremelimumab (Ib, A), durvalumab, tislelizumab, or nivolumab (Ib, B) should be considered. Patients who are not suitable for targeted therapy or immunotherapy may receive FOLFOX chemotherapy (Ib, A). Alcoradine may be considered conditionally for patients who are not suitable for or refuse to receive standard treatment and have not previously received systemic treatment (Ib, B).

Recommendation 4

The choice of first-line treatment must involve taking into consideration the patient's general physical status, liver function status, tumor characteristics, treatment risks, and treatment goals. Targeted therapy combined with immunotherapy is the preferred systemic treatment. For patients with contraindication or patients who are unwilling to use immune checkpoint inhibitors, a single targeted drug can be considered. For patients at high risk of bleeding, dual-immune combined therapy or immunotherapy with a single drug can be selected.

Second-Line Treatment Options. Many factors need to be considered for second-line treatment of HCC, such as the time and sequence of treatment switching and the efficacy and safety of drugs [43]. After first-line treatment, when the disease progresses or unacceptable adverse reactions occur, changing the treatment plan should be considered. Symptom aggravation, ascites, and elevated AFP or protein induced by vitamin K absence or antagonist-II (PIVKA-II) are generally not used as indications of changing systemic therapeutic drugs. However, in this situation, clinical efficacy should be assessed in a timely, accurate, and comprehensive manner. Currently, the approved drugs for second-line treatment are based on the progress of first-line sorafenib and/or chemotherapy, and there is still a lack of sufficient clinical data on new first-line targeted drugs and progress after combination therapy with second-line regimens. Drugs for second-line targeted therapy, including regorafenib [44], apatinib [45], ramucirumab (AFP ≥400 ng/mL) [46] (approved by FDA and NMPA), and cabozantinib (approved by FDA) [47], had mPFSs of 2.8–5.2 months, mOSs of 8.5–10.6 months, and ORRs of 4–11% and ≥ grade 3 TRAEs in 50%–77% patients. Drugs for second-line immune monotherapy, including pembrolizumab [48] (approved by FDA and NMPA), tislelizumab [49], and camrelizumab [50] (approved by NMPA), had mPFSs of 2.1–2.6 months, mOSs of 13.8–14.6 months, ORRs of 12.7–14.7%, and ≥ grade 3 TRAEs in 14.4–22% patients. A small phase II study showed that second-line combination therapy may have better efficacy than monotherapy: treatment with nivolumab combined with ipilimumab (FDA approved) [51] and apatinib combined with camrelizumab [52] reached mOSs of 22.2 months and 21.8 months, respectively, and the ORR reached 32% and 22.5%, respectively (see Table 4 for details).

Recommendation 5

The second-line treatment options for HCC are regorafenib, apatinib, ramucirumab (AFP ≥400 ng/mL), cabozantinib, pembrolizumab (Ib, A), camrelizumab, and tislelizumab (IIb, A). Apatinib combined with camrelizumab (IIb, B) and nivolumab combined with ipilimumab (IIb, B) may be considered.

Recommendation 6

Second-line treatment should be based on the first-line treatment regimen and the status of tumor progression, and adverse events (AEs) resulting from first-line treatment should be considered appropriate. The targeted or immunotherapy monotherapies currently were approved for second-line indications after sorafenib or oxaliplatin-containing chemotherapy failure, and second-line targeted therapy combined with immunotherapy or dural immunotherapy may be more effective. There is no phase III clinical research supporting second-line treatments after first-line treatment progresses except for sorafenib. From the perspective of treatment strategy, sequential targeted therapy or targeted therapy switching to immunotherapy or immunotherapy switching to targeted therapy can be considered. Continuation of immunotherapy beyond progression may be beneficial for some patients with progressed disease after first-line treatment combined with immunotherapy.

Management of Adverse Reactions to Systemic Therapy. Regarding the management of AEs resulting from systemic therapy, emphasis should be placed on baseline examination and assessment before treatment, monitoring during treatment, adjusting treatment and dynamically monitoring after adverse reactions occur. The aim is to reduce the incidence of adverse reactions and improve the outcome of adverse reactions. Antineoplastic drugs for HCC mainly include molecular targeted drugs,

