Anti-angiogenics in Hepatocellular Cancer Therapy

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Contents

Abstract

Hepatocellular carcinoma (HCC) is one of the most common and deadly malignancies worldwide. HCC is a highly vascularized malignant tumor providing a rationale to consider angiogenesis as a therapeutic target. Anti-angiogenic strategies include locoregional and systemic treatments in HCC. Depending on the stage of the disease, different anti-angiogenic approaches are currently being employed in the treatment of HCC.

For patients at intermediate stage disease, transarterial chemoembolization (TACE) has been widely accepted as the standard of care and is the most common therapy for this patient group. TACE is a locoregional intervention, and its main mechanism of action is the embolization of the tumor-feeding arteries. For patients with advanced HCC, the multiprotein

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kinase inhibitors sorafenib and regorafenib provide systemic treatment options. Their efficacy in terms of survival prolongation has been shown in the palliative setting. Both drugs target among others the receptor of the vascular endothelial growth factor (VEGF), and their antitumor efficacy is believed to partly depend on the anti-angiogenic properties.

Keywords
Hepatocellular carcinoma · VEGF · VEGFR · PDGFR · PLGF · FGFc-MET · TACE · HAP · STATE · Regorafenib · Tivantinib · Lenvatinib · Brivanib · Sorafenib · Bevacizumab · Ramucirumab

Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers in men worldwide and represents the third most frequent cause of cancer death (El-Serag 2011; Bosetti et al. 2014). The prognosis of patients with HCC is dismal and the mortality rates are almost the same as the incidence rates. In the year 2008, 748,300 new HCC and 695,900 deaths have been registered (Jemal et al. 2011). In 70–80% of the cases, HCC is diagnosed in patients with liver cirrhosis and a compromised hepatic function. For these patients, the cumulative 5-year risk to develop a HCC is 5–30% (El-Serag 2011). Major risk factors to develop liver cirrhosis and subsequently HCC are chronic infections with hepatitis B and C and alcohol abuse. Additionally, nonalcoholic fatty liver disease (NAFLD) is increasingly recognized as an additional risk factor for the development of liver tumors.

In clinical practice, several therapeutic options are available for patients with HCC depending on the stage of the disease, which depends on tumor burden and liver function. Potentially curative treatments for patients at early stage disease are liver transplantation, resection, and radiofrequency or microwave ablation (Bruix et al. 2011). Early stage disease is characterized by a low tumor burden with small tumor lesions, no more than three lesions, lack of vascular invasion and extrahepatic spread, and a preserved hepatic function. However, HCC is most often diagnosed at intermediate or advanced stage, where therapeutic options are mostly restricted to palliation due to high tumor burden and/or impaired liver function (Llovet et al. 2003; Park et al. 2015). HCC is a highly vascularized malignant tumor providing the rationale for anti-angiogenic strategies through locoregional and systemic treatments. Intermediate stage patients have liver-limited disease, with multiple and large HCC lesions, but no vascular invasion or extrahepatic spread, making them appropriate candidates for local treatment. Transarterial chemoembolization (TACE) has been widely accepted as the standard of care for patients at intermediate stage disease and is the most common therapy in clinical practice for this patient group (Park et al. 2015; Llovet et al. 2002; Lo et al. 2002; Malek et al. 2014; Kirstein et al. 2016). TACE combines the administration of cytotoxic drugs, with or without lipiodol, and embolizing agents by means of a catheter directly to the hepatic artery.

For patients with advanced disease, high hepatic tumor burden, and/or evidence of vascular invasion or extrahepatic tumor manifestations, the multi-tyrosine kinase inhibitor sorafenib is so far the only approved systemic drug (Llovet et al. 2008). Sorafenib targets the receptor of the vascular endothelial growth factor (VEGF) among others suggesting that inhibition of angiogenesis is one of its anti-tumoral mechanisms of action. More recently, evidence has been provided for the efficacy of the multi-tyrosine kinase inhibitor regorafenib in patients with progressive disease upon sorafenib. In the following we will summarize the anti-angiogenetic approaches for patients with HCC at intermediate and advanced stage disease.

Inhibition of Angiogenesis in HCC

HCC is a highly vascular tumor, and angiogenesis, mediated mainly through VEGF, is thought to play a major role in development, progression, and prognosis of this cancer. Inhibition of angiogenesis is achieved through local and systemic

therapies in HCC. TACE is a local, embolizing procedure most commonly performed in combination with the administration of local chemotherapy. On the other hand, sorafenib is the established therapy for patients at advanced stages with higher hepatic tumor burden and/or vascular invasion and extrahepatic metastases. Up to date, sorafenib is the only approved agent for HCC. After the approval of sorafenib, multiple molecular agents with anti-angiogenic properties have been investigated to improve overall survival in patients with advanced HCC. Most of these drugs failed in phase II or III clinical trials until very recently, when the positive phase III trial with the multi-kinase inhibitor regorafenib has been reported. In the following, we will describe and discuss the different approaches that have been undertaken to target angiogenesis in HCC.

