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Treatment of Intermediate/Advanced Hepatocellular Carcinoma in the Clinic: How Can Outcomes Be Improved?

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ABSTRACT

Hepatocellular carcinoma (HCC) is a complex condition associated with a poor prognosis. Treatment outcomes are affected by multiple variables, including liver function, performance status of the patient, and tumor stage, making a multidisciplinary approach to treatment essential for optimal patient management. Only ~30% of patients are eligible for curative therapies (surgery or ablation); palliative treatments include transcatheter arterial chemoembolization (TACE) and sorafenib. Treatment choice is guided by staging systems and treatment guidelines, although numerous systems exist and treatment guidelines vary by region. The current standard of care for patients unsuitable for potentially curative therapy is locoregional therapy with TACE. This treatment is associated with survival benefits, but there is no consensus regarding the optimum treatment/retreatment strategy. For patients with more advanced disease or who have failed locoregional therapy, sorafenib is the standard of care. Sorafenib is a targeted agent with proven survival benefits as monotherapy in these patients, and ongoing studies will clarify its role in combination with other agents and in patients with impaired liver function. Although other novel agents and therapeutic approaches are emerging, such as radioembolization and various targeted agents, further suitably designed randomized clinical trials (RCTs) comparing these agents with the standard of care are needed. In addition to RCTs, the collection of real-life data will also be important to allow physicians to make fully informed treatment decisions. The Global Investigation of therapeutic DEcisions in hepatocellular carcinoma and Of its treatment with sorafeNib (GIDEON) study is a global, noninterventional study of patients with unresectable HCC receiving sorafenib. The aim of that study is to compile a large robust database to evaluate local, regional, and global factors influencing the management of patients with HCC. It is hoped that findings from the GIDEON study along with phase III RCT data will lead to better outcomes for patients with intermediate–advanced HCC. *The Oncologist* 2010;15(suppl 4):42–52

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Introduction

Hepatocellular carcinoma (HCC) is a complex condition with multiple variables affecting the disease course and response to treatment, including liver function and performance status of the patient and tumor stage [1]. Most patients with HCC present with underlying liver disease, usually cirrhosis, and so both conditions must be considered when making treatment decisions. Patients with hepatitis B or hepatitis C virus infection are also at a higher risk for developing HCC, and 85.5% of patients with HCC present with one of these two viruses [2]. These confounding factors mean that no single treatment strategy can be applied to all patients, and therapy should be tailored to the individual. Specialists in gastroenterology, hepatology, surgery, transplant surgery, interventional and diagnostic radiology, medical oncology, radiation oncology, and nuclear medicine are all involved in the treatment and care of patients with HCC, and so a truly integrated multidisciplinary approach is essential for optimal patient management [1].

Surgical treatment options for patients with HCC include resection and transplantation. Local ablation, like surgery, is also considered as a potentially curative therapy, but only ~30% of patients in the west and <10% of patients in Asia are eligible for such options at diagnosis [3, 4]. Although the introduction of screening programs among high-risk populations (especially patients with chronic hepatitis C virus infection) can lead to earlier diagnosis, the majority of patients present with intermediate or advanced-stage disease, and therefore palliative treatments play a central role in the treatment of HCC. Such treatments include transcatheter arterial chemoembolization (TACE) and radioembolization, and the oral multikinase inhibitor sorafenib (Nexavar®; Onyx Pharmaceuticals, Inc., Emeryville, CA; Bayer HealthCare Pharmaceuticals, Inc., Wayne, NJ; Bayer Schering Pharma AG, Berlin, Germany) [5]. TACE is the most widely used locoregional therapy for patients with intermediate HCC. Treatment is associated with partial responses in 15%–55% of patients, and overall survival (OS) benefits were reported in a meta-analysis of randomized controlled trials (RCTs) [6]. Sorafenib is the first targeted agent to lead to better outcomes in patients with advanced-stage HCC. Results from a large phase III RCT showed that treatment was associated with a 31% relative lower risk for death than placebo among patients with advanced HCC, defined as those patients who are ineligible for or have progressed following surgery or locoregional therapy [7].

Treatment choices are guided by staging classification systems and treatment guidelines. However, as reviewed by Marrero and colleagues and Ye and colleagues [8, 9], the number and range of classification systems, as well as treatment variability from region to region, have a considerable impact on treatment approaches and outcomes. In this article, we review the available data supporting current locoregional and systemic treatment strategies for patients who are ineligible for or have failed treatment with potential curative treatments, such as surgical resection or ablation therapy. We discuss how patient management might be affected by the staging classification system used and how outcomes could be further improved.

Staging Systems: How Do They Influence Treatment Choices for Patients with Unresectable Disease?