Table 4. Second-line treatment of HCC

Research protocol	Name	Research design	Patients, *n*	mOS, months	mPFS, months	ORR, % (RECIST v1.1)	Level of TRAE ≥3, %	NMPA approval
Regorafenib vs. placebo [44]	RESORCE	Stage III	379 vs. 194	10.6 vs. 7.8	3.1 vs. 1.5	11 vs. 4 (mRECIST)	50 vs. 17	Yes
Apatinib vs. placebo [45]	AHELP	Stage III	261 vs. 132	8.7 vs. 6.8	4.5 vs. 1.9	11 vs. 2	77 vs. 19	Yes
Ramucirumab vs. placebo [46]	REACH-2	Stage III	197 vs. 95	8.5 vs. 7.3	2.8 vs. 1.6	4.6 vs. 1.1	/	Yes
Cabozantinib vs. placebo [47]	CELESTIAL	Stage III	470 vs. 237	10.2 vs. 8.0	5.2 vs. 1.9	4 vs. 1	68 vs. 36	No
Pembrolizumab vs. placebo [48]	KEYNOTE-394	Stage III	300 vs. 153	14.6 vs. 13.0	2.6 vs. 2.3	12.7 vs. 1.3	14.4 vs. 5.9	Yes
Camrelizumab [50]	/	Stage II	217	13.8	2.1	14.7	22	Yes
Tislelizumab [49]	RATIONALE 208 (second line)	Stage II	138	13.8	2.6	13.8	17.4	Yes
Nivolumab+ipilimumab* (NIVO1+IPI3 Q3W vs. NIVO3+IPI1 Q3W vs. NIVO3 Q2W+IPI1 Q6W) [51]	CheckMate040 cohort 4	Stage I/II	50 vs. 49 vs. 49	22.2 vs. 12.5 vs. 12.7	/	32 vs. 31 vs. 31	55 vs. 31 vs. 35	No
Apatinib combined with camrelizumab [52]	RESCUE	Stage II	120	21.8	5.5	22.5	76.7	No

*NIVO1+IPI3 Q3W, nivolumab 1 mg/kg + ipilimumab 3 mg/kg Q3W×4 cycles, followed by nivolumab 240 mg Q2W; NIVO3+IPI1 Q3W, nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W×4 cycles, followed by nivolumab 240 mg Q2W; NIVO3 Q2W+IPI1 Q6W, nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W.

ICIs, and chemotherapy drugs. The mechanism, toxicity spectrum and specific treatment of AEs associated with the three types of drugs are different, and the management of AEs should be classified according to the type and degree of AEs. All the targeted drugs for HCC have antitumor angiogenesis effects. The common adverse reactions include hypertension, hand-foot skin reaction, diarrhea, fatigue, albuminuria, etc., which should be identified and dealt with in a timely manner [53]. Previous studies have shown that TRAEs, such as hypertension and hand-foot skin reaction, resulting from small molecule tyrosine kinase inhibitors (TKIs) may be associated with a better prognosis of HCC patients [54–59]. Therefore, improving the tolerance of patients to TKI drugs and reducing the dose modification or withdrawal of drugs due to AEs can not only improve the quality of life of patients but also improve therapeutic efficacy. Immune-related adverse reactions (irAEs) induced by ICIs often involve the skin, colon, endocrine organs, liver, and lungs. Although most irAEs are mild to moderate, there are very few cases in which they are severe and even life-threatening. There are currently relevant guidelines regarding the management of irAEs, including "National Comprehensive Cancer Network (NCCN) Guideline: Management of Immunotherapy-Related Toxicities," "Chinese Expert Consensus on Immunotherapy for Hepatocellular Carcinoma (2021 Edition)" [60], etc.

Recommendation 7

Before antineoplastic systemic treatment, the medical history, physical examination, laboratory and imaging examinations must be completed, and the baseline organ function and tumor condition should be fully evaluated. Close follow-up should be implemented after treatment so that adverse reactions can be detected through symptoms, signs, and laboratory tests, and then the patients can be evaluated and treated in time. According to the type and severity of adverse reactions, targeted drugs should be considered for reduction, suspension, or permanent discontinuation, and ICIs should be considered for suspension or permanent discontinuation (Ib, A).

Systemic Therapy Combined with Local Therapy

Local treatment can improve the efficacy of immunotherapy by improving the tumor microenvironment. In addition, the antineoplastic angiogenesis effect of targeted treatment helps eliminate the risk of tumor recurrence caused by tumor angiogenesis after local therapy. Therefore, local therapy in addition to systematic therapy can effectively decrease the size of the tumor, control symptoms, and improve the survival rate. A combination of systematic and local therapy may be considered for patients with intermediate/high tumor burden, vascular invasion, and poor response to solely local treatment but good liver function [61–63].