Inhibition of Angiogenesis with *Transarterial Chemoembolization*

TACE is the most common first-line treatment for patients with HCC. Two early randomized trials have confirmed significantly improved survival rates of patients with intermediate stage disease treated with TACE so that TACE has become the standard treatment in these patients. In the first trial reported by Llovet et al., more than 900 Caucasian patients were screened during a period of 4 years. Out of these 903 patients, 113 were included in the trial, and a survival benefit was reported for 35 patients treated with TACE as compared to 38 patients treated with best supportive care (BSC); only survival in the BSC arm was very long with 17.8 months indicating that a highly selected patients population was included in the trial with a good liver function and low tumor burden. Survival in the TACE arm was significantly improved to 28.7 months. In contrast to the survival the pivotal trial, outcome of patients treated with TACE in clinical practice is still very poor with median overall survival rates of 20 months or less (Sieghart et al. 2013; Kadalayil et al. 2013; Hucke et al. 2014).

TACE is frequently part of a multimodal treatment strategy at any stage. A high variability of second-line treatments after TACE has been reported in real-life cohorts, where TACE was most often followed by other local therapies rather than by systemic therapies (Park et al. 2015; Kirstein et al. 2016). In order to select the best patients for TACE, several prognostic scores such as the *hepatoma arterial-embolization prognostic* score (HAP), the modified HAP-II, *Selection for TrAnsarterial chemoembolization TrEatment* (STATE), as well as an individual prognostic calculator have been established (Kadalayil et al. 2013; Park et al. 2016; Hucke et al. 2014; Cappelli et al. 2016). In addition, predictive scores have been proposed in order to select the most appropriate patients for continuation with TACE (Sieghart et al. 2013; Adhoute et al. 2015). It still remains unclear though, at which time patients should be switched from TACE to systemic therapy according to the currently available scores. Specifically, it has never been shown that patients with a poor prognosis would benefit from a switch to systemic therapy and to which extent frequent TACE sessions may compromise post-TACE survival due to impairing liver function.

The most popular TACE technique has been established by the administration of lipiodol followed by embolic agents. Lipiodol is used as a vehicle to carry the chemotherapeutic agent inside the tumor and as a microembolic agent for tiny tumor vessels. A recent systematic review of 101 mostly single-arm and/or non-randomized studies including 10,108 subjects revealed that the most commonly used chemotherapeutic agents, either as single agents or in combination regimens, are doxorubicin, epirubicin, cisplatin, and mitomycin (Lencioni et al. 2016a). Median overall survival (OS) in these studies was 19.4 months, which is consistent with the data reported in previous meta-analyses. The survival rates were 81.0% at 6 months post-TACE, 70.3% at 1 year, 51.8% at 2 years, 40.4% at 3 years, and remarkably 32.4% at 5 years indicating that TACE can be very efficacious in in specific subgroups. Median PFS was only evaluated in a few studies and ranged between 3 and 9 months, and the objective response rate, defined as sum of complete and partial response, was approximately 50%.

Using TACE with lipiodol, local embolization (conventional TACE) of the vessels that supply HCC induces inflammation and necrosis of the lesions (Shim et al. 2008). Several attempts have been made to improve the efficacy of TACE in intermediate stage HCC. One approach, which is increasingly used and standard of care in several prospective trials, is the use of drug-eluting beads. TACE with embolic doxorubicin-eluting beads (DC Bead; Biocompatibles UK Ltd.; DEB-TACE) was developed to simplify the procedure, reduce peak concentrations and total systemic exposure to doxorubicin, and ensure high concentrations in the tumor and adequate arterial occlusion. One randomized phase II trial found that DEB-TACE reduced the rates of systemic adverse events and liver toxicity compared with conventional TACE with lipiodol and doxorubicin. The drug-eluting bead group showed numerical higher rates of complete response, objective response, and disease control compared with the conventional TACE group (27% vs. 22%, 52% vs. 44%, and 63% vs. 52%, respectively) in the intention-to-treat (ITT) population of 212 patients, which however did not reach the level of significance (Lammer et al. 2010). Similarly, in one randomized study, comparing conventional TACE and DEB-TACE, there was no significant difference in median OS with 28 and 29 months, respectively, suggesting equal antitumor efficacy for lipiodol TACE compared to beads TACE (Golfieri et al. 2014). One very recent study readdressed the question, whether the addition of doxorubicin has any additional effect on response and outcome after embolization with beads (Brown et al. 2016). In this single-center study, 92 patients with comparable characteristics underwent 129 embolizations to complete their initial treatment, with a total of 209 embolizations during the entire study. Median progression-free survival (PFS) was 6.2 versus 2.8 months (HR 1.36, $p = 0.11$) and median PFS 19.6 versus 20.8 months (hazard ration [HR], 1.11, $p = 0.64$) for TACE without and with doxorubicin, respectively. Moreover, there was no significant difference in the response rate measured by Response Evaluation Criterial In Solid Tumor (RECIST) 1.1 and modified RECIST (mRECIST). This finding supports a previous study in which patients were randomized to TAE with polyvinyl alcohol (PVA) particles alone or sequential TACE with cisplatin 50 mg administered intra-arterially 4–6 h before PVA embolization (Meyer et al. 2013). In this study, median OS and median PFS were 17.3 versus 16.3 ($p = 0.74$) months and 7.2 versus 7.5 ($p = 0.59$), respectively, indicating that the efficacy of TACE primarily depends on the mechanical anti-angiogenic effect than on the antitumor effect of the chemotherapy.