Although staging classification systems are important for predicting prognosis in patients with HCC and guiding the therapeutic approach, the lack of a globally applicable staging system is problematic. Given the complexity of the disease, it is accepted that unidimensional systems such as the Child-Pugh, tumor–node–metastasis (TNM), or performance status (PS) classification lack prognostic accuracy and have limited usefulness in guiding therapy when used in isolation. However, a number of systems that combine liver function parameters and cancer staging have been proposed, and comparisons of a number of these systems indicate varying prognostic stratification and prediction ability, depending on the country and patient population studied [8, 10–13].

The Barcelona Clinic Liver Cancer (BCLC) staging system, which was devised from the results of cohort studies and RCTs, is widely recognized and endorsed [14–16]. It includes variables linked to tumor stage and function, physical status, and cancer-related symptoms to stage patients, and it combines each stage with a treatment algorithm (Fig. 1). Using this system, patients classified as having early-stage HCC, defined as a single nodule or three nodules <3 cm in diameter and a PS score of 0, are suitable for treatment with potentially curative therapies (resection, transplantation, or ablation). Patients with intermediate-stage HCC are asymptomatic (PS score, 0) with multinodular tumors but without vascular invasion or extrahepatic spread, and are eligible for locoregional therapy (TACE). Those with advanced-stage HCC are either symptomatic (PS score, 1–2) or have evidence of vascular invasion or extrahepatic spread; these patients are eligible for sorafenib. Finally, patients with terminal-stage HCC have either severe cancer symptoms (PS score, 3–4) or severely decompensated cirrhosis (Child-Pugh class C) and should receive symptomatic treatment only. Unlike many of the proposed staging systems, the BCLC system has been externally val-

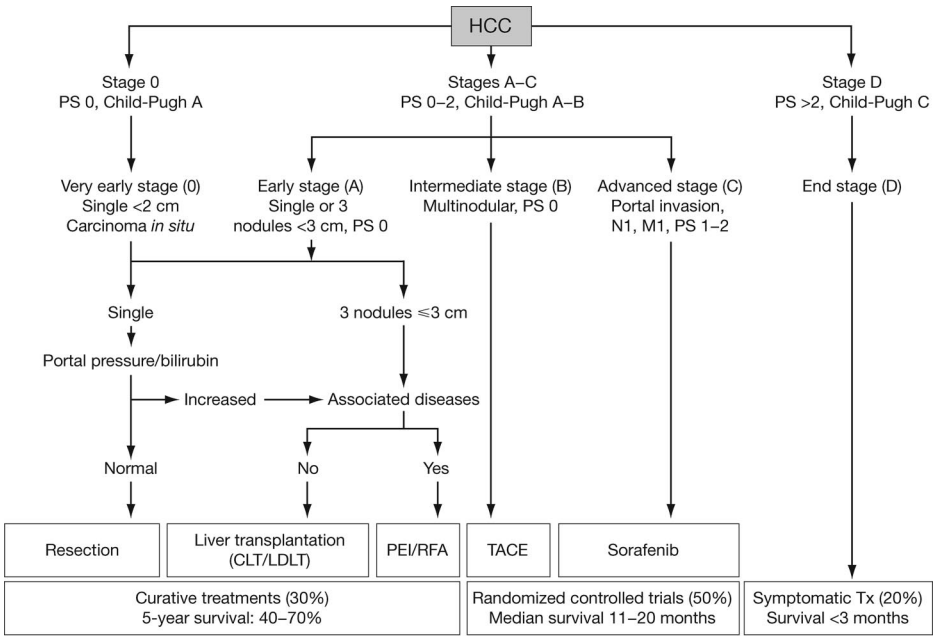

Figure 1. Barcelona Clinic Liver Cancer staging system and recommended treatment strategy.

Abbreviations: CLT, cadaveric liver transplant; HCC, hepatocellular carcinoma; LDLT, living donor liver transplant; M, metastasis; N, node; PEI, percutaneous ethanol injection; PS, performance status; RFA, radiofrequency ablation; TACE, transcatheter arterial chemoembolization; Tx, treatment.

From Llovet JM, Di Bisceglie AM, Bruix J et al. Design and endpoints of clinical trials in hepatocellular carcinoma. J Natl Cancer Inst 2008;100:698–711. Reproduced with permission from Oxford University Press.

idated [11, 13] and is endorsed by both the American Association for the Study of Liver Diseases (AASLD) [17] and the European Association for the Study of the Liver (EASL) [18].

In the Asia-Pacific regions, the Japan Integrated Staging (JIS) and subsequent biomarker-combined JIS scoring systems appear to be the most promising candidates for a standard classification system [19, 20]. The JIS scoring system (0–5) combines the TNM stage based on the Liver Cancer Study Group of Japan criteria and the Japanese version of the Child-Pugh system. Patients with a JIS score of 0 have early-stage disease, whereas those with a score of 5 have end-stage disease. The JIS scoring systems have been externally validated [21, 22] but have not been validated in a western population.

