

Review

Treatment of Hepatocellular Carcinoma: A Systematic Review

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Key Words

Chemotherapy · Hepatocellular carcinoma · Liver resection · Liver transplantation · Intervention therapy

Abstract

Hepatocellular carcinoma (HCC) is one of the most common malignancies, with an increasing incidence. With advances in surgical techniques and instrumentation and the development of molecular-target drugs, a number of potentially curative treatments have become available. Management of HCC patients depends on the stage of their tumor. Liver resection remains the first choice for very early-stage HCC, but it is being challenged by local ablative therapy. For early-stage HCC that meet the Milan criteria, liver transplantation still offers a better outcome; however, local ablative therapy can be a substitute when transplantation is not feasible. Local ablation is also used as a bridging therapy toward liver transplantation. HCC recurrence is the main obstacle to successful treatment, and there is currently no effective means of preventing or treating HCC recurrence. Transarterial therapy is considered suitable for intermediate-stage HCC, while sorafenib is recommended for advanced-stage HCC. This stage-based approach to therapy not only provides acceptable outcomes but also improves the quality of life of HCC patients. Because of the complexity of HCC, therapeutic approaches must be adapted according to the characteristics of each individual patient. This review discusses the current standards and trends in the treatment of HCC.

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Introduction

Hepatocellular carcinoma (HCC) is the fifth most common form of cancer and the third leading cause of cancer-related death worldwide [1]. The number of cases diagnosed with HCC is expected to increase in Western countries [2]. Therapeutic approaches for the treatment of HCC can be classified into three categories: potentially curative, palliative, and symptomatic. Potentially curative treatments, including liver resection, transplantation, and local ablation, are associated with promising 5-year survival rates of up to 75% [3]. However, because of a shortage of donor livers, advanced tumor stage, or liver dysfunction, less than 20% HCC patients are eligible for such treatments [4, 5]. The majority of HCC patients are subjected to palliative or symptomatic treatment. The 3-year survival rate for palliative treatment is 10–40%, and the duration of survival for patients who receive symptomatic treatment is <3 months [6]. The choice of therapy is mainly based on by the stage of HCC, severity of the underlying liver disease, availability of treatment resources, and clinical expertise [7]. Selection criteria for these treatments have been recommended by Bruix and Sherman et al. [8, 9].

Stage evaluation is essential to assess the resectability of the tumor mass, choose an appropriate therapy, and predict the prognosis of HCC patients. Numerous staging evaluation systems have been proposed and applied in clinical practice, including the Cancer of the Liver Italian Program (CLIP) score, Barcelona Clinic Liver Cancer (BCLC) staging, Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire (GETCH) classification, Chinese University Prognostic Index (CUPI) grade, Japan Integrated Staging (JIS) score, modified JIS (mJIS) score, Okuda staging, and the Tokyo score. Comparisons of the different staging systems are mainly based on retrospective analyses. We collected data from the past five years, and these are summarized in table 1. Although these data do not suggest any consensus, the BCLC staging system has been proposed as a standard for the assessment of prognosis in Europe and the United States [7, 9]. The exclusion of risk factors in the current staging systems may potentially decrease prognostic accuracy.

Therapeutic Strategies Based on HCC Stage

Very early stage HCC

Very early stage HCC is defined as asymptomatic solitary HCC with a diameter of <2 cm. Surgical resection is recommended by the European Association for the Study of the Liver–American Association for the Study of Liver Diseases (EASL–AASLD) for patients who present with very early-stage HCC and Child–Pugh A liver function [8]. The overall 5-year survival and recurrence rates after liver resection of very early-stage HCC are reportedly 70 and 68%, respectively [10]. The presence of satellite nodules and platelet counts <150,000/μl are independently associated with survival, whereas the presence of satellite nodules and cirrhosis and the use of nonanatomic resection are independently associated with tumor recurrence [10]. Percutaneous ablation can achieve an acceptable outcome for very early-stage HCC: a 5-year disease-free survival rate of 62% and a 5-year overall survival rate of 78% [11]. Furthermore, it has been suggested that radiofrequency ablation (RFA) leads to better overall survival in patients with operable HCC than in those with inoperable HCC. Some groups have suggested that RFA should be considered as first-line therapy even when resection is possible because it is associated with fewer side effects [12]. The question of whether surgical resection is superior to RFA remains controversial. Wang et al. suggested that although surgical resection was equivalent to RFA in terms of overall survival, it yielded better disease-free survival [13]. Markov model analysis also indicated that surgical resection was preferable to RFA in terms of overall survival [14]. However, Peng et al. reported