Systemic Therapy Combined with TACE. The improvement in OS by sorafenib combined with TACE was controversial in previous studies [64–70]. The phase II TACTICS study showed that TACE combined with sorafenib can significantly improve PFS compared with TACE alone (25.2 vs. 13.5 months), but the improvement in OS was not significant (36.2 vs. 30.8 months, $p = 0.40$) [69]. A meta-analysis showed that in HCC patients with PVTT, compared with TACE alone, TACE combined with sorafenib significantly improved the ORR (OR = 3.59, $p = 0.0005$) and OS (HR = 0.62, $p < 0.00001$) [70]. The phase III clinical study LAUNCH, which was carried out in China, showed that, compared with lenvatinib alone, lenvatinib combined with TACE significantly prolonged mOS (17.8 vs. 11.5 months, $p < 0.001$) and mPFS (10.6 vs. 6.4 months, $p < 0.001$) and improved ORR (54.1% vs. 25.0%, $p < 0.001$) [71]. In recent years, triple combination regimens of targeted therapy, immunotherapy and TACE have been widely implemented in the clinic and have shown high ORR and transformational therapeutic potential [10, 72–76]. According to the retrospective study, in 114 patients with unresectable HCC treated with lenvatinib, PD-1 monoclonal antibody, and TACE, the mPFS was 10.4 months, the mOS was 18.0 months, and the ORR was 69.3% (mRECIST) [74]. A real-world study showed that, in comparison to TACE alone, TACE plus TKI, and TACE plus ICI, TACE plus TKI and ICI had the longest PFS (8.3 vs. 5.3 vs. 7.1 vs. 7.4 months, $p = 0.004$) and mOS (21.9 vs. 15.1 vs. 17.6 vs. 18.5 months, $p = 0.030$) [75]. A number of phase III clinical studies of targeted therapy and immunotherapy combined with TACE versus TACE alone are underway.

Recommendation 8

For intermediate- and advanced-stage HCC, targeted therapy combined with TACE can improve the survival of patients to some extent (Ib, B); targeted therapy plus immunotherapy combined with TACE has a greater tumor response and better potential for transformational therapy (IIb, B). Phase III clinical study is still needed to confirm this conclusion; the implementation of TACE combined with immunotherapy needs to be further explored.

Systemic Therapy Combined with Hepatic Arterial Infusion Chemotherapy (HAIC). In recent years, Chinese scholars have made great progress in the treatment of HCC with HAIC of FOLFOX chemotherapy regimen. In the phase III clinical study FOHAIC-1, 65.6% of the HCC patients had PVTT and a high intrahepatic tumor burden. The results showed that the mPFS (7.8 vs. 4.3 months, $p < 0.001$) and mOS (13.9 vs. 8.2 months, $p < 0.001$) were significantly better in the HAIC group than in the sorafenib group, and 11.5% of the patients were transformed and underwent surgery or radiofrequency [77]. The combination of systemic therapy with HAIC therapy also has shown some promising. A phase III clinical study has shown that for patients with PVTT, the efficacy of sorafenib combined with HAIC is better than that of sorafenib alone (ORR: 40.8% vs. 2.46%, $p < 0.001$; mPFS: 7.03 vs. 2.6 months, $p < 0.001$; mOS = 13.37 vs. 7.13 months, $p < 0.001$) [78]. From a retrospective study, it was reported that the combination of an anti-PD-1 monoclonal antibody improved the efficacy of HAIC in the mOS (14.6 vs. 18.0 months, $p = 0.018$) and mPFS (5.6 vs. 10.0 months, $p = 0.006$) [79]. The triple regimen of HAIC combined with targeted therapy and immunotherapy has initially shown good safety and excellent efficacy [80, 81]. A retrospective study [82] reported that compared with lenvatinib alone, HAIC combined with lenvatinib plus PD-1 monoclonal antibody treatment group had longer PFS (11.1 vs. 5.1 months, $p < 0.001$), OS (not reached vs. 11 months, $p < 0.001$) and ORR (59.2% vs. 9.3%, $p < 0.001$). In addition, 14.1% of patients in the triple regimen treatment group achieved complete remission according to the mRECIST criteria.

Recommendation 9

For HCC patients with PVTT, targeted therapy combined with HAIC treatment of the FOLFOX regimen can further improve survival (Ib, A); targeted therapy plus immunotherapy combined with HAIC initially showed a greater tumor response, better

survival and translational therapeutic potential in patients with intermediate and advanced-stage HCC (IIb, B).

Systemic Therapy Combined with Radiotherapy. For symptomatic locally advanced-stage and/or metastatic HCC, palliative radiotherapy for liver and/or vascular tumor thrombi or extrahepatic metastases is recommended as a single treatment or in sequence with systemic therapy when the condition allows [83]. Radiotherapy can relieve pain, recanalize some portal vein tumor thrombi, and restore portal vein blood flow. Research on radiotherapy combined with systemic therapy is still in the early stage. Laboratory research has shown that radiotherapy combined with targeted drugs or immune checkpoint inhibitors will produce synergistic antineoplastic effects, but there is a lack of high-quality evidence [62, 84, 85]. Radiotherapy, including SBRT, yttrium-90 radioembolization, and proton radiotherapy combined with immune checkpoint inhibitors, has potential synergistic effects, and its efficacy has also been confirmed in some clinical studies [85–94]. However, further prospective clinical research is still needed, and the specific method, sequence of combined therapy, division method used in radiotherapy, and complications should be thoroughly investigated. At present, the combination of radiotherapy and immune checkpoint inhibitors is still under clinical research. Radiotherapy combined with TACE is also an effective therapy. A systematic review that included 25 studies with 2,577 patients in total showed that radiotherapy combined with TACE treatment was associated with higher 1-year OS and CR rates than TACE treatment alone [95]. A prospective randomized controlled study showed that, in patients with PVTT, radiotherapy combined with TACE was associated with longer PFS and OS than was sorafenib alone [96].