Although the BCLC and JIS staging systems have demonstrated good prognostic ability in some patient populations, validation across both eastern and western regions is required before any one system can be applied globally because of the distinct differences between these patient populations [23]. In the absence of such a global system, no universal definitions exist for the various stages of HCC as the disease progresses. However, because the aim of this article is to review treatment options for patients who are not suitable for curative treatments, we describe each of the palliative treatment options available as the disease progresses, including key eligibility criteria for each therapy, and review the associated outcomes for each of these therapies.

Treatment Guidelines for HCC Patients Unsuitable for Curative Treatment

Although there is no global consensus for the optimal management of HCC, there are a number of different treatment guidelines that cover the U.S., Canada, Japan, and Europe [5, 17, 18, 24, 25]. As such, the choice of guidelines used varies by region, with some guidelines more applicable to a single country [9]. For example, in Japan, treatment guidelines were compiled based on findings from a review of the global literature (mainly from MEDLINE) together with country-specific considerations, such as the <1% mortality rate associated with surgical resection in Japan as well as the extremely low availability of cadaveric donors for liver transplantation [24]. Accordingly, these guidelines state that patients are considered suitable for resection if they have Child-Pugh class A or B liver damage and ≤3 tumors, and for transplantation if they have Child-Pugh class C liver damage and ≤3 tumors, none >3 cm in diameter [26]. In contrast, the EASL treatment guidelines recommend surgical resection only for patients with solitary tumors and very well-preserved liver function [18], as measured by Child-Pugh class as well as a range of functional tests of liver reserve [27].

If patients are considered unsuitable for resection or transplantation, ablation therapy using ethanol or an alteration in temperature (achieved via, e.g., radiofrequency) is proposed when tumors are ≤3 cm in diameter [5, 17]. However, for patients with large, multifocal tumors, locoregional therapy with TACE is recommended [5, 17, 25]. Radioembolization is a newer method than TACE, and although preliminary antitumor activity has been reported [28], both the National Comprehensive Cancer Network (NCCN) and the AASLD recommend further evaluation of its effect on OS in RCTs [5, 18]. Finally, sorafenib is a targeted agent that has demonstrated a survival benefit as monotherapy in patients who are ineligible for or have progressed following surgery or locoregional therapy [7]. Consequently, it is recommended in the NCCN treatment guidelines for use in selected patients with unresectable extensive HCC and liver function characterized as Child-Pugh class A or B, although the NCCN recommends caution in patients with elevated bilirubin levels [5].

Unfortunately, a number of agents that are highly effective in other tumor types, including tamoxifen, antiandrogens, and octreotide, do not improve outcomes in patients with HCC and are therefore not recommended [17]. Systemic chemotherapy regimens tested to date have also been associated with a lack of efficacy in these patients, and the evaluation of other chemotherapy regimens is therefore confined to the clinical trial setting [25].

In summary, although the classification of patients considered suitable for curative therapy appears to differ among treatment guidelines, treatment options for patients with unresectable disease are limited to locoregional therapy with TACE, and systemic therapy with sorafenib for those with more extensive disease.

What Is the Current Trend in Treatment of Intermediate/Advanced HCC?

Locoregional Therapy

TACE

TACE is the most widely used locoregional treatment for patients with intermediate HCC [6], and it is considered the standard treatment option for patients with reasonable liver function, with large (>5 cm) or multifocal tumors that do not occlude the portal venous vessels, and without extrahepatic spread [29].

Survival benefits from TACE were reported in two RCTs [30, 31]. In the first of these, Llovet and colleagues evaluated the effects of transarterial embolization (TAE) with Gelfoam® (Pfizer Inc., New York) or TACE with Gelfoam® and doxorubicin compared with symptomatic treatment in 112 patients with unresectable HCC and Child-Pugh class A or B liver function [30]. Treatment was administered at baseline, 2 months, and 6 months, then every 6 months thereafter, and patients were assessed every 3 months. The trial was stopped early at the ninth assessment because of a significant survival advantage in favor of TACE over the control (hazard ratio [HR] for death, 0.47; 95% confidence interval [CI], 0.25–0.91; $p = .025$). At the time of that analysis, the 1- and 2-year survival probabilities were 82% and 63% versus 63% and 27% for the TACE and control groups, respectively ($p = .009$).

In the second of these studies, Lo and colleagues evaluated the effect of TACE every 2–3 months with gelatin-sponge particles and an emulsion of cisplatin with Lipiodol® (Guerbet, Villepinte, France) or symptomatic treatment only in 80 patients with newly diagnosed, unresectable HCC, a PS score ≤3, and no extrahepatic spread, main portal vein thrombosis (PVT), or arteriovenous shunting [31]. At the final analysis, the relative risk for death in the TACE group versus the control group was 0.50 (95% CI, 0.31–0.81; $p = .005$). The estimated 1- and 2-year survival probabilities were 57% and 31% versus 32% and 11% for the TACE and control groups, respectively. In a univariate analysis, comparison of survival between the TACE and control groups, stratified by the baseline prognostic variables of presenting symptom, unilobar portal vein obstruction, tumor size, and Okuda stage, revealed a significant survival benefit for TACE in each subgroup, except for those with tumors >5 cm in diameter or unilobar portal vein obstruction.