Inhibition of Angiogenesis with Systemic Therapy

Sorafenib

Sorafenib is an oral multi-kinase inhibitor, which inhibits proliferation of tumor cells and induces apoptosis. Target structures are the serine-threonine kinases Raf-1 und B-Raf, the platelet-derived growth factor receptor-b (PDGFR-b), and also the receptor tyrosine kinases of the vascular endothelial growth factor (VEGF). The VEGF family consists of five ligands VEGFA, VEGFB, VEGFC, VEGFD, and placental growth factor (PIGF) and the three receptor tyrosine kinases VEGFR1, VEGFR2 and VEGFR3. Of the VEGF receptors, VEGFR2 expression is restricted to the vasculature and appears to play a key role in angiogenesis.

The safety and efficacy of sorafenib have been shown with the multicentric, randomized, placebo-controlled SHARP trial (Sorafenib HCC Assessment Randomized Protocol) (Llovet et al. 2008). Six hundred two patients with advanced disease were included from 21 countries. The study was preliminary stopped after the second interims analysis, which revealed a significant survival benefit for sorafenib. The median OS was 10.7 months in the sorafenib arm and 7.9 months in the placebo group (HR 0.69; $p < 0.001$). Time to radiological progression was also significantly prolonged from 2.8 to 5.5 months with sorafenib (HR 0.58; $p < 0.00001$). The results of the SHARP trial led

to the approval by the FDA and EMA in 2007 for advanced HCC, not suitable for local therapy.

Later on, the survival benefit for sorafenib treatment was confirmed in Asian patients also within another large phase III trial, the Asia-Pacific Trial (HR 0.68, $p < 0.05$) (Cheng et al. 2009). Moreover, for differentiated conclusions of HCC-therapy in real-life clinical practice, 2,770 patients were selected from 37 countries for a systemic treatment with sorafenib to participate within the GIDEON trial (Global Investigation of Therapeutic Decisions in Hepatocellular Carcinoma and of its Treatment with Sorafenib) (Lencioni et al. 2010). The survival advantage and the delay in progression were particularly confirmed for patients with a well-preserved hepatic function (Child-Pugh A). Accordingly, sorafenib is recommended for patients with Child-Pugh A within the current German and international guidelines (Bruix et al. 2011; Malek et al. 2014). The efficacy of sorafenib has formally not been shown in patients with advanced disease and more impaired hepatic function (CP B) and is accordingly not recommended by the guidelines. A more profound prolongation of OS may also be conceivable in patients with a less advanced tumor stage. However, an "earlier" administration of sorafenib at intermediate stage disease has so far not been sufficiently investigated, and there are no head-to-head trials comparing sorafenib with TACE.

In order to better understand the mechanism of action of sorafenib and to identify patients that respond to the drug alone or in combination with other systemic drugs, several biomarkers have been investigated in previous studies. One prospective study found that lower baseline plasma levels of insulin-like growth factor-1 and higher plasma VEGF levels correlate with advanced clinical pathologic parameters and poor OS in 288 patients with HCC suggesting that high VEGF levels are of prognostic relevance in HCC (Kaseb et al. 2011). Subsequently, an analysis of the 602 patients in the SHARP trial also observed that baseline plasma concentrations of angiopoietin 2 and VEGFA were independent prognostic predictors of patient survival in the entire patient population (Llovet et al. 2012). These data were further supported by a recent analysis aimed to identify biomarkers predicting prognosis or response to sorafenib with or without erlotinib in HCC patients from the phase III SEARCH trial. Treatment arm-independent analyses showed that elevated hepatocyte growth factor (HGF; HR,1.687 (high vs. low expression) and elevated plasma VEGFA (HR, 1.386) were significantly associated with poor overall survival (OS) in multivariate analyses (Zhu et al. 2016a). Furthermore, a multi-marker signature of HGF, VEGFA, KIT, EPGN, and VEGFC correlated with improved median OS in the multivariate analysis. These biomarkers were also tested in predictive analyses in both trials to determine whether their baseline concentrations correlated with treatment benefit. However, none of them – either alone or in combination – significantly predicted benefit from sorafenib.