Table 1. Comparative trials of HCC staging systems in the past 5 years

Author	Year	Number of patients	Staging system	Treatment	Method	Favor of the staging system
Kim [114]	2012	1717	BCLC, JIS, Tokyo, CLIP, CUPI, GETCH	Multiple	prospectively	BCLC: prognosis
Sirivatanauksorn [115]	2011	99	TNM, CLIP, BCLC, CUPI, JIS, Okuda	Hepatectomy	retrospectively	TNM and Child-Pugh: representative survival prediction
Chan [116]	2011	595	TNM, CLIP, BCLC, CUPI	NA	prospectively	CUPI: for HBV-related HCC. CUPI and CLIP offer good risk stratification for advanced HCC
Kawaoka [117]	2010	214	mJIS, JIS, BCLC, LCSG)/TNM, CLIP	TACE	retrospectively	mJIS: better discriminate ability score and prognostic predictive power
Hsu [118]	2010	1713	BCLC, CLIP, JIS, TNM, Tokyo	NA	prospectively	CLIP: best long-term prognostic model
Huitzil-Melendez [119]	2010	187	BCLC, TNM, CLIP, CUPI, GETCH	NA	retrospectively	CLIP, CUPI, and GETCH: survival prediction
Zhang [120]	2010	306	TNM, Okuda, CLIP, BCLC, JIS	Hepatectomy	retrospectively	BCLC: strongest potential in prognosis evaluation
Chung [121]	2008	290	JIS, BCLC, Tokyo	Radical treatment	retrospectively	JIS: best prognostic stratification
Lu [122]	2008	234	Okuda, CLIP, TNM, CUPI	Curative resection	retrospectively	TNM: best for prognostic stratification and prognosis prediction.
Camma [123]	2008	406	BCLC, CLIP, GETCH	LT or none	prospectively	CLIP: best discriminative capacity BCLC: predicting survival in treated patients
Collette [124]	2008	538	Okuda, CLIP, BCLC	Palliative treatment	randomized	CLIP: prognosis
Cho [125]	2008	131	Child-Pugh, Okuda, BCLC, CLIP, mCLIP, JIS, mJIS	TACE	retrospectively	CLIP for palliative setting
Guglielmi [126]	2008	112	Okuda, TNM, BCLC, CLIP, GETCH, CUPI, JIS	percutaneous RFA	retrospectively	BCLC: superior discriminatory power and prognostic information
Kondo [127]	2007	235	CLIP, BCLC, GETCH, CUPI, JIS, mJIS, Tokyo	Hepatectomy	retrospectively	JIS
Chen [128]	2007	382	Okuda, AJCC, CLIP, BCLC, JIS, CUPI, MELD	Hepatectomy	retrospectively	CLIP: stage major hepatectomy patients, JIS: stage minor hepatectomy patient

NA = not available.

Table 2. Summary of trials analyzing liver resection vs. local ablative therapies in the past 5 years

Author	Year	Methodology	Treatments	Patients number	Tumor number	D (cm)	OSR	ORS	RFSR	DFSR
Feng [129]	2012	RCT	SR RFA	84 84	≤2	≤4	×	×	×	NA
Ruzzenente [130]	2012	Retrospective, Case matched	SR LAT	88 88	≤3	≤5	×	NA	NA	×
Wang [13]	2012	Retrospective	SR RFA	208 254	≤3	≤5	SR>RFA	SR<RFA	NA	SR>RFA
Huang [131]	2011	Retrospective	SR RFA	311 212	1	≤3	SR>RFA	×	×	SR>RFA
Huang [131]	2011	Retrospective	SR RFA	337 201	≤3	3<D<5	SR>RFA	×	SR>RFA	SR>RFA
Hung [132]	2011	Retrospective, Case matched	SR RFA	229 190	≤3	≤5	×	SR<RFA	NA	NA
Nishikawa [133]	2011	Retrospective	SR RFA	69 162	1	≤3	×	NA	×	NA
Huang [134]	2010	RCT	SR RFA	115 115	≤3	≤5	SR>RFA	SR<RFA	SR>RFA	NA

SR = surgical resection; PTA = percutaneous thermal ablation; D = Diameter of tumor mass; OSR = overall survival rates; ORS = overall recurrence rates; RFSR = recurrence-free survival rates; DFSR = disease-free survival rates; × = no significance.

that RFA was associated with better overall survival compared with surgical resection [15]. Therefore, further research is warranted before local ablation can be recommended as first-line therapy for very early-stage HCC or as a substitute for surgical resection.