TACE has been evaluated in other RCTs, with two of these showing that active treatment did not lead to a longer survival time than seen in the respective control groups [32, 33]. Despite this, findings from a robust meta-analysis of all RCTs indicate that treatment with TAE/TACE is associated with a significantly higher 2-year survival rate than in the control group (odds ratio [OR], 0.53; 95% CI, 0.32–0.89; $p = .017$) [3]. A summary of the trials included in that meta-analysis is shown in Table 1. Sensitivity analyses showed a significant benefit with TACE (OR, 0.42; 95% CI, 0.20–0.88; $p = .021$), but none with TAE alone (OR, 0.59; 95% CI, 0.29–1.20; $p = .14$).

A common treatment-related side effect that occurs in >50% of patients treated with TAE or TACE is postembolization syndrome, comprising fever, abdominal pain, and a moderate degree of ileus [17]. Other infrequent but more serious complications include hepatic abscess and cholecystitis. As expected, additional side effects consistent with systemic chemotherapy use are reported with TACE. The occurrence and severity of side effects is also affected by the frequency of TAE/TACE therapy. The Groupe d'Etude et de Traitement du

Table 1. Summary of randomized clinical trials included in a meta-analysis of transarterial embolization or transcatheter arterial chemoembolization versus conservative management [3]

	n of patients	Percent with cirrhosis (Child-Pugh class A)	Okuda stage I/II/III (%)	Objective response (%)	1-yr survival (%)	2-yr survival (%)
Lin et al. [61]	63	ND	ND			
TAE (Ivalon[a] + Gelfoam® powder/cubes)	21			13 (61.9)[b]	42	25
TAE + i.v. 5-FU (1 g/m^2 for 5 days)	21			10 (47.6)[b]	20	20
i.v. 5-FU	21			2 (9.5)	13	13
Pelletier et al. [62]	42	88	26/52/22			
TACE (Gelfoam® powder; doxorubicin, 50 mg)	21			7 (33)[c]	24	NA
Conservative management	21			0	33	NA
Group d'Etude et de Traitement du Carcinome Hépatocellulaire [33]	96	91 (100)	90/10/0			
TACE (Gelfoam® particles; cisplatin, 70 mg)	50			7 (16)[c]	62	38
Conservative management	46			2 (5)[c]	43	26
Bruix et al. [63]	80	100 (82)	67/23/0			
TAE (Gelfoam® + coils)	40			22 (55)[b]	70	49
Conservative management	40			0	72	50
Pelletier et al. [64]	73	89 (76)	60/40/0			
TACE (Gelfoam®; cisplatin, 2 mg/kg; tamoxifen)	37			9 (24)	51	24
Tamoxifen	36			2 (5.5)	55	26
Lo et al. [31]	79	ND	47/53/0			
TACE (1 Gelfoam®; cisplatin, max 30 mg)	40			11 (27)[d]	57	31
Conservative management	39			1 (2.6)	32	11
Llovet et al. [30]	112	100 (70)	65/35/0			
TAE (Gelfoam®)	37			16 (43)[e]	75	50
TACE (Gelfoam®; doxorubicin, 25–75 mg/m^2)	40			14 (35)[e]	82	63
Conservative management	35			0	63	27

[a]Ivalon® (Fabco®, New London, CT).
Objective responses sustained for [b]1, [c]2, [d]3, and [e]6 months.
Abbreviations: 5-FU, 5-fluorouracil; NA, not available; ND, not described; TACE, transcatheter arterial chemoembolization; TAE, transarterial embolization.
From Llovet JM, Bruix J; the Barcelona-Clinic Liver Cancer Group. Systematic review of randomized trials for unresectable hepatocellular carcinoma: Chemoembolization improves survival. Hepatology 2003;37:429–442. Reproduced with permission from John Wiley & Sons.

Carcinome Hépatocellulaire evaluated treatment with Lipiodol® chemoembolization every 2 months in patients with unresectable HCC but without severe liver disease [33]. This schedule was associated with frequent acute liver failure, with 30 of the 50 treated patients reporting this adverse event. Conversely, Llovet and colleagues evaluated a schedule of TAE or TACE treatment at baseline, 2 months, and 6 months, then every 6 months thereafter, without any unexpected adverse events reported [30].

