Treatment Lines in Hepatocellular Carcinoma

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Abstract

Background: Hepatocellular carcinoma (HCC) is the most frequent primary liver cancer and the second most lethal malignancy worldwide. In the Western world, HCC predominantly develops in patients with liver cirrhosis. Therefore, application of locoregional interventions and systemic agents should be based on an interdisciplinary evaluation, most importantly, taking the functional liver reserve into account. This review summarizes current treatment lines and novel strategies in the management of HCC. For the most part, randomized controlled trials and large meta-analyses are reported, with an emphasis on systemic therapies. **Summary:** In patients with limited hepatic disease and sufficient liver function, resection and local ablation are the most frequently employed curative locoregional therapies. Due to recurrence rates of up to 70% within 5 years and in patients with compromised liver function not amenable to these local modalities, liver transplantation remains superior in terms of tumor control and long-term survival. However, its applicability is limited because of the increasing gap between available donor organs and patients on the waiting list. Transarterial chemoembolization is commonly employed to bridge patients to transplantation and also serves as standard of care for patients not suitable for other local therapies. Recently, various phase 3 trials have reported a clinical benefit for the tyrosine

kinase inhibitors lenvatinib, regorafenib, and cabozantinib in HCC. In addition, ramucirumab, an angiostatic antibody, also improves survival in second-line systemic therapy. This opens new avenues in the sequential application of treatment lines, and thus early response assessment is necessary to fully utilize the clinical impact of locoregional therapies and systemic therapies and to shift patients to further treatment lines before hepatic deterioration. **Key Messages:** Clinical decision-making in hepatocellular carcinoma is based on an interdisciplinary evaluation. Liver transplantation should always be considered as long-term curative treatment option, especially in T2 patients. In palliative treatment, early response assessment is required to advance patients to the next treatment line before decompensation.

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Introduction

Worldwide, liver cancer is the fourth most frequent cause of cancer-related death [1]. Despite the reported improvement in survival in most cancer types, liver cancer is still associated with rising rates of mortality, with more than 1 million annual deaths predicted by the World Health Organization for 2030. Liver cancer incidence has continuously increased to more than 800,000 annual cases. In Germany, approximately 10,000 new cases are diagnosed each year [2]. With an incidence rate of up to 90%, hepatocellular carcinoma (HCC) constitutes the dominant form of primary liver cancer; it develops in patients with chronic hepatitis in the advanced fibrotic or

cirrhotic stage, and it is more than twice as common in men as in women [3]. Early diagnosis in patients with a well-preserved liver function, for example by the implementation of routine surveillance programs, is essential to facilitate curative therapy. Therapeutic decision-making should be based on an interdisciplinary evaluation, including tumor stage, liver function, and performance status, as well as comorbidities and center expertise. After a decade of negative studies, recent phase 3 trials have introduced new systemic agents [3]. These tyrosine kinase inhibitors (TKI) should preferentially be offered to patients with a stable liver function. Therefore, early identification of patients with systemic disease and/or failure of local therapies will be crucial to fully employ the benefit of sequential systemic therapy [4]. In patients with decompensated liver function (especially Child-Pugh C), best supportive care (BSC) is still the only reasonable option.

Curative Therapy

Resection and Local Ablation

Curative local treatment options are established for patients with early stage HCC (stage 0 and A according to the Barcelona Clinic Liver Cancer [BCLC] staging system [3]). In patients with a preserved liver function (normal liver parenchyma or Child-Pugh A cirrhosis) and without clinically significant portal hypertension (determined for instance by the thrombocyte count and liver elastography [5]), resection is the foremost curative therapy. In experienced centers, the 1-, 3-, and 5-year overall survival (OS) rates are 95, 80, and 61%, respectively, while the 1-, 3-, and 5-year disease-free survival rates have been reported to be 77, 41, and 21% [6]. With recent advances in expanding surgical treatment in patients with portal hypertension, laparoscopic liver resection has been introduced as an alternative to open resection [7] and associating liver partition and portal vein ligation for staged hepatectomy as an approach for tumors otherwise unresectable because of an insufficient future liver remnant [8]. Based on the available evidence, laparoscopic resection should be selected for subcapsular nodules and centrally located nodules ≥ 2 cm in the left liver lobe, while open liver resection is more suitable for centrally located lesions ≥ 2 cm in the right liver lobe. Nodules in contact with the Glissonean pedicles should preferentially be scheduled for resection (open or laparoscopic) independently of their size. As an alternative curative treatment modality, especially for centrally located nodules of up to 3–5 cm, thermoablation is frequently performed with similar results [9]. In this regard, microwave ablation is more convenient and, based on a recent systematic review and meta-analysis, as effective, if not superior to, radiofrequency ablation [10].