Recommendation 10

For symptomatic locally advanced-stage and/or metastatic HCC, radiotherapy is conditionally recommended for palliative treatment of liver and/or vascular tumor thrombi or extrahepatic metastases, either alone or in sequence with systemic therapy (III, B). Radiotherapy combined with systemic therapy and TACE therapy has a potential synergistic effect, but this still needs to be verified by prospective studies.

Systemic Therapy Combined with Ablation. The combination of systemic therapy and ablation is still in the stage of clinical exploration. In patients with small HCC, recent studies have shown that the OS rate of patients treated with ablation combined with targeted therapy has not improved significantly, and controversies and uncertainties persist in reducing the local recurrence rate. There is a lack of large sample randomized controlled studies. In patients with intermediate-to advanced-stage HCC and in patients with PVTT, clinical studies have shown that targeted drugs can enhance ablation efficacy and delay tumor progression [97, 98]. A small-sample randomized controlled study showed that, compared with sorafenib, sorafenib combined with radiofrequency ablation significantly improved the 3-year survival of HCC patients with main PVTT (1-year and 3-year OS rates: 60% vs. 37% and 26% vs. 0%). According to multivariate analysis, sorafenib combined with radiofrequency ablation was the only prognostic factor ($p < 0.001$) [97]. Preclinical studies have shown that the combination of ablation and immunotherapy can have synergistic antineoplastic effects [99, 100]. Prospective clinical studies have shown that tremelimumab combined with ablation therapy achieved PR rate of 26.3% and mOS of 12.3 months in advanced-stage HCC patients with disease progression after standard therapy [101].

Recommendation 11

The combination of ablation and systemic therapy remains to be further explored. In patients with intermediate and advanced-stage HCC and in patients with PVTT, targeted drugs combined with ablation may enhance treatment efficacy (IIa, B); ablation combined with immunotherapy may have a synergistic effect (IIb, B).

Conversion Therapy

Conversion therapy refers to convert unresectable HCC to a resectable state by means of intervention. Unresectable HCC includes unresectable cases in the surgical sense, such as patient's inability to tolerate surgery for the poor general condition, liver function intolerance or insufficient future liver remnant, and oncologically unresectable cases. The latter requires treatment to shrink the tumor or reduce its stage to achieve transformation. From the perspective of oncological conversion therapy, a multimodal, high ORR treatment strategy while taking safety into account is recommended. The development of new antineoplastic

drugs has provided new options for conversion treatment. A number of clinical studies on targeted therapy combined with immunotherapy or systemic therapy combined with local therapy as conversion means have obtained preliminary results (online suppl. Table 4). Based on the current research, the rate of successful conversion surgery ranged from 10% to 51%, and the ORR ranged from 23% to 84%, which influenced by the differences in tumor characteristics enrolled in the studies and treatments. In terms of safety, the incidence of ≥3 grade AEs ranged between 19% and 72%, and the incidence of AEs in patients receiving triple regimens seems to be higher [72, 76, 102–107].

In patients after conversion therapy, according to previous retrospective studies and prospective exploratory studies, the original regimen or a part of the drugs ± TACE was often used as adjuvant therapy, the optimal duration of adjuvant therapy was still unclear, and at least 6 months were recommended. If there is no tumor recurrence or metastasis in two consecutive imaging examinations and the tumor marker levels remained normal for 3 months, adjuvant therapy withdrawal can be considered [7, 72, 102, 103]. In patients who do not achieve successful conversion, the following treatment needs to be considered comprehensively, such as a second-line treatment or a combination of systemic and local treatment [7]. Chemotherapy combined with bevacizumab has been commonly used as conversion therapy regimens for unresectable colorectal cancer with liver metastases. In NCCN Guideline for Colon Cancer, the panel recommends an interval of at least 6 weeks (which corresponds to two half-lives of the drug) between the last dose of bevacizumab and conversion surgery. Regarding the interval of medication stoppage before the HCC operation, bevacizumab should be stopped for more than 6 weeks before the operation due to the increased risk of bleeding and influence on wound healing [7]. It is recommended that TKI drugs be stopped for more than 1–2 weeks, and PD-1/PD-L1 monoclonal antibodies are to be stopped for more than 2–4 weeks [7, 108].

Recommendation 12

In unresectable (potentially resectable) HCC patients, a more aggressive conversion therapy strategy can be adopted, a treatment plan with a high ORR should be selected, and surgery should be performed after the tumor is decreased in size or downstaged. First-line targeted drugs plus immunotherapy with or without local therapy represents the main option for conversion therapy (IIa, B). Patients with tumor remission or a descending tumor stage are recommended for multidisciplinary discussion to evaluate surgery, and patients with tumor lesions that fail to conversion can continue treatment according to the treatment principles for unresectable HCC.