Taken together, these findings show that treatment with TACE is common and is associated with OS benefits, although the level of benefit reported varies significantly. Treatment is also linked with considerable side effects, making patient selection imperative. Frequency of TACE

administration also appears to impact on outcome, but no RCTs have been designed to fully evaluate the optimum frequency of delivery. There is also a lack of consensus regarding the use and type of chemotherapy agent, as well as the optimum type of embolic particle. Additional large RCTs are therefore needed to further evaluate the optimum TACE treatment strategy.

Drug-Eluting Bead TACE

Another avenue of investigation is the use of drug-eluting beads (DEBs) to optimize TACE. In this approach, doxorubicin-loaded beads are used rather than the conventional doxorubicin Lipiodol® emulsion. Preliminary results suggest that this approach is associated with a favorable toxicity profile and encouraging antitumor activity, with response rates in the range of 13.3%–80.7% [34–37]. In a recent prospective, randomized phase II study comparing conventional TACE with DEB-TACE, the DEB-TACE group showed a trend for a higher objective response rate than the TACE group (51.6% versus 43.5%, respectively), together with better tolerability [38]. In another prospective, randomized study, DEB-TACE resulted in a better local response, fewer recurrences, and a longer time to progression than bland TACE with nonloaded beads [39]. Further studies evaluating DEB-TACE are ongoing, including a phase II study evaluating the combination of DEB-TACE with sorafenib in patients with unresectable HCC.

Radioembolization

Attempts to improve locoregional therapies for patients with unresectable HCC are ongoing; as a result, novel liver-directed therapies are emerging. Radioembolization is one such therapy, comprising a catheter-based delivery of yttrium-90 (^{90}Y)-embedded microspheres into the hepatic artery [40]. Once administered, these microspheres selectively emit high-energy, low-penetration radiation to the tumor, resulting in necrosis. Currently, phase I and phase II studies are under way to evaluate the efficacy of this approach, and a number of cohort studies, retrospective analyses, and case reports have already been published [28, 40, 41]. Indeed, a recent literature review conducted by Ibrahim and colleagues showed that there is a growing body of literature to suggest that radioembolization might be an effective treatment approach for patients with HCC [40]. A phase II study conducted by Kulik et al. [42] evaluated radioembolization with ^{90}Y glass microspheres in 108 patients with unresectable HCC with and without PVT (further delineated anatomically by branch or main PVT). Treatment was well tolerated, with liver-related adverse events reported more frequently among patients with cirrhosis and main PVT (elevation of bilirubin, 40%; ascites, 18%; hepatic encephalopathy, 4%, compared with 4%, 4%, and 0%, respectively, for patients without main PVT or cirrhosis). Tumor response rates according to the World Health Organization and EASL criteria were 42.2% and 70%, respectively; median survival times for patients with main PVT and thrombosis were 304 days and 813 days for those without cirrhosis. These findings therefore suggest that treatment with ^{90}Y glass microspheres could be an effective locoregional treatment option, especially for patients with PVT, for whom TAE/TACE is not suitable. However, further evaluation of this novel approach, including direct comparisons with established locoregional therapies (i.e., TAE or TACE), is needed.

Systemic Therapy

Chemotherapy

Until recently, no survival benefit was demonstrated with any systemic treatment for patients with HCC [29]. For patients with unresectable disease not amenable to or having failed TACE, systemic doxorubicin has been used, mainly in the U.S.; however, its use was based on findings from a large number of single-arm efficacy trials rather than RCTs, and these studies reported a wide variation in response rates [43]. Combination chemotherapy has also been investigated, and results from a phase II study among 50 patients with either unresectable or metastatic disease suggested that cisplatin, interferon, doxorubicin, and 5-fluorouracil (PIAF) was associated with antitumor activity [44]. However, a subsequent randomized phase III study of PIAF versus doxorubicin in patients with unresectable or metastatic HCC showed that, although PIAF treatment was associated with a higher response rate (20.9% versus 10.5%), there was no significant difference in OS (median OS time, 8.67 months versus 6.83 months for PIAF and doxorubicin, respectively; HR, 0.97; 95% CI, 0.71–1.32; $p = .83$). Consequently, treatment guidelines do not support the use of any single-agent or combination chemotherapy regimen in patients with HCC [5, 17, 18, 24, 25] and advise that any systemic chemotherapy should be investigated only in the context of a clinical trial.