Early-stage HCC

Early-stage HCC is defined according to the Milan criteria as follows: a single tumor nodule ≤5 cm in diameter or ≤3 nodules ≤3 cm in diameter [16]. Approximately 25% of all HCC patients are diagnosed with early-stage HCC [17]. According to the EASL-AASLD guidelines, early-stage HCC is an indication for liver transplantation or RFA [8]. Liver transplantation is the optimal approach, but local ablation can be a substitute when liver transplantation is not feasible. Liver resection should be considered when patients present with a solitary tumor and no portal hypertension [7]. The 4- and 5-year survival rates of patients who meet the Milan criteria and subsequently undergo liver transplantation are 85 and 70%, respectively [16, 18]. Farinati et al. reported that for patients with early-stage HCC, liver transplantation offers the best chances of survival (106 months) compared with surgical resection (52 months), RFA (62 months), percutaneous ethanol injection (PEI, 44 months), and transarterial chemoembolization (TACE, 34 months) [17]. Despite the excellent efficacy of liver transplantation in early-stage HCC treatment, a shortage of donor livers or tumor progression during the waiting period inevitably leads to patients dropping out from the waiting list. The monthly drop-out rate is approximately 4% [18, 19]. Local ablative therapies, primarily RFA, have therefore been investigated as alternative treatments for early-stage HCC that meet the Milan criteria. Although a recent meta-analysis indicated that surgical resection is superior to RFA because it results in longer overall survival, longer recurrence-free survival, and a low rate of local recurrence, the analysis was mainly based on nonrandomized controlled trials and did not include the latest 3-year survival data [20]. The conclusion should therefore be interpreted with caution. To address the efficacy of local ablative therapy in comparison with

Table 3. Summary of transarterial therapies for HCC

Author	Year	Treatment	Number of patients	Overall survival (OS) (%)				OS (Months)
				1 year	2 years	3 years	4 years	Median
Doffoël [95]	2008	TACE+tamoxifen	62	51	25	NA	NA	13.8
		tamoxifen	61	46	22	NA	NA	11.0
Lo [94]	2002	TACE	40	57*	31*	26*	NA	NA
		symptomatic	40	32	11	3	NA	NA
Llovet [93]	2002	TACE	38	82*	63*	29	NA	28.7*
		TAE	34	75	50	29	NA	25.3
Bruix [97]	1998	symptomatic	35	63	27	17	NA	17.9
		TAE	40	NA	49	NA	13	NA
GETCH [135]	1995	symptomatic	40	NA	50	NA	27	NA
		TACE	50	62	37.8	NA	NA	NA
		Conservative	46	43.5	24.3	NA	NA	NA

*P < 0.05

that of surgery, we have summarized data from recent clinical trials in table 2. As shown in the table, the superiority of surgical resection remains controversial. More randomized controlled trials are warranted to elucidate whether local ablative therapy and surgical resection have equivalent efficacy for the treatment of early-stage HCC.

Intermediate-stage HCC

HCC patients with Child–Pugh A and B liver function who present with a large or multifocal tumor mass without cancer-related symptoms, macrovascular invasion, or extrahepatic spread are diagnosed with intermediate-stage HCC. Transarterial therapy, especially TACE, is recommended for this stage of HCC by the EASL-AASLD guidelines. Randomized controlled trials of treatments for intermediate-stage HCC are summarized in table 3. Of the five trials reported, only two favored TACE over symptomatic treatment in terms of overall survival. Approximately 20–30% HCC patients are diagnosed with intermediate-stage HCC, and more trials are required to elucidate the efficacy of transarterial therapy for these patients [21, 22]. A surgical approach has also been adopted in this patient population. Vitale et al. reported that the 3-year survival rate among patients with intermediate-stage HCC who underwent surgery was 56% compared to 13% among those who did not [22]. It has been suggested that liver transplantation should be considered critical for intermediate-stage HCC [23]. However, surgical resection for intermediate-stage HCC is associated with poor long-term survival rates; the 3-, 5-, and 10-year survival rates after surgical resection are reportedly 35.1, 18.2, and 3.5%, respectively [24].