Sunitinib

Sunitinib is an oral, multi-targeting tyrosine kinase inhibitor of VEGFR-1, VEGFR-2, and VEGFR-3 and other receptor tyrosine kinases such as platelet-derived growth factor receptors (PDGFRs), c-Kit, Flt-3, and RET receptors. The drug has shown promising antitumor activity in three phase II studies of patients with advanced HCC (Raymond et al. 2007; Faivre et al. 2009; Zhu et al. 2009). Each study evaluated a different dosing regimen: 37.5 mg/d on a 4-week-on-2-week-off schedule (schedule 4/2), 50 mg/d on schedule 4/2, and 37.5 mg via continuous daily dosing. The 50 mg/d schedule 4/2 regimen was associated with pronounced toxicities, and the 37.5 mg CDD schedule was selected for further study in the large phase III SUN1170-HCC study in order to compare the efficacy of sunitinib against sorafenib (Faivre et al. 2009; Cheng et al. 2013). The primary objective was to demonstrate at least non-inferiority of sunitinib as compared to sorafenib in terms of OS. As a result of a planned safety review by the independent data monitoring committee, carried out after the first interims analysis, the trial was terminated and enrolment was stopped for futility and safety

reasons. Moreover, interims analysis revealed that 18% of the death in the sunitinib arm were related to the drug. Despite similarities in PFS and TTP, the lack of OS benefit emphasizes the limitations of surrogate endpoints in HCC. In the final analysis, an OS of 7.9 months in the sunitinib arm and 10.2 months in the sorafenib arm was reported (HR 1.30, $p < 0.01$) and confirmed therefore the approval data for sorafenib from the SHARP trial. Interestingly, the survival difference between sunitinib and sorafenib was specifically seen in patients from non-Asian regions, many of whom were HCV positive. In contrast, median OS was similar in HBV-infected patients. These data are in agreement with an exploratory subgroup analysis from the SHARP study, in which survival with sorafenib was longer in HCV-infected patients compared to patients with alcohol- or HBV-related HCC suggesting that HBV-related and HCV-related HCC may respond differently to targeted therapies (Bruix et al. 2012).

Brivanib

Another anti-angiogenic agent, which has been extensively investigated in HCC, is brivanib. Brivanib is an oral, selective dual inhibitor of the VEGFR and the FGFR, which exhibit both antiproliferative and anti-angiogenic activity (Bhide et al. 2010). Preclinical evidence suggested that both pathways play a role in the pathogenesis of HCC and that the FGFR family at least partly mediate resistance to VEGF-driven angiogenesis. Based on promising preclinical and phase II data that indicated that brivanib could have a comparable activity as sorafenib, three phase III trials were initiated in the first-line (BRISK-FL) and second-line (BRISK-SL) setting and in combination with chemoembolization (BRISK-TA). The BRISK-PS study investigated the efficacy of brivanib compared to best supportive care after failure of sorafenib or intolerance to sorafenib (Llovet et al. 2013). The primary endpoint for the study was OS, which was however not reached. While the study was mostly well stratified, there was an imbalance in the number of patients that had vascular invasion, which was masked by the fact that the majority of patients had extrahepatic spread. In contrast to OS, TTP, objective response rate, and disease control rate were significantly improved with brivanib suggesting that these imbalances in the patient population could have contributed to missed OS benefit.

Similarly, the BRISK-FL study did not meet its primary endpoint of non-inferiority compared to sorafenib (Johnson et al. 2013). This study enrolled over 1,100 patients randomized 1:1 to brivanib or sorafenib and stratified similarly to the SHARP study. mOS did not differ significantly from the sorafenib survival of 9.9 months but exceeded the upper-limit HR 95% CI of 1.08 to prove non-inferiority. Results of the BRISK-TA study are reported below. After these discouraging results, all investigations on brivanib in HCC were stopped.