Multikinase Inhibitors

Sorafenib is the first targeted therapy to demonstrate an OS benefit in patients with HCC who are ineligible for or have progressed following surgery or locoregional therapy [7], thereby offering these patients an effective systemic treatment option where none previously existed. Sorafenib is a small molecule that blocks tumor cell proliferation and angiogenesis by inhibiting the activity of:

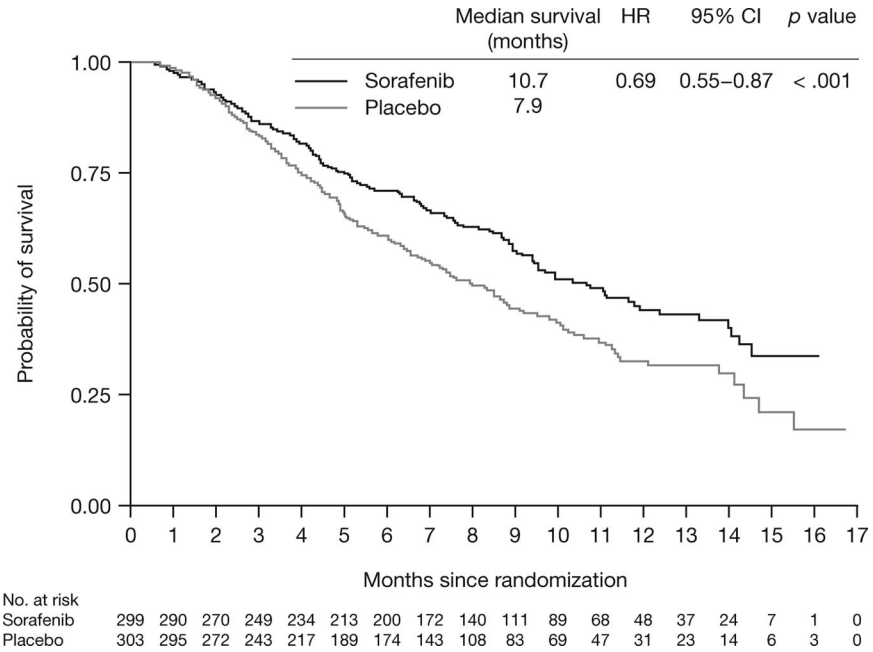

Figure 2. Kaplan–Meier estimate of overall survival for the phase III Sorafenib HCC Assessment Randomized Protocol (SHARP) study of sorafenib versus placebo in patients unsuitable for or having failed surgery or locoregional therapy.

Abbreviations: CI, confidence interval; HR, hazard ratio.

From Llovet JM, Ricci S, Mazzaferro V et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378–390, with permission. ©2008 Massachusetts Medical Society. All rights reserved.

vascular endothelial growth factor receptors 1, 2, and 3; platelet-derived growth factor receptor β; *Raf-1;* and *B-Raf* [45, 46]. In the phase III Sorafenib HCC Assessment Randomized Protocol (SHARP) trial [7], 602 patients with HCC, who were ineligible for or had progressed following surgery or locoregional therapy and who had an Eastern Cooperative Oncology Group (ECOG) PS score of 0–2 and Child-Pugh class A liver function, were randomly assigned to treatment with sorafenib or placebo. The study was stopped at the second planned interim analysis because of a significant difference in the survival time between the two treatment arms in favor of sorafenib (median survival time, 10.7 months versus 7.9 months for sorafenib and placebo, respectively; HR, 0.69; 95% CI, 0.55–0.87; $p < .001$) (Fig. 2). There was no significant difference between the two arms in the median time to symptomatic progression (4.1 months versus 4.9 months, respectively; $p = .77$). Treatment with sorafenib was also associated with a significantly longer time to radiologic progression (median, 5.5 months versus 2.8 months for sorafenib and placebo, respectively; HR, 0.58; 95% CI, 0.45–0.74; $p < .001$), despite a very low response rate to sorafenib treatment (2%, versus 1% in the placebo group). Overall, 17% of patients were BCLC stage B, which may have contributed to high survival rates in the placebo and sorafenib arms. However, only patients who were not eligible for or who had disease progression after surgical or locoregional therapies were recruited. Diarrhea, weight loss, hand–foot skin reaction (HFSR), and hypophosphatemia were more frequent in the sorafenib group. Subanalyses from this phase III study also suggest that sorafenib is effective in patients with alcohol-related HCC [47] and in those with hepatitis C infection [48].

A second phase III RCT evaluated sorafenib in the Asia-Pacific region and included 226 patients with unresectable or metastatic HCC, an ECOG PS score of 0–2, and Child-Pugh class A liver function who were randomized 2:1 to receive sorafenib or placebo [49]. Again, treatment with sorafenib was associated with a significantly longer OS time (median, 6.5 months versus 4.2 months for sorafenib and placebo, respectively; HR, 0.68; 95% CI, 0.50–0.93; $p = .014$) and time to progression (median, 2.8 months versus 1.4 months for sorafenib and placebo, respectively; HR, 0.57; 95% CI, 0.42–0.79; $p = .0005$). The most frequent grade 3 or 4 drug-related adverse events with sorafenib were HFSR (10.7%), diarrhea (6%), and fatigue (3.4%). These data confirmed findings from the SHARP study in terms of the magnitude of benefit associated with sorafenib, as shown by the similarity in HR values. The absolute survival benefits reported in the Asia-Pacific trial were lower; however, the authors suggest that this may be because of differences in patient characteristics between the two trials, with more patients in this study having extrahepatic spread,