Advanced-stage HCC and terminal-stage HCC

HCC with cancer-related symptoms, vascular invasion, or extrahepatic spread is considered to be in the advanced stage. The therapeutic recommendation for this stage is oral sorafenib treatment. Despite improvements in survival after sorafenib administration, the prognosis for patients with this stage of HCC is still poor, with a median overall survival rate of 6.5–10.7 months [25]. Terminal-stage HCC includes severe deterioration of physical capacity and symptoms related to liver failure, vascular invasion, or extrahepatic spread. At this stage, only symptomatic treatments are available, and the median survival is <3 months [9].

Therapeutic Approaches for HCC

Liver resection

Surgical resection is considered a potentially curative treatment and offers an acceptable outcome for carefully selected HCC patients [26, 27]. Refinements of surgical techniques and staging systems have led to 5-year survival rates of approximately 50–70% after surgical resection [28–31]. The application of advanced surgical techniques and instrumentation decreases blood loss, increases outcomes such as survival and quality of life, and decreases the need for the Pringle maneuver compared with that for portal triad clamping [32–35]. As mentioned above, the best candidates for surgical resection are patients with very early- or early-stage HCC, although resection in patients with more advanced stages of HCC has been reported with acceptable outcomes [24, 36, 37]. Tumor size, tumor nodules, liver function, and portal pressure have been identified as prognostic predictors after liver resection [29, 38, 39]. Surgical resection is likely to remain the primary approach for patients who present with very early- and early-stage HCC, given its apparent superiority to liver transplantation and local ablative therapy. Although liver transplantation offers a better outcome, the shortage of donor livers remains indisputable. Surgical resection also enables complete pathological analysis of a cancerous sample, which cannot be achieved by local ablative therapy. Complete resection (R0) is indispensable for decreasing recurrence, but an adequately sized liver remnant is required to avoid postoperative liver failure [40]. Major liver resection is feasible, and up to 70% of a noncirrhotic liver can be resected considering that liver regeneration, which is compensatory growth that restores liver mass and function after liver resection, occurs [41, 42]. The minimal critical remnant liver volume for resection is approximately 25% (15–40%) for noncirrhotic and 50% (25–90%) for cirrhotic livers [43]. When the estimated volume of the future liver remnant does not meet these criteria, preoperative portal vein embolization (PVE) is recommended [44]. Preoperative PVE reportedly decreases the rate of postoperative complications in cirrhotic patients but not in patients with normal livers [45]. Recurrence after liver resection remains the major obstacle to achieving ideal survival, and the 5-year recurrence rates are approximately 70% [10, 46]. The prognosis for HCC patients after liver resection is mainly influenced by the recurrence of HCC, either a real recurrence or a de-novo tumor growth in a cirrhotic liver [47, 48]. The risk factors contributing to recurrence after curative resection have yet to be elucidated. The intrahepatic spread of resected primary HCC has been conceptually attributed to early recurrence (within 2 years after resection), while precancerous lesions in the remnant liver after resection may be involved in later recurrence [49]. Re-resection, RFA, and salvage liver transplantation are potential therapeutic approaches to intrahepatic recurrence. Chan et al. reported 1-, 3-, and 5-year overall survival rates of 89.7, 56.5, and 35.2% after re-resection and 83.7, 43.1, and 29.1% after RFA in patients with recurrent HCC [50]. If the recurrent HCC meets the Milan criteria, salvage liver transplantation can also be considered [51]. For carefully selected patients, salvage liver transplantation can achieve a 5-year survival rate of approximately 70%, which is similar to that achieved with primary liver transplantation [52].