Linifanib

Linifanib is an ATP-competitive inhibitor of all VEGF and PDGF receptor tyrosine kinases. In an open-label, phase II trial, linifanib demonstrated clinical activity as monotherapy in mainly Asian patients with advanced HCC with an TTP of 5.5 months and a mOS of 9.7 months. Based in these promising data, the efficacy and tolerability of linifanib versus sorafenib were tested in patients with advanced HCC who had not received prior systemic therapy. Patients receiving linifanib had a longer TTP, PFS, and ORR than patients receiving sorafenib. These improvements however did not translate to an improvement in OS, which was not significantly different between the two treatments all in prespecified subgroups. None of the predefined superiority and non-inferiority OS borders for linifanib were met within the trial (Cainap et al. 2015).

Cabozantinib and Tivantinib

Another class of drugs of increasing interest in HCC is the inhibitors of the receptor tyrosine kinase c-MET with its ligand the hepatocyte

growth factor (HGF), either alone or in combination with VEGF inhibition. C-MET has been implicated in tumorigenesis, and overexpression or activation of c-MET has been shown within several retrospective trials in HCC (Kaposi-Novak et al. 2006; Ke et al. 2009). Cabozantinib is a dual MET/VEGFR2 inhibitor. Cabozantinib has been tested against placebo in a phase II discontinuation trial with 41 patients with progressive HCC (Verslype et al. 2012). With a PFS of 4.4 months and a promising OS of 15.1 months, a relevant antitumor activity was assumed, and a phase III trial has been initiated testing cabozantinib against placebo in sorafenib-pretreated patients (Abou-Alfa et al. 2015). The trial is designed to enroll 760 patients with advanced HCC who received prior sorafenib. Patients are randomized 2:1 to receive 60 mg of cabozantinib daily or placebo. Following an interims analysis in 2016, which was scheduled to take place when 50% of the events for the primary endpoint of OS had occurred, the trial's Independent Data Monitoring Committee (IDMC) determined that the study should continue without modifications of the study protocol.

However, challenging the assumption that VEGF inhibition is the key mediator of the antitumor activity of cabozantinib, tivantinib, a selective, non-ATP-competitive inhibitor of the MET-tyrosine kinase, also showed promising results. Tivantinib has been investigated in a multicenter, placebo-controlled phase II trial (Santoro et al. 2013), in which 107 patients after failure of sorafenib or intolerance to sorafenib were included. Primary endpoint was time to progression. In the total population, there was no improvement, but in patients with an immunohistochemically high c-MET expression, median OS was improved from 3.8 to 7.2 months as compared to placebo. Moreover, a negative prognostic value of c-MET has been reported as c-MET high-expressing patients had a significant shorter OS compared to patients with a low c-met expression. Based on these data, a phase III trial with tivantinib in the second-line setting in c-MET-overexpressing patients has been conducted and the results are awaited for 2017 (NCT01755767).

Regorafenib

Regorafenib is a multi-tyrosine kinase inhibitor that is structurally almost identical to sorafenib with the addition of only one fluorine atom in the center phenyl ring (Ravi and Singal 2014). In addition to VEGFR-1, VEGFR-2, and VEGFR-3, additional angiogenic targets of regorafenib are PDGFR and FGFR-1 and FGFR-2 and, to a lesser degree, the tyrosine kinase of the immunoglobulin and epidermal growth factor homology domain 2 (TIE-2) receptor, another promoter of angiogenesis. Within a phase II trial, regorafenib revealed an acceptable safety profile and a relevant efficacy with an OS of 13.8 months and a TTP of 4.3 months in patients after sorafenib failure (Bruix et al. 2013). Based on these results, the phase III RESORCE trial (REgorafenib after SORafenib in patients with hepatoCEllular carcinoma) has been conducted, and for the first time following the SEARCH study, a significant improvement of OS could be demonstrated within a phase III trial. Importantly, a significant benefit of regorafenib versus placebo could be demonstrated in all efficacy endpoints: mOS was prolonged from 7.8 to 10.6 months (HR 0.62, $p < 0.001$); mPFS was 3.1 months for regorafenib versus 1.5 months for placebo (HR = 0.46; $p < 0.001$). Accordingly, median TTP was 3.2 months for regorafenib versus 1.5 months for placebo (HR 0.44; $p < 0.001$). ORR was 10.6% versus 4.1% ($p = 0.005$). The most frequent adverse events (≥grade 3) were hypertonia (15.2% vs. 4.7%), hand and foot reaction (12.6% vs. 0.5%), fatigue (9.1% vs. 4.7%), and diarrhea (3.2% vs. 0%). Based on these results, regorafenib is expected to be approved as second-line treatment option for patients with HCC following progression on sorafenib.