Table 2. Selected phase II monotherapy trials of targeted agents in hepatocellular carcinoma

	n of patients	Patient characteristics	Dosing regimen	Grade 3 AEs occurring in >10% of patients plus any grade 4 AE	Efficacy			
					ORR	SD	PFS	OS
Zhu et al. [52]	34	Locally advanced, recurrent, or metastatic HCC; ECOG PS score, 0 or 1; CLIP score ≤3	Sunitinib, 37.5 mg/day, 4 wks on/2 wks off	Grade 4 thrombocytopenia, 6%; one case (3%) of pulmonary embolism; grade 3 leukopenia, neutropenia, AST and lymphopenia, 18%; fatigue, 12%	2.9%	50%	3.9 mos	9.8 mos
Zhu et al. [53]	30	Locally advanced, recurrent, or metastatic HCC; ECOG PS score, 0–2; CLIP score ≤3	Cetuximab, 400 mg/m^2 i.v. followed by weekly 250 mg/m^2 i.v. infusions	No grade 4 events reported; no grade 3 events reported in >10% of patients	0%	17%	1.4 mos	9.6 mos
Thomas et al. [55]	40	Advanced HCC not amenable to surgery or locoregional therapy; PS score, 0–2; Child-Pugh class A or B	Erlotinib, 150 mg/day for 28-day cycles	No grade 4 events reported; no grade 3 events reported in >10% of patients	0%	42.5%	13.3 wks	43.1 wks
Philip et al. [54]	38	Unresectable or metastatic HCC; ECOG PS score, 0–2; Child-Pugh class A or B	Erlotinib, 150 mg/day for 28-day cycles	One case of grade 4 hypophosphatemia; grade 3 skin rash, 13%	7.9%	50%	3.2 mos	13 mos
Siegel et al. [56]	46	Organ-confined, unresectable HCC; ECOG PS score, 0–2; Child-Pugh class A or B	Bevacizumab, 5 mg/kg or 10 mg/kg i.v. infusion every 2 wks	Grade 3 or 4 hypertension, 15%; bilirubin, 11%; hemorrhage, 11%	13%	ND	6.9 mos	12.4 mos

Abbreviations: AE, adverse event; AST, aspartate aminotransferase; CLIP, Cancer of the Liver Italian Program; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; ND, not described; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; SD, stable disease.

a greater number of hepatic lesions, a poorer ECOG PS score, and a higher α-fetoprotein level than the SHARP study population.

Although these two phase III RCTs provide definitive evidence of the survival benefits associated with sorafenib treatment, both were conducted in patients with preserved liver function (Child-Pugh class A), and data regarding the effects of sorafenib in patients with Child-Pugh class B liver function are limited. In a phase II study, 38 (28%) of the 137 patients treated with sorafenib were classed as having Child-Pugh class B liver function [50]. Encouraging efficacy was reported and no clinically relevant interpatient pharmacokinetic or tolerability differences were observed between patients with Child-Pugh class A and class B liver function. Similarly, a phase I study of 27 Japanese patients with HCC, including 14 patients with Child-Pugh class B liver function, reported no clinically relevant differences in the tolerability or pharmacokinetic profile of sorafenib between patients with Child-Pugh class A and class B liver function [51]. Based on these data, the NCCN treatment guidelines recommend treatment with sorafenib in patients with unresectable HCC and adequate liver function (Child-Pugh class A or B), although caution is advised when treating patients with Child-Pugh class B liver function [5]. Additional data are required to determine the optimal sorafenib treatment strategy. Nevertheless, sorafenib represents an important advance in the treatment of this poorly served patient population, and these findings have undoubtedly encouraged research efforts of targeted therapies in this setting. Indeed, phase II clinical trials evaluating the efficacy and safety of a number of other agents as monotherapy, including sunitinib [52], cetuximab [53], erlotinib [54, 55], and bevacizumab [56], have all been reported (Table 2), and a phase III study of sorafenib in combination with erlotinib is in progress. In a recent systematic review and meta-analysis of clinical trials, there was a significant threefold higher risk for arterial thromboembolic events with sorafenib and sunitinib than in control patients [57]. A phase III open-label study of sunitinib in advanced HCC patients was recently discontinued because of a higher incidence of serious adverse events in the sunitinib arm than in the sorafenib arm, together with a lack of difference in survival compared with sorafenib.