Laparoscopic liver resection is a minimally invasive surgical approach that is gaining importance in the treatment of HCC. Till date, most of segmental liver resections can be performed laparoscopically, but major laparoscopic hepatectomy (LH) has also been reported [53, 54]. However, selection criteria must be adapted to the clinical expertise of the surgeon to avoid any unnecessary conversion to open hepatectomy (OH) or serious complications. Although LH is a more sophisticated surgical procedure compared with OH, the use of laparoscopic ultrasound and a hand port, cavitron ultrasonic aspirator (CUSA™), vessel sealing system (Ligasure™), and ultrascissors (Autosonix™) decreases intraoperative bleeding, facilitates safe parenchyma transection, and increases the scope for vessel division.

Hemorrhage and insufficient tumor excision are the two main reasons for conversion to OH. Potential complications are similar to those for open resection and include bile leakage, hemorrhage, hepatic failure, and infections [55]. Recent evidence has indicated that there is no difference between LH and OH in terms of margin status, recurrence, and survival [56]. Furthermore, LH decreases blood loss, frequency of transfusion, frequency of use of the Pringle maneuver, postoperative morbidity, recovery time, length of hospital stay, and the incidence of incisional hernia when compared with OH [57]. These advantages were confirmed in a recent meta-analysis [58]. However, all of this evidence is based on retrospective or case-matched retrospective analyses, and no randomized controlled trials have been reported. The proposed advantages need to be validated using such trials to confirm the long-term effects of laparoscopic liver resection on survival and tumor metastasis.

Liver transplantation

Liver transplantation offers a better oncological outcome than surgical resection because it not only removes all precancerous and cancerous lesions within the liver but also cures the coexisting liver disease. Early outcomes of liver transplantation for HCC were poor, with 5-year survival rates of 15–40% [59–61]. However, after the establishment of the Milan criteria, the 5-year survival rate increased to 70–80% [62, 63]. Yet, there is a tendency to expand the Milan criteria for liver transplantation, and 5-year survival rates of 45–55% are considered acceptable even though such an extension of the Milan criteria increases the incidence of HCC recurrence [63–65]. The outcomes of liver transplantation for HCC patients who were treated at our center and exceeded the Milan criteria were comparable with those of patients in a previous study [66]. The scarcity of donor livers remains the main obstacle for HCC patients and increases the waiting time for transplantation. HCC progression during the waiting period leads to patients dropping out from the waiting list; the monthly drop-out rate is reportedly 4% [18, 19]. One potential solution to this problem is increasing the donor pool by live donation, which is mostly practiced in Asia, using bridging therapy such as local ablative treatments for HCC patients on the waiting list, and applying prioritization policies [67].

The first living donor liver transplantation (LDLT) was reported in 1989 by Raia [68], and successful LDLT from an adult to a child was achieved one year later [69]. Successful adult-to-adult LDLT was reported in 1994 [70]. LDLT is now performed worldwide and has become an alternative to deceased donor liver transplantation (DDLT) [71]. The surgical protocols and evaluation criteria for donors as well as recipients are now well established [72, 73]. Recent reports suggest that outcomes for LDLT are similar to those for DDLT in terms of overall survival and recurrence rates, but the waiting time is lower with LDLT than with DDLT [74]. Both left- and right-lobe LDLT are performed, and the more preferable option remains controversial. Taketomi et al. reported that the long-term outcome of HCC patients who underwent left-lobe LDLT was similar to that of patients who underwent right-lobe LDLT; however, those with left-lobe LDLT achieved lower peak postoperative total bilirubin levels and had a shorter hospital stay after transplantation [75]. In contrast, Saidi et al. reported that recipients of left-lobe LDLT had a greater mean duration of stay (24.9 days vs. 18.2 days), higher re-transplantation rates (20.3% vs. 10.9%), lower allograft survival, and inferior survival compared with recipients of DDLT [76]. LDLT should be carefully considered because donor morbidity and mortality still exist, and problems such as matching the graft size with the recipient area and postoperative complications cannot be avoided [77].