Bevacizumab

Bevacizumab is a monoclonal antibody targeting VEGFA and is the classical inhibitor of angiogenesis approved for various cancer types. By targeting VEGFA, bevacizumab impacts on VEGFR1 and VEGFR2 and the non-catalytic

co-receptors neuropilin-1 and neuropilin-2. VEGFA is a central regulator of endothelial cell proliferation and survival, tumor angiogenesis, and vascular permeability. Although the precise mechanism of action is incompletely understood, bevacizumab is thought to decrease tumor vascularity and growth by directly binding to VEGF. Bevacizumab may also help to normalize tumor vasculature, improving oxygenation and the delivery of cytotoxic drugs. Bevacizumab has been evaluated in several small trials in HCC. A recently published meta-analysis summarized the results of eight trials with more than 300 patients (Fang et al. 2012). In six trials, bevacizumab was given as first- or second-line treatment and in seven trials in combination therapy with erlotinib, capecitabine, and/or oxaliplatin. The response rate in most trials was approximately 20% with a disease control rate of 20–79%. Median PFS was between 1.5 and 6.9 months, and median OS was between 5.9 and 15.7 months. In all trials, though accompanied with manageable, drug-typical toxicities, bevacizumab was generally well tolerated. Overall, these published data suggest that bevacizumab could be an effective treatment for advanced HCC, but to our knowledge, further investigations regarding bevacizumab have been largely stopped.

Ramucirumab

Ramucirumab is a monoclonal antibody against VEGFR-2, where it binds to the extracellular VEGF-binding domain with high degree of specificity and affinity, thereby preventing the binding of the VEGF ligand to the VEGFR2 receptor. In a small phase II and biomarker study, patients with advanced HCC and no prior systemic treatment received ramucirumab 8 mg/kg every 2 weeks until disease progression or limiting toxicity (Zhu et al. 2013). In this study, median PFS was 4.0 months, ORR 9.5%, and median OS 12.0 months suggesting that the drug may confer anticancer activity in advanced HCC. The exploratory biomarker studies revealed that there was an increase in serum VEGF and placental growth factor (PlGF) and a transient decrease in soluble VEGFR-2 following treatment with ramucirumab.

Based on these data, the global, randomized, double-blind REACH trial was initiated comparing ramucirumab to placebo as a second-line treatment in patients with HCC after being treated with sorafenib in the first-line setting. Median OS was 9.2 months on the ramucirumab arm compared to 7.6 months on the placebo arm (HR 0.866; 95% CI: 0.717–1.046; $p = 0.1391$). While the median OS was not statistically significant, a prespecified subgroup of patients with an elevated baseline of alpha-fetoprotein (AFP) $\geq$400 ng/mL showed a greater survival improvement with ramucirumab treatment regardless of Child-Pugh score (Zhu et al. 2016b). Median OS in this subgroup of patients was 7.8 months in the ramucirumab arm compared to 4.2 months in the placebo arm (HR 0.674; 95% CI 0.508–0.895; $p = 0.0059$) supporting the use of baseline AFP as a method to identify those patients most likely to benefit from ramucirumab. Serum AFP has long been recognized as a diagnostic and prognostic marker, and the analyses from this study thus confirmed elevated AFP levels as a marker of poor prognosis in HCC. The association between efficacy and baseline AFP could be because of the unique selective inhibition of only VEGFR-2 by ramucirumab, which might be relevant in this poor prognosis group. Further investigation of the efficacy and safety of ramucirumab in patients with HCC and elevated baseline AFP are ongoing in the phase III REACH-2 trial (NCT02435433).

Combination of Local and Systemic Therapy

TACE in Combination with Systemic Therapy

As both TACE and systemic therapy can target angiogenesis and the existing tumor-feeding arteries and do not have overlapping toxicities, a combination of both has been thought to increase clinical outcome in patients with intermediate stage HCC. Moreover, TACE has been shown to lead to a spike in the intratumoral concentration of

VEGF and FGF, which have been shown to be associated with increased risk of tumor growth, recurrence, metastasis, and poor survival providing a rationale to combine both treatments. The addition of systemic therapy to TACE may therefore shrink or stabilize tumors remaining after TACE, prevent tumors from spreading outside of the liver, and may also suppress growth of microscopic lesions not treatable by TACE. Several single-arm phase I and II trials have explored the combination of sorafenib plus conventional TACE or DEB-TACE indicating that these combinations are feasible in patients with intermediate stage HCC. Two reviews and meta-analysis including four and, respectively, two randomized trials concluded that the combination of TACE and sorafenib does not improve OS or overall response rates but improves time to progression (Zeng et al. 2016; Wang et al. 2016). However, recent data from four well-performed randomized, placebo-controlled trials have shown discouraging results for the combination of TACE with sorafenib, brivanib, and orantinib.