Whole-Process Management in Specific Groups

Most clinical studies have excluded specific HCC populations, such as patients who had undergone organ transplantation or had decompensated cirrhosis, autoimmune diseases (ADs), renal insufficiency, etc. This consensus summarizes the current status, contraindications, challenges, and unresolved issues of therapy in specific populations of HCC patients.

Liver Transplantation. Radioembolization and TACE are effective bridging treatments for controlling tumor progression while waiting for liver transplantation [109]. There are no special restrictions on the clinical application of targeted drugs before or after liver transplantation. However, studies with small sample sizes have shown that pretransplantation sorafenib treatment [110] or Y-90 combined with sorafenib [111] may increase postoperative biliary complications and be associated with the risk of acute rejection after liver transplantation. Studies have shown that the efficacy and safety of lenvatinib are similar in patients with recurrent HCC after liver transplantation and in patients who have not received liver transplantation [112]. Because the use of ICIs may lead to an increased risk of organ transplant rejection and mortality, patients with HCC tumor recurrence after liver transplantation were excluded from the immunotherapy clinical research or routine clinical treatment. A retrospective analysis of 57 patients showed that the mortality rate of graft patients treated with ICIs was 40.4%, and the mortality rate of liver transplantation reached 76.5% (13/17), which was significantly greater than that of kidney transplantation (OR = 3.1, $p = 0.04$) [113]. A Chinese study showed that the expression of programmed death ligand-1 (PD-L1) in transplanted liver may be used as a biomarker for rejection reactions: 5 liver transplant recipients with negative PD-L1 expression and receiving PD-1 monoclonal antibody treatment showed no rejection; however, one recipient with positive PD-L1 expression developed acute rejection and died [114]. According to the current studies, treatment with ICIs before liver transplantation in HCC patients is not contraindicated. A retrospective study reported that one of seven transplant recipients treated with PD-1

immunotherapy plus lenvatinib experienced transplant rejection, and after adjustment of the immunosuppressant, liver function recovered [115]. A pooled analysis of 20 patients who received anti-PD-1 monoclonal antibody therapy before liver transplantation showed that although ICIs may increase the risk of early acute rejection after surgery, liver transplantation can still be performed safely in patients receiving long-term ICIs. The washout period between the last ICI treatment and liver transplantation is considered to be an important factor in predicting transplantation outcome, but further research is needed [116].

Recommendation 13

Safety is the primary concern in systemic therapy for liver transplantation patients. Targeted therapy is not subject to special restrictions before or after liver transplantation (III, B). For patients with tumor recurrence after liver transplantation, in view of the high risk of transplant rejection and mortality, ICI treatment is not routinely recommended (III, D); if there is no other treatment option, whether to start ICI treatment needs to be discussed with the patient and transplant surgeons. For pretransplantation treatment, although ICIs are not contraindicated (III, B), caution is still needed, and the optimal time to stop the drug before transplantation also needs to be further explored.

Hepatic Decompensation. Liver function reserve (Child-Pugh B vs. Child-Pugh A) is correlated with prognosis in patients treated with radiofrequency ablation [117]. The different chemotherapeutic drugs and embolic agents used in TACE treatment may have different effects on liver function. Patients with severe hepatic decompensation (Child-Pugh class B with signs of decompensation and Child-Pugh class C) have a higher risk of liver failure after TACE [117, 118]. In previous prospective clinical studies of approved HCC drugs, almost all included patients had liver function classified as Child-Pugh class A, and only a very small number of patients had liver function classified as B7. A meta-analysis showed that sorafenib treatment in patients with Child-Pugh class B liver function was associated with poorer OS (p = 0.001) [119]. According to the GIDEON study, the mOSs for patients with Child-Pugh class A, B, or C liver function were 13.6, 5.2, and 2.6 months, respectively [120]. Retrospective analysis revealed that the mPFS and mOS of patients with Child-Pugh class B liver dysfunction treated with lenvatinib were 3.7 months and 6.8 months, respectively, while those of patients treated with sorafenib were 0.5 months and 4.5 months, respectively [121]. The results suggest that lenvatinib may be a choice for HCC patients with liver function classified as Child-Pugh class B. The CheckMate040 study-cohort 5 included patients with Child-Pugh class B7-8 liver function, and the results demonstrated that the ORR for nivolumab in the treatment of sorafenib-naïve or treated HCC patients was 10.2%, the DCR was 55.1%, and the mOS was 7.6 months. The safety of this approach was similar to that of the Child-Pugh class A cohort [122]. A real-world study showed that atezolizumab plus bevacizumab in patients with Child-Pugh class B liver function had a safety profile similar to that of patients in the Child-Pugh A cohort but had a worse prognosis (mOS: 6.7 vs. 16.8 months, p = 0.0003; mPFS: 3.4 vs. 7.6 months, p = 0.03) [123]. A recent phase II study showed that the A3 adenosine receptor agonist (Namodenoson) is likely to be used as a second-line treatment for HCC patients with liver function in Child-Pugh class B [124]. After more patients with a Child-Pugh score of 9 were included, no significant difference in mOS between the Namodenoson group and the placebo group was observed (4.1 vs. 4.3 months, p = 0.46). In the subgroup with a Child-Pugh score of 7, the 1-year OS rate of the Namodenoson group was significantly greater than that of the placebo group (44% vs. 18%, p = 0.028). The incidence of TRAEs of grade 1/2 and grade 3/4 were 20% and 2%, respectively. Phase III clinical trials are currently under investigation. Other studies have shown that the albumin bilirubin grading system may be a simpler and more accurate method for assessing liver function than the Child-Pugh grading system [125, 126]. Systemic antineoplastic therapy is not recommended for patients with liver function classified as albumin bilirubin class 3 or Child-Pugh class C.