Future Directions to Improve Outcomes Among Patients with Unresectable HCC

Compared with other prevalent cancers, only a few suitably powered RCTs have been conducted to evaluate potential therapeutic interventions in patients with HCC who are unsuitable for or have failed curative therapy. As a result, treatment guidelines and common procedures are based on the best evidence available and can include information from nonrandomized trials, case studies, and evidence proposed by panels of experts. Appropriately designed RCTs

will therefore be instrumental in bridging current data gaps to fully clarify and establish the optimum treatment algorithm for patients with unresectable HCC as their disease progresses. In patients eligible for locoregional therapy, the optimum TACE therapeutic strategy is yet to be established and the use of radiation-emitting microspheres or DEB as part of embolization therapy also warrants further investigation. In addition, further studies are needed to clarify the possible role of targeted agents in combination with or following embolization.

Consideration should be given to the extent that TACE should be repeated, or a switch to sorafenib made, when objective response is not achieved after at least two courses of TACE. The availability of sorafenib warrants careful consideration of these decisions in a multidisciplinary discussion. In fact, in an analysis of the effect of baseline predictors of poor prognosis on the outcome of patients with advanced HCC treated with sorafenib in the SHARP trial, sorafenib was found to be effective irrespective of the presence or absence of vascular invasion/extrahepatic spread, although the magnitude of benefit of sorafenib over placebo was greater in the absence of invasion/spread (HR, 0.52; 95% CI, 0.32–0.85) than in the presence of invasion/spread (HR, 0.77; 95% CI, 0.60–0.99) [58].

Investigation of the combination of targeted agents with TACE is important, because there is a rationale for potential synergy between these therapies. In a study of tumor specimens from patients with HCC treated with TACE, the production of the proangiogenic vascular endothelial growth factor was higher than in samples from patients treated with surgery alone [59]. Furthermore, in an experimental tumor model, hypoxia, caused by embolization of liver tumors, activated hypoxia-inducible factor 1α, a transcription factor that, in turn, regulates other proangiogenic factors [60]. Given the known antiangiogenic properties of sorafenib, the combination of TACE with sorafenib holds promise and clinical trials investigating this therapeutic approach are ongoing (Sorafenib or Placebo in Combination with Transarterial Chemoembolization for Intermediate-stage HCC [SPACE] trial; ClinicalTrials.gov identifier, NCT00855218). Indeed, given that DEB-TACE has shown better tolerability than TACE, the combination of sorafenib with DEB-TACE is also promising.

For patients unsuitable for locoregional therapy, further studies are needed to confirm the efficacy and safety of systemic treatment with sorafenib among patients with impaired liver function. Studies combining sorafenib with other treatments, including targeted agents, are also of interest; indeed, a large phase III study to evaluate the efficacy of sorafenib in combination with erlotinib among patients with HCC who are not suitable for potentially curative therapy is in progress (ClinicalTrials.gov identifier, NCT00901901), and results from that study are eagerly awaited.

It is very important to consider appropriate trial design and endpoints for future studies in HCC patients. Response rate is consistently associated with survival after locoregional therapy; however, given the findings from the phase III RCTs of sorafenib, in which significant OS benefits were achieved despite low response rates, the response rate might not be the most suitable endpoint for clinical trials that include a targeted therapy. OS remains the most important endpoint, but disease-free survival may be misleading in HCC because it is often difficult to ascertain if the cause of death among patients with impaired liver function is tumor-related [15]. Patient selection is also critical when evaluating agents in HCC patients, and an expert panel recently convened by the AASLD recommended that all new agents initially be evaluated in patients with Child-Pugh class A liver function [15]. That panel also recommended that future trials use the standard of care (i.e., TACE for patients with unresectable disease who are eligible for locoregional therapy and sorafenib for those ineligible for or having failed surgery or locoregional therapy) for the comparator arm.

In addition to RCTs, because the treatment of HCC is complex and confounded by comorbidities, studies evaluating therapy in the real-life setting are also essential to allow physicians to make fully informed treatment decisions. Among these is the Global Investigation of therapeutic DEcisions in hepatocellular carcinoma and Of its treatment with sorafeNib (GIDEON) study. This is an international, prospective, open-label, multicenter, noninterventional study of patients with unresectable HCC for whom the decision has been taken to treat with sorafenib. The aim of the GIDEON study is to compile a large robust database of information from sorafenib-treated patients that can be analyzed to gain a detailed understanding of the local, regional, and global factors influencing the management of patients with HCC. As such, detailed medical information from ≥3000 patients globally over 5 years will be obtained, and information regarding the practice patterns of the treating physicians will also be collected, making it potentially the largest study of its kind in this patient population. The primary objective of this study is to evaluate the safety of sorafenib in the real-life clinical setting. Secondary objectives include: efficacy evaluations (OS, progression-free survival, time to progression, response rate, and rate of stable disease); duration of therapy; regional and global methods of patient evaluation, diagnosis, and follow-up;

evaluation of comorbidities and their influence on treatment and outcome; and evaluation of regional and global practice patterns of the physicians involved in the care of these patients.

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