Three hundred and seven patients were randomized in the phase II SPACE-trial (Lencioni et al. 2016b). Patients were 1:1 randomized to receive either sorafenib or placebo. Systemic treatment started on day 1, and the first TACE was performed on days 3–7 using drug-eluting beads (DEB-TACE). The primary outcome was time to progression. Sorafenib plus DEB-TACE improved TTP according to the predefined statistical threshold for this exploratory study, but the median TTP was the same (169 vs. 166 days, respectively; HR 0.8; $p = 0.072$), and the combination did not improve TTP in a clinically meaningful manner compared with DEB-TACE alone. The overall response rates (ORRs) for patients in the sorafenib and placebo groups were 55.9% and 41.3%, respectively, and not significantly different. Similarly, the HR of OS in the sorafenib plus DEB-TACE versus the placebo plus DEB-TACE group was 0.898 ($p = 0.295$), with the median OS not reached in either group after a median follow-up of approximately 270 days.

The results of the randomized-controlled phase III TACE-2 trial have recently been presented (ASCO 2016 annual meeting, abstract #4018)). Patients with intermediate stage HCC were randomized 1:1 to continuous sorafenib (400 mg BD) or placebo. After randomization patients were treated with the study drug. DEB-TACE was performed at 2–5 weeks. The primary outcome progression-free survival (PFS) was not met (7.8 for sorafenib vs. 7.7 months for placebo; HR 1.03; $p = 0.85$). Moreover, there were no differences between both arms in the secondary measures OS (18.8 vs. 19.6 months; HR 1.03; $p = 0.87$) and overall response (34.7% vs. 31.3%).

The efficacy of brivanib in combination with TACE was evaluated in large prospective trials with more than 500 patients. The final analysis did not reveal an improvement in the primary endpoint of mOS with a mOS of 26.4 months in the brivanib group and 26.1 months in the placebo group (HR: 0.9). There was also no improvement in the composite endpoint of time to disease progression (TTDP) (defined as the time from the first TACE to the development of extrahepatic spread or vascular invasion, deterioration of liver function or ECOG-PS, or death) with brivanib versus placebo (median 12.0 vs. 10.9 months) and in respect to ORR (48% in the brivanib group and 42% in the placebo group). In contrast, TTES/IV (time to extrahepatic spread or vascular invasion) (median not reached vs. 24.9 months; HR, 0.64; $p = 0.0096$) and TTP (median, 8.4 vs. 4.9 months; HR, 0.61; $p < 0.0001$) were longer in the brivanib group than in the placebo group, suggesting that brivanib may have some antitumor efficacy in this setting, which was however not sufficient to improve OS.

The combination of TACE has also been tested with another multi-kinase inhibitor, orantinib in a smaller phase II study. The results of the study have so far been only reported in abstract form. Similarly, data of a combination of TACE with sunitinib are awaited for full publication.

Conclusion

Impairing arterial perfusion and vascularization of HCC by means of TACE is effective and is recommended as the standard of care for intermediate stage patients and as bridging therapy at

earlier stage disease. Systemic therapy has been shown to be effective in the first-line setting with sorafenib and in the second-line setting with regorafenib. So far, sorafenib is the only approved drug for patients with advanced HCC. Regorafenib however is the first drug, following the SHARP study, to show a significant survival benefit in patients with failure of sorafenib and provides now a treatment option in second line. For both drugs, however, the respective impact on anti-angiogenesis for their antitumor efficacy has never been proven and likely involves additional impact on other signal cascades within the tumor cells.

References

Abou-Alfa GK, Cheng AL, Meyer T, El-Khoueiry AB, Ikeda M, Chun HG, Furuse J et al (2015) Phase 3 randomized, double-blind, controlled study of cabozantinib (XL184) versus placebo in subjects with hepatocellular carcinoma who have received prior sorafenib (CELESTIAL; NCT01908426). J Clin Oncol 33

Adhoute X, Penaranda G, Naude S, Raoul JL, Perrier H, Bayle O, Monnet O et al (2015) Retreatment with TACE: the ABCR SCORE, an aid to the decision-making process. J Hepatol 62:855–862

Bhide RS, Lombardo LJ, Hunt JT, Cai ZW, Barrish JC, Galbraith S, Jeyaseelan R Sr et al (2010) The anti-angiogenic activity in xenograft models of brivanib, a dual inhibitor of vascular endothelial growth factor receptor-2 and fibroblast growth factor receptor-1 kinases. Mol Cancer Ther 9:369–378

Bosetti C, Turati F, La Vecchia C (2014) Hepatocellular carcinoma epidemiology. Best Pract Res Clin Gastroenterol 28:753–770