Recommendation 14

Liver function is closely related to the prognosis and treatment options of HCC patients. Systemic antineoplastic therapy can be considered for HCC patients with Child-Pugh A/B ≤7 points. Targeted drugs or ICI monotherapy can be considered cautiously in patients with relatively good Child-Pugh class B liver function (IIb, B). Supportive treatment is recommended for patients with Child-Pugh class C liver function, and systemic antineoplastic therapy can be evaluated after liver function has improved.

Autoimmune Diseases. AD is not a contraindication to targeted therapy, but there is an increased risk of toxicity

from ICI therapy, which is usually excluded from clinical research. According to previous retrospective reports, most of the patients treated with ICIs had mild active AD or AD that did not require treatment, and they still seemed to experience good efficacy and safety. According to a systematic review of 512 patients with combined AD, the incidence of irAEs was 68.0% (grade 3/4 18.2%), and the ORR was 34.2% [127]. A meta-analysis of 619 tumor patients with AD showed that the ORR of ICI treatment was 30%, and the use of immunosuppressants tended to reduce the ORR; 60% of the patients experienced an exacerbation of existing AD and/or new irAEs (35% and 33%, respectively), of which grade 1 and 2 accounted for 80% and 68%, respectively [128]. Although AD is not an absolute contraindication to ICI treatment, many issues still need to be resolved. For example, the question of how to use selective and nonselective immunosuppressants to reduce the impact on ICI efficacy, the risk of ICI treatment in patients with different types of AD, the risk of immunotherapy in HCC patients combined with autoimmune liver disease are unclear.

Recommendation 15

There are no special restrictions on the use of targeted therapy in HCC patients with ADs (III, B). In patients with mild active AD or AD that does not require treatment, ICI therapy is not an absolute contraindication but should be used with caution (III, C). Patients with autoimmune neurological diseases or life-threatening AD whose symptoms cannot be relieved by immunosuppressive drugs or require high doses of corticosteroids are not suitable for ICI treatment.

Renal Insufficiency

A retrospective study provided results regarding 58 HCC patients (conforming to up to 7 criteria) receiving hemodialysis who underwent surgical resection (23 patients) or RFA (35 patients), there was no significant difference in efficacy (OS or DFS); RFA-related complications were all hemorrhagic (11.4%), and surgery-related complications were infection, liver failure and pleural effusion (17.4%) [129]. Renal insufficiency is considered a relative contraindication to TACE [130]. It was reported that the risk of death after TACE increased by 43% in HCC patients with chronic kidney disease and was significantly associated with acute kidney injury and sepsis [131]. A multicenter study reviewed 6156 HCC patients treated with sorafenib and summarized 22 patients (0.36%) with chronic kidney disease and hemodialysis: 31.8% of patients experienced ≥3 grade AEs, 77.3% of the patients needed to reduce the dose of the drugs, 22.2% of the patients (4/18) discontinued treatment due to AEs, and the mOS was 17.5 months [132]. The results of the study suggest that the use of sorafenib in HCC patients with renal insufficiency receiving hemodialysis is feasible. Anti-PD-1, PD-L1, or CTLA-4 monoclonal antibodies are large molecular drugs that are not metabolized by the liver or kidney but rather through proteolysis of proteins in cells, which generates peptide fragments and amino acids. Renal insufficiency has no significant impact on clearance [133]. The researchers retrospectively summarized the data from 56 reports with advanced RCC who were receiving concurrent hemodialysis and multiple targeted drugs and immunotherapy (including bevacizumab, n = 6; sorafenib, n = 55; nivolumab, n = 18; etc.). The results showed that hemodialysis did not appear to affect the expected efficacy or safety [134]. Another retrospective study that included 17 patients who had renal insufficiency (creatinine ≥2 mg/dL or glomerular filtration rate ≤30 mL/min) and received Anti-PD-1 inhibitor therapy and (no HCC patients and 3 patients on dialysis) showed that 3 patients developed non-immunotherapy-related mild acute renal injury, which improved after rehydration and diuretics treatment; additionally, no renal injury was caused by irAEs [135]. However, the results from other types of tumors cannot be fully applied to systemic treatment for HCC.