Progression of HCC during the waiting period for liver transplantation is inevitable and can lead to patients dropping out from the waiting list. The current strategy is to use RFA or TACE as bridging therapy to decrease tumor progression when the estimated waiting time for transplantation is longer than six months [67]. Percutaneous treatments are more cost-effective than surgical resection [78]. The use of RFA as a bridge to liver transplantation re-

Table 4. Meta-analysis of local ablative therapy and liver resection

Methods	Conclusions
RFA vs. LR [20, 136]	1: LR exhibited higher overall and recurrence-free survival rates of 1, 3, and 5 years compared with RFA. 2: the rate of local recurrence was lower with hepatectomy than with RFA. 3: postoperative morbidity was higher with hepatectomy.
RFA vs. PEI [137, 138]	1: RFA was superior to PEI in terms of survival, complete necrosis of tumor, and local recurrence. 2: For tumors <2 cm, RFA was not significantly better than PEI. 3: The overall rate of adverse events was higher with RFA than with PEI.
PAI vs. PEI [137, 139]	PAI did not differ significantly from PEI in terms of overall survival, recurrence-free survival, and local recurrence; however, it required lesser sessions.
RFA vs. PAI [137]	RFA resulted in lower local recurrence

LR = liver resection; PAI = percutaneous acetic acid injection.

portedly enables HCC patients to remain on the waiting list for longer without influencing post-transplantation outcomes [79]. Furthermore, a poor response to TACE before transplantation is an indicator of post-transplantation recurrence [80]. Downstaging of HCC to within the Milan criteria may be another benefit of these treatments, with acceptable survival rates [81–84].

The Model for End-Stage Liver Disease (MELD) allocation policy is a widely accepted allocation system that decreases the waiting time and drop-out rates [85, 86]. A recent analysis indicated that MELD provided reasonable patient and graft survival but increased the financial burden and post-transplantation morbidity [87]. A new allocation system, the BAR system, has been proposed. This appears to predict survival in a better manner [88]. This system includes the six strongest predictors of post-transplantation survival: recipient MELD score, cold ischemia time, recipient age, donor age, previous orthotopic liver transplant, and life support dependence prior to transplantation. However, its efficacy needs to be clinically validated.

Local ablative therapy

Local ablative therapy can be classified into two categories: chemical ablation and thermal ablation. The substances involved in chemical ablation are ethanol and acetic acid, whereas thermal ablation uses radiofrequency, microwaves, cryoablation, lasers, and ultrasound. Local ablation is recommended for patients with small HCCs confined to the liver, which are unresectable because of compromised liver function [89]. Local ablative therapy, especially RFA, has already been proven to be effective, particularly for very early- and early-stage HCC; however, its superiority to surgical resection remains controversial. We have summarized evidence-based meta-analysis findings of such comparisons in table 4. RFA appears to be superior to all other local ablative therapies. For unresectable HCC, local ablative therapy has also been shown to be efficacious when combined with TACE. Lubienski et al. reported that the 3-year survival rate was longer with a combination of TACE and PEI (22%) than with TACE alone (4%) in patients with large and unresectable HCC [90].

Transarterial therapy

Differences in blood supply to the liver and HCC form the theoretical basis of transarterial therapy. The liver receives 25% of its blood supply from the hepatic artery and 75%

from the portal vein, whereas HCC receives 90% of its blood supply from the hepatic artery and only 10% from the portal vein [91]. This difference provides the rationale for transarterial obstruction with or without regional chemotherapy to block the blood supply to HCC and induce tumor necrosis without significantly influencing the blood supply to the liver [92]. Transarterial therapies includes TACE, transarterial embolization (TAE), transarterial bland embolization, transarterial chemotherapy, and transarterial radioembolization, but the optimal procedure remains controversial [92]. The efficacy of transarterial therapy is also controversial [93–97]. The latest meta-analysis, which included six trials assessing TACE versus a control and three trials assessing TAE versus a control, concluded that TACE or TAE did not significantly increase survival in patients with unresectable HCC compared with controls, and there was no firm evidence to support or refute the use of TACE or TAE [96]. Of note, transarterial therapy has increased the risk of liver failure in some reports [92, 94]. The hepatic artery supplies 50% of the oxygen consumed by the liver [98]; therefore, blocking the hepatic artery decreases the oxygen supply, which may be responsible for transarterial therapy-related liver failure.

Sorafenib

The emergence of sorafenib highlights the treatment of advanced HCC. Sorafenib is a tyrosine kinase inhibitor of Raf serine/threonine kinases, vascular endothelial growth factor receptor (VEGFR-1, VEGFR-2, VEGFR-3), and platelet-derived growth factor receptor-h (PDGFR-h) tyrosine kinases [99]. A prospective randomized controlled trial concluded that sorafenib significantly improved the median overall survival and the median time to radiological progression in patients with advanced HCC [25]. These results were further confirmed by Cheng et al. in Asian patients [100]. Sorafenib was approved by the FDA for the treatment of unresectable HCC and recommended as the first-line therapy for HCC patients who cannot benefit from therapies that are potentially more effective, such as TACE or local ablative therapy [8]. A subanalysis was conducted to assess the multiple risk factors involved in HCC oncogenesis, and this revealed that sorafenib can also be beneficial for patients with alcohol-related HCC or hepatitis B or hepatitis C infection [101].