Liver Transplantation

Despite complete resection or local ablation, approximately 50–70% of patients develop recurrent intrahepatic HCC lesions within 5 years [11]. In most cases, these lesions are not de novo but rather represent growing micro-metastases already existing at the time of resection or ablation. Therefore, liver transplantation constitutes a superior curative treatment option with better long-term results. In Germany, patients with liver cirrhosis and T2 tumors (1 lesion of 2–5 cm or 3 lesions of 1–3 cm, without extrahepatic spread and without macrovascular invasion) have priority on the transplant waiting list. Overall the 5- and 10-year OS after liver transplantation for patients with cirrhosis and early-stage HCC range between 60–80 and 50–60%, respectively [12]. Although the data clearly support the primary role of transplantation for patients with cirrhosis and early-stage HCC, the disease incidence, the economic and psychosocial impact of transplantation, and the fact that some patients will have equivalent outcomes with liver resection dictate further employment of all curative treatment options [13]. A possible solution would be the implementation of salvage liver transplantation for patients receiving resection or ablation [14].

Locoregional Therapy

Transarterial Chemotherapy

According to most international guidelines for the treatment of HCC, palliative transarterial chemoembolization (TACE) is the standard of care for patients without a curative treatment option, with liver-only disease, and without macrovascular invasion (BCLC stage B) [15]. TACE is defined by the intraarterial application of a cytotoxic drug with or without oily contrast agents followed by particle embolization. The transarterial application of doxorubicin, cisplatin, or mitomycin results in high intratumoral drug levels in an otherwise chemotherapy-resistant tumor with low systemic side effects. The oily contrast agent serves mainly as a drug carrier from which the cytotoxic drug is slowly released [16]. The subsequent particle embolization is intended to prevent the drug from washing out and to induce ischemia as second cytotoxic mechanism. As embolization material a wide variety of products are available (e.g., gelatin sponges, calibrated microspheres between 40–1,000 μm). In a prospective cohort study in more than 8,000 patients with unresectable HCC and without extrahepatic metastases, the 1-, 3-, and 5-year OS was 82, 47, and 26%, with a procedural mortality rate of 0.5% [17]. Embolization with drug-eluting beads (DEB), called DEB-TACE, allows targeted application and defined release of the cytotoxic drug from spherical particles that provide a reversible chemical bond. Studies report lower plasma concentrations and systemic area under the curve levels for the cytotoxic drug in patients

treated with DEB-TACE compared to conventional TACE [18], with a median OS of 43.8 months and a 5-year survival rate of 22.5% in unresectable BCLC stage A and B patients with well-preserved liver-function [19]. DEB-TACE showed higher rates of complete response, objective response, and disease control compared to conventional TACE (27 vs. 22%, 52 vs. 44%, and 63 vs. 52%, respectively) and an improved tolerability, a lower liver toxicity, and a reduced rate of doxorubicin-related side effects, but it was not superior regarding the tumor response after 6 months [20]. Therefore, regarding OS as most important endpoint in palliative therapy, conventional TACE remains the standard of care to bridge patients to liver transplantation and as palliative local therapy in BCLC stage B patients.

Local Radiotherapy as an Alternative Modality

Selective internal radiotherapy (SIRT) allows for a selective application of radiation doses up to 150 Gy intratumorally without experiencing the complications of external radiotherapy. The used radioactive particles labeled with yttrium-90 as a β -emitter have a half-life of about 62 h and a mean tissue penetration of a few millimeters. A retrospective analysis of SIRT versus BSC in BCLC stage B and C patients showed a significant benefit for SIRT, with a median OS of 16 months after SIRT versus 8 months in the BSC group [21]. However, based on the recently reported SARAH, SIRVENIB, and SORAMIC trials comparing SIRT versus systemic therapy in patients with advanced HCC (BCLC stage C) or progressive disease (PD) after TACE, SIRT should not be selected as a downstream transarterial treatment line [22]. In intermediate-stage HCC (BCLC stage B), patients with single large tumors and Child-Pugh A may benefit from early SIRT as an alternative to TACE; however, a large RCT to clearly position SIRT in the treatment algorithm of such patients is currently not available.