Recommendation 16

Due to the lack of large-scale research data and sufficient clinical applications, targeted therapy or ICIs should be used with caution in HCC patients with severe renal dysfunction or who are receiving hemodialysis, and a comprehensive evaluation with nephrologists should be performed before treatment (III, C).

Symptomatic and Supportive Treatment of HCC

The prognosis of HCC patients is affected not only by the tumor itself but also by liver function [136]. Liver dysfunction may be caused by the patient's baseline liver disease, intrahepatic tumor, or treatment. A study showed that approximately 43% of HCC patients died of liver dysfunction rather than tumor progression [137]. Therefore, it is recommended that appropriate liver-protective treatments be administered to patients in a timely manner. Moreover, according to the disease condition, liver function status, treatment methods, side

effects of the drugs, etc., regular liver function review, dynamic monitoring, and whole-process management should be implemented. Complications such as pain, ascites, jaundice, hepatic encephalopathy, hepatorenal syndrome, and malnutrition often occur in HCC patients in the terminal stage, and appropriate supportive treatment should be implemented in a timely manner. Symptomatic and supportive treatment should be implemented throughout the entire process of antineoplastic treatment.

Antiviral Therapy Strategies

Since viral hepatitis is the main cause of HCC in China and some antineoplastic treatments have the potential to activate the hepatitis virus, it is recommended that HCC patients with HBV/HCV infection receive antiviral treatment [6, 138]. For HBV-related HCC, first-line nucleotide analog (NUC) antiviral therapy, such as entecavir, tenofovir disoproxil fumarate, tenofovir alafenamide, or tenofovir amibufenamide, should be given immediately. (1) In HbsAg (+) patients, regardless of whether HBV-DNA is detectable, first-line NUC antiviral treatment should be given immediately. (2) In HCC patients who are HBsAg (−) but HBcAb (+), with the negative high-precision HBV-DNA, prophylactic antiviral therapy is not recommended. Antiviral treatment should be given immediately once the HBV is reactivated. Patients who are HBsAg (−) but HBcAb (+) and receive high-intensity TACE are at high risk of HBV reactivation. These patients must be under close surveillance so that HBV reactivation can be monitored and antiviral treatment can be carried out as early as possible. (3) Patients without contraindications for the application of pegylated interferon can be treated with pegylated interferon combined with NUCs after surgery to improve OS. (4) In patients who underwent liver transplantation, antiviral therapy with first-line NUCs is recommended before transplantation as early as possible [6, 138, 139]. For HCV-related HCC, direct-acting antiviral agents (DAAs) are recommended. In patients coinfected with HCV and HBV, corresponding HBV antiviral therapy can be given, and first-line NUCs can be selected. For the patients with HBsAg (+) but HBV-DNA (−), preventive treatment for HBV should be administered before patients receive anti-HCV treatment with DAAs and anti-HBV treatment should be administered at least 3 months after the end of DAAs treatment. For the patients with HBcAb (+) and HBV-DNA (−), the levels of HBsAg and HBV-DNA should be monitored, and antiviral therapy should be initiated if necessary 6, 138].

Liver Injury Induced by Antineoplastic Therapy

Liver dysfunction is likely to occur after hepatic artery interventional therapy. Generally, transaminase levels increase slightly 1–2 days after interventional therapy, and severe liver injury and even liver failure can occur occasionally. In addition to routine examinations of liver and kidney function before interventional therapy, the use of drugs that can damage liver function, such as sedatives and sleeping pills, should be minimized. The use of a microcatheter for selective intubation, insertion into the supplying arteries of the tumor, or accurate injection of chemotherapy drugs is recommended. For patients with HBV-related HCC, preoperative preventive hepatoprotective therapy should be considered. Radiation therapy-induced liver injury is called radiation-induced liver disease (RILD) and is a clinical subacute and chronic liver injury. The onset of RILD varies with the patient condition and radiation dose, volume, and segmentation method and usually occurs 4–12 weeks after radiotherapy. There is currently no predictive examination for RILD. It is necessary to perform physical examinations and monitor routine blood and biochemical indices of patients every week during treatment and every 1–2 months after treatment. The main treatment for RILD involves improvement of liver function, management of ascites, and administration of other symptomatic and supportive treatments, including glucocorticoids and hepatoprotective drugs, which can also be considered [140, 141]. Drug-induced liver injury (DILI) is one of the most common adverse reactions in clinical practice. Liver injury can be caused by the drug itself and/or its metabolites. In severe cases, the disease can progress to acute liver failure and even death [142]. Due to the lack of specific biomarkers, the diagnosis of DILI relies mainly on exclusion. Treatment for DILI includes appropriate hepatoprotective therapy. For immune-related liver injury caused by ICIs, glucocorticoids can be used. For DILI caused by antitumor drugs, the drug should be considered for reduction, suspension, or permanent discontinuation.