The prognosis for patients with advanced HCC is poor. Although sorafenib has a positive effect on the survival of patients with advanced HCC, the response to sorafenib remains low and the median overall survival is only extended by 2.8 months [25]. To optimize the beneficial effects of sorafenib, combination therapies comprising sorafenib and conventional chemotherapy or TACE have been investigated. A randomized trial comparing the combination of sorafenib and doxorubicin with doxorubicin alone found a median time to progression of 6.4 months vs. 2.8 months, median overall survival of 13.7 months vs. 6.5 months, and progression-free survival of 6.0 months vs. 2.7 months, respectively [101]. These findings confirm the efficacy of sorafenib for advanced HCC but do not prove that the combination of sorafenib and doxorubicin is superior to sorafenib alone. Moreover, doxorubicin-based chemotherapy for HCC has already been ruled out by another randomized controlled trial [102]. Further trials comparing the combination of sorafenib and chemotherapy with sorafenib alone are warranted. Interestingly, sorafenib modulates the gene expression of multi-drug resistance mediating, ATP-binding cassette proteins in experimental HCC [103].

It has been reported that HCC patients who respond to TACE do not benefit from sorafenib treatment [104]. However, a randomized trial that included 80 patients with chronic HCV infection found that conventional TACE followed by sorafenib resulted in a significantly longer time to progression [105]. Based on these controversial results, further trials with a larger number of patients are required to validate the effects of sequential sorafenib treatment after TACE. Synchronous therapy with sorafenib and TACE has also been retrospectively analyzed, and researchers have found that the median overall survival for the combined treatment

group was 27 months compared with 17 months for the TACE-alone group [106]. A phase III clinical study evaluating sorafenib and TACE versus TACE alone is ongoing [107]. Further trials comparing sorafenib combined with TACE with sorafenib alone are also needed to validate the efficacy of combination therapy.

Chemotherapy

Chemotherapeutic choices for HCC are limited. Systemic chemotherapy with doxorubicin, gemcitabine, or combined regimens for palliative care reportedly provide only marginal improvements in survival of HCC patients [102, 108, 109]. The high intrinsic and acquired drug resistance of HCC is mainly responsible for the failure of systemic chemotherapy [110]. Doxorubicin is a common anticancer agent in clinical practice. However, intravenous doxorubicin treatments only have limited efficacy in HCC patients [111]. A prospective randomized controlled trial revealed that doxorubicin monotherapy only provided a 3-week increase in median survival compared with no chemotherapy. Moreover, doxorubicin treatment resulted in severe complications such as septicemia and cardiotoxicity, which could not be tolerated by the patients [102]. The toxicity of gemcitabine is less severe than that of doxorubicin, but its therapeutic efficacy is similar. A phase II study of gemcitabine in patients with advanced HCC showed that gemcitabine only had marginal anti-tumor effects [108, 112]. A randomized phase III study was conducted to investigate whether the combination of cisplatin, interferon, doxorubicin, and fluorouracil (PIAF) was more effective in treating HCC compared with doxorubicin alone [109]. A total of 188 HCC patients were included in the trial. The median survival rate of the doxorubicin and PIAF groups was 6.83 months and 8.67 months, respectively, and no significant difference was detected. However, treatment with the PIAF regimen significantly increased the incidence of chemotherapeutic complications such as neutropenia, thrombocytopenia, and hypokalemia. Together, these findings indicate that conventional chemotherapy is ineffective for HCC.

Summary

HCC is a complex disease associated with multiple risk factors that have direct impacts on the characteristics of HCC patients, the therapy chosen, the disease course, and the prognosis [2, 113]. Current evidence indicates that potentially curative treatments result in excellent outcomes for very early- and early-stage HCC. However, the therapeutic efficacy of treatments for the vast majority of HCC patients urgently needs to be enhanced.

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