Resection in Selected Patients with Intermediate Stage HCC

As an alternative approach in selected intermediate stage HCC (BCLC stage B) (laparoscopic) resection may be technically feasible in patients with sufficient functional liver reserve. In a large study in 2,046 patients from 10 experienced centers, an impressive 1-, 3-, and 5-year OS of 88, 71, and 57% has been reported [6]. Therefore, therapeutic decision-making in intermediate-staged HCC with a well-preserved liver function should be based on center experience and interdisciplinary risk-benefit assessment. Depending on tumor size and intrahepatic location, both, (laparoscopic) resection and TACE or SIRT are options for local tumor control. Nowadays, the most important aspect in treatment selection has to be the prevention of hepatic decompensation to allow downstream systemic therapy.

Systemic Therapy

First-Line Systemic Therapy

Despite substantial progress in the characterization of genetic events driving hepatocarcinogenesis, HCC is still a tumor with limited druggable mutations. Therefore, small molecules targeting multiple receptor tyrosine kinases are the backbone of systemic therapy in HCC (Table 1). As a milestone in the systemic treatment of HCC, the international, randomized, and controlled SHARP trial demonstrated a significant benefit in OS for sorafenib (10.7 months) vs. placebo (7.9 months) [23]. Importantly, in a subgroup analysis, patients with hepatitis C-associated HCC had a better response to sorafenib (14.0 vs. 7.4 months, HR = 0.50; 95% CI 0.32–0.77). SHARP recruited patients with a preserved liver function (Child-Pugh A). Recently, a prospective study from Brazil reported an OS of 6.5 months for Child-Pugh B patients treated with sorafenib, which is better than the expected OS in the literature [24]. In addition, the global, prospective, noninterventional GIDEON trial with more than 3,000 patients worldwide demonstrated that sorafenib is administered to patients beyond the strict SHARP inclusion criteria in real-life practice [25]. After several years of disappointing failures in phase 3 clinical trials [26], the TKI lenvatinib has been demonstrated to be noninferior to sorafenib (OS 13.6 months vs. 12.3 months) in the REFLECT trial [27]. The longer OS in the REFLECT trial in both arms compared to the SHARP data is mainly due to patient selection, i.e., patients with main portal vein invasion or a tumor burden >50% of the liver volume were excluded. In contrast to sorafenib, lenvatinib also targets fibroblast growth factor receptors 1–4. Interestingly, lenvatinib demonstrated superior results in major secondary endpoints, revealing better tumor control with an objective response rate (ORR) of 24.1% (95% CI 20.2–27.9) versus 9.2% (95% CI 6.6–11.8) in patients treated with sorafenib. A partial response based on the modified Response Evaluation Criteria in Solid Tumors (RECIST) for HCC [28] was observed in 23% of patients treated with lenvatinib compared to 9% in the sorafenib arm.

Second Line Systemic Therapy

The TKI regorafenib was the first agent that tested positive in a phase 3 clinical trial, with benefit in terms of OS after PD (Table 1). The RESORCE trial compared treatment with regorafenib versus placebo in patients with tumor progression who tolerated sorafenib (OS 10.6 vs. 7.8 months) [29]. That study further demonstrated a significant improvement in progression-free survival, time to progression, and an ORR of 11 versus 4% in the placebo arm ($p < 0.005$). The positive phase 3 CELESTIAL trial tested cabozantinib, a small molecule that also inhibits the tyrosine kinase MET among other signaling pathways