Portal Hypertension

Patients with HCC often have cirrhosis and portal hypertension, which can be further aggravated by PVTT. Patients with portal hypertension often exhibit hypersplenism, esophagogastric fundic varices, impaired liver function, and even serious complications such as upper gastrointestinal bleeding, ascites, and liver failure. Portal hypertension is also a major factor influencing the choice of treatment for HCC, including the choice of local radical therapies, interventions, radiotherapy, and risk assessment of antiangiogenic targeted drugs. Treatment

of portal hypertension includes pharmacological, endoscopic, interventional and surgical means to reduce portal pressure, prophylactic treatment of esophageal varices, treatment of ruptured bleeding, etc. [143, 144].

Recommendation 17

HCC patients should receive symptomatic supportive therapy beginning at diagnosis and throughout the whole-course management of HCC. Antiviral therapy in patients with HBV-related HCC is an important part of delaying disease progression, preventing HCC recurrence, and prolonging OS (Ia, A). Liver function should be closely monitored, and appropriate hepatoprotective therapy should be given before and during antitumor treatment. Severe complications for HCC patients, such as severe ascites, jaundice, bleeding, and hepatic encephalopathy, should be actively discussed in a multidisciplinary manner, and interventions should be initiated in a timely manner.

Follow-Up Management

The follow-up of HCC patients mainly includes assessing tumor conditions, monitoring baseline liver disease and assessing AEs to treatment. Regarding patients receiving local radical treatment, including surgical resection, liver transplantation, and ablation, although the optimal reexamination interval lacks the support of large sample size clinical research data, some relevant consensuses have been reached [6]. Reexamination of liver imaging and tumor marker (AFP and abnormal prothrombin) levels should be performed 1–2 months after surgery, every 3–6 months within 2 years, and every 6–12 months thereafter. In addition to paying attention to the liver, we should also be alert to metastases outside the liver. Patients who are at risk of rejection after liver transplantation, and need long-term administration of immunosuppressants requires regular monitoring of liver function and drug concentrations in blood. Assessment of intrahepatic disease relies mainly on dynamic contrast-enhanced CT/MRI, hepatobiliary-specific contrast agent-enhanced MRI, and contrast-enhanced ultrasound. CT can be used for the examination of extrahepatic metastases, and if necessary, bone scan or PETCT can be used. For patients with baseline liver diseases such as hepatitis virus infection, the viral load and liver and kidney function should be monitored every 3–6 months, and patients should regularly visit a liver specialist in outpatient clinics. After the first TACE treatment, contrast-enhanced CT/MRI and tumor biomarkers are usually rechecked at 4–6 weeks, and follow-up evaluations can be performed at intervals of 1–3 months or longer. Whether TACE should be repeated depends mainly on the patient's response to the previous tumor treatment, liver function, and other basic conditions. The first imaging evaluation should take place approximately 1 month after the end of radiation therapy, and the decrease in tumor size may be more significant 3–9 months after the end of radiation therapy. Imaging should be evaluated every 6–8 weeks during the first 6 months of systemic antineoplastic treatment, and subsequent imaging can be combined with tumor marker analysis every 9–12 weeks. AEs should be regularly monitored through various examinations and tests, including regular blood routine, biochemical, urine routine and urine protein (for targeted treatment), thyroid function (for targeted treatment and immunotherapy), myocardial markers and function assessments of pituitary and adrenal (for immunotherapy), etc.

Recommendation 18

Regular follow-up is recommended for HCC patients. According to the patient's tumor-bearing status and treatment methods, intrahepatic and extrahepatic tumor conditions should be evaluated regularly, and baseline liver disease and adverse reactions to treatment should be monitored.

Conclusion

The whole-course management of HCC involves managing the disease from a long-term, developmental, and systematic perspective and is based on the standardized diagnosis and treatment of HCC. This approach emphasizes multidisciplinary cooperation and individualized treatment plans, and runs through the entire process of diagnosis, treatment, evaluation, and follow-up, aiming to maximize the survival and quality of life of patients. Systematic treatment of HCC is still the core of the whole-course management, and many problems in treatment still need to be further studied, such as the postoperative adjuvant treatment, the optimization of conversion treatment, the deployment of systemic drugs, the choice of the third-line treatment, etc. This consensus proposes whole-course management pathways for HCC,

mainly expounds on the whole-course treatment of the disease based on systemic therapy and suggests treatment opinions to provide a reference for clinicians. With the emergence of new evidence generated in the future, this consensus still needs to be continuously updated and supplemented by peers.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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