Table 1. Positive phase 3 trials on the systemic treatment of HCC

Trial (treatment line)	Relevant inclusion criteria	Substances	Patients, <i>n</i>	Median OS, months	HR (95% CI)	Significance
SHARP (first line)	Child-Pugh A, ECOG 0–1 ^a	Sorafenib vs. placebo	299 vs. 303	10.7 vs. 7.9	0.69 (0.55–0.87)	<i>p</i> < 0.001
REFLECT (first line)	Main portal vein invasion excluded	Lenvatinib vs. sorafenib	478 vs. 476	13.6 vs. 12.3	0.92 (0.79–1.06)	noninferiority design
RESORCE (second line)	Patients tolerated prior sorafenib	Regorafenib vs. placebo	379 vs. 194	10.6 vs. 7.8	0.63 (0.50–0.79)	<i>p</i> < 0.0001
CELESTIAL (second line)	1–2 prior treatment lines	Cabozantinib vs. placebo	470 vs. 237	10.2 vs. 8.0	0.76 (0.63–0.92)	<i>p</i> = 0.005
REACH-2 (second line)	AFP ≥400 ng/mL	Ramucirumab vs. placebo	197 vs. 95	8.5 vs. 7.3	0.71 (0.53–0.95)	<i>p</i> = 0.0199

^a All listed trials recruited patients with Child-Pugh A and ECOG 0–1.

Table 2. Important side effects of TKI in the systemic treatment of HCC

Adverse event	Incidence of the event ^a			
	sorafenib (SHARP)	regorafenib ^b (RESORCE)	lenvatinib (REFLECT)	cabozantinib (CELESTIAL)
Fatigue	22 (4)	40 (9)	30 (4)	45 (10)
Diarrhea	39 (8)	41 (3)	39 (4)	54 (10)
Hand-foot skin reaction	21 (8)	53 (13)	27 (3)	46 (17)
Hypertension	5 (2)	31 (15)	42 (23)	29 (16)

Values are presented as numbers (%). ^a All grades (grades 3 and 4) according to CTCAE. ^b All patients in the RESORCE trial tolerated prior treatment with sorafenib.

[30]. As an alternative agent in patients with high α -fetoprotein (AFP) >400 ng/mL, ramucirumab, a monoclonal antibody inhibiting the vascular endothelial growth factor receptor, was shown to prolong survival compared to placebo in second-line systemic therapy in the REACH-2 trial [31]. In summary, all agents approved for second-line therapy prolong survival to approximately 10 months compared to 7–8 months without further treatment (Table 1). Approximately one third of patients with intolerance of the first-line agent or PD are suitable to receive a second-line systemic therapy. Regarding patient allocation, those patients who tolerated sorafenib should be treated with regorafenib, patients with elevated AFP may be switched to ramucirumab, and all other patients as well as progressors under second-line therapy are eligible to receive cabozantinib (Fig. 1) if the liver function is still sufficient. With these sequential treatments, OS has been reported to be between 24 and 30 months from the start of systemic therapy in responders [32].

Future Advances in Systemic Therapy

Monoclonal antibodies disrupting programmed cell death protein 1 or cytotoxic T-lymphocyte-associated protein 4 signaling may represent an alternative systemic treatment option in the near future [33]. Phase 2 studies have demonstrated a benefit, with impressive results for nivolumab (CHECKMATE 040) [34] and pembrolizumab (KEYNOTE-224) [35] in first- and second-line treatment. For example, the ORR was 20% in the dose expansion phase with 3 mg/kg nivolumab every 2 weeks. The US Food and Drug Administration approved both substances for the systemic treatment of HCC. However, according to recent press releases and conference presentations, both, pembrolizumab and nivolumab, have failed to reach a statistically significant improvement in OS in phase 3 trials (KEYNOTE-240, Merck Sharp & Dohme; CHECKMATE 459, Bristol-Myers Squibb). Most likely, the combination of angiogenesis inhibitors (mainly TKI) and checkpoint inhibitors will be the next step in the systemic treatment of HCC. Three large phase

Fig. 1. Palliative treatment lines for HCC.

3 studies combining atezolizumab and bevacizumab (IMBRAVE 150), pembrolizumab and lenvatinib (LEAP-002), and atezolizumab and cabozantinib (COSMIC) are underway.

Side-Effects Using TKI

Common side effects with varying incidence rates based on the selected TKI are dermatological reactions, mainly hand-foot skin syndrome, fatigue, diarrhea, and arterial hypertension (Table 2). Besides dose reduction or interruption of treatment, complementary supportive regimens are required for these adverse events. For hand-foot skin syndrome, topical urea, avoidance of hot water, moisturizing lotions, and salicylate creams are useful options [36]. Regarding fatigue, the role of comorbidities such as cirrhosis, hypothyroidism, anemia, and depression has to be taken into consideration as the target of accompanying treatment approaches. Loperamide is the choice of symptomatic treatment in cases of TKI-associated diarrhea. Although most patients with HCC suffer from liver cirrhosis and systemic hypotension, some patients might present with arterial hypertension after initiating TKI treatment, especially when taking lenvatinib [37]. With coexisting varices, a nonselective β -blocker is the first choice; otherwise sartans or hydrochlorothiazide should be preferred.

Biomarkers and Imaging to Guide Systemic Therapy

With the recent advances in systemic treatment and available sequential treatment options [32], response monitoring is crucial to move patients to further treatment lines before decompensation of liver function (Fig. 1). Response assessment is based on contrast-enhanced imaging and serial AFP testing in patients with elevated AFP. In this regard, the dynamics of AFP levels under treatment with sorafenib have been investigated. A 20% decrease after 4–8 weeks of treatment is commonly defined as AFP response. A small Italian study showed a correlation of AFP response with a higher median OS (13.3 vs. 8.2 months; $p < 0.05$) and TTP (7.9 vs. 2.4 months; $p < 0.01$) [38]. Similar results have been reported for cabozantinib and ramucirumab. In addition, the occurrence of typical side effects, in particular hypertension, diarrhea, or skin toxicities, has a predictive value for treatment response to TKI. For example, in a multicenter prospective cohort study, sorafenib-related diarrhea (HR 0.76; 95% CI 0.61–0.95; $p = 0.017$), hypertension (HR 0.531; 95% CI 0.37–0.76; $p < 0.0001$) and hand-foot skin syndrome (HR 0.65; 95% CI 0.51–0.81; $p < 0.0001$) were all significant independent predictors of OS after adjusting for age, severity of liver disease, tumor stage, and sorafenib dose [39]. Consequently, adjustment of the TKI dose because of relevant side effects to induce tolerability rather than stopping the drug pro-

longs OS and TTP and achieves better results. The modified RECIST criteria, i.e., the evaluation of tumor vascularization as a key hallmark to identify the response to targeted systemic therapy, have been implemented to identify patients responding to angiostatic therapy [28]. In a retrospective study, OR versus stable disease or PD analyzed by these modified criteria was significantly correlated to OS and predicted OS under treatment with sorafenib (18.2 vs. 7.7 months), while RECIST was not able to distinguish between these patients [40]. Recently, the role of contrast-enhanced ultrasound has also been investigated with regard to treatment response. Short-term changes in perfusion characteristics 15 days after the start of treatment with sorafenib predicted OS and progression-free survival [41]. In summary, in clinical practice AFP should be monitored in patients with an elevated AFP and in all patients imaging should be scheduled to identify patients with PD. All patients with PD according to mRECIST should be switched to an alternative downstream treatment line to avoid deterioration before the full potential of systemic therapy has been applied.

Conclusion

Patients with HCC limited to the liver (T2) should be listed for liver transplantation, even if local curative therapies are applied. In patients with a well-preserved liver function and intermediate stage HCC (BCLC stage B), TACE is the standard of care, but the decision between (laparoscopic) resection, ablation, and/or TACE or SIRT

should be based on an interdisciplinary evaluation. Lenvatinib and sorafenib are the first-line systemic agents for palliative treatment. Sorafenib may also be an option in patients with reduced liver function parameters, especially in patients without ascites and jaundice. Typical TKI side effects and a decline >20% in AFP are early clinical and biochemical markers for treatment response. Nonresponders have to be identified before further decompensation of the liver function to advance the patient to second-line systemic treatment, including regorafenib, cabozantinib, and ramucirumab. If a patient develops relevant liver decompensation (Child-Pugh C), the patient should receive BSC. Within the next few years, systemic treatment of HCC will be further improved based on immunoncology agents and combination strategies.

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