Brown KT, Do RK, Gonen M, Covey AM, Getrajdman GI, Sofocleous CT, Jarnagin WR et al (2016) Randomized trial of hepatic artery embolization for hepatocellular carcinoma using doxorubicin-eluting microspheres compared with embolization with microspheres alone. J Clin Oncol 34:2046

Bruix J, Raoul JL, Sherman M, Mazzaferro V, Bolondi L, Craxi A, Galle PR et al (2012) Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: subanalyses of a phase III trial. J Hepatol 57:821–829

Bruix J, Sherman M, American Association for the Study of Liver Diseases (2011) Management of hepatocellular carcinoma: an update. Hepatology 53:1020–1022

Bruix J, Tak WY, Gasbarrini A, Santoro A, Colombo M, Lim HY, Mazzaferro V et al (2013) Regorafenib as second-line therapy for intermediate or advanced hepatocellular carcinoma: multicentre, open-label, phase II safety study. Eur J Cancer 49:3412–3419

Cainap C, Qin S, Huang WT, Chung IJ, Pan H, Cheng Y, Kudo M et al (2015) Linifanib versus Sorafenib in patients with advanced hepatocellular carcinoma: results of a randomized phase III trial. J Clin Oncol 33:172–179

Cappelli A, Cucchetti A, Cabibbo G, Mosconi C, Maida M, Attardo S, Pettinari I et al (2016) Refining prognosis after trans-arterial chemo-embolization for hepatocellular carcinoma. Liver Int 36(5):729–736

Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, Luo R et al (2009) Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 10:25–34

Cheng AL, Kang YK, Lin DY, Park JW, Kudo M, Qin S, Chung HC et al (2013) Sunitinib versus sorafenib in advanced hepatocellular cancer: results of a randomized phase III trial. J Clin Oncol 31:4067–4075

El-Serag HB (2011) Hepatocellular carcinoma. N Engl J Med 365:1118–1127

Faivre S, Raymond E, Boucher E, Douillard J, Lim HY, Kim JS, Zappa M et al (2009) Safety and efficacy of sunitinib in patients with advanced hepatocellular carcinoma: an open-label, multicentre, phase II study. Lancet Oncol 10:794–800

Fang P, Hu JH, Cheng ZG, Liu ZF, Wang JL, Jiao SC (2012) Efficacy and safety of bevacizumab for the treatment of advanced hepatocellular carcinoma: a systematic review of phase II trials. PLoS One 7

Golfieri R, Giampalma E, Renzulli M, Cioni R, Bargellini I, Bartolozzi C, Breatta AD et al (2014) Randomised controlled trial of doxorubicin-eluting beads vs conventional chemoembolisation for hepatocellular carcinoma. Br J Cancer 111:255–264

Hucke F, Pinter M, Graziadei I, Bota S, Vogel W, Muller C, Heinzl H et al (2014) How to STATE suitability and START transarterial chemoembolization in patients with intermediate stage hepatocellular carcinoma. J Hepatol 61:1287–1296

Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D (2011) Global cancer statistics. CA Cancer J Clin 61:69–90

Johnson PJ, Qin S, Park JW, Poon RT, Raoul JL, Philip PA, Hsu CH et al (2013) Brivanib versus sorafenib as first-line therapy in patients with unresectable, advanced hepatocellular carcinoma: results from the randomized phase III BRISK-FL study. J Clin Oncol 31:3517–3524

Kadalayil L, Benini R, Pallan L, O'Beirne J, Marelli L, Yu D, Hackshaw A et al (2013) A simple prognostic scoring system for patients receiving transarterial embolisation for hepatocellular cancer. Ann Oncol 24:2565–2570

Kaposi-Novak P, Lee JS, Gomez-Quiroz L, Coulouarn C, Factor VM, Thorgeirsson SS (2006) Met-regulated expression signature defines a subset of human

hepatocellular carcinomas with poor prognosis and aggressive phenotype. J Clin Invest 116:1582–1595

Kaseb AO, Morris JS, Hassan MM, Siddiqui AM, Lin E, Xiao LC, Abdalla EK et al (2011) Clinical and prognostic implications of plasma insulin-like growth factor-1 and vascular endothelial growth factor in patients with hepatocellular carcinoma. J Clin Oncol 29:3892–3899

Ke AW, Shi GM, Zhou J, Wu FZ, Ding ZB, Hu MY, Xu Y et al (2009) Role of overexpression of CD151 and/or c-met in predicting prognosis of hepatocellular carcinoma. Hepatology 49:491–503

Kirstein MM, Schweitzer N, Ay N, Boeck C, Lappas K, Hinrichs JB, Voigtlander T et al (2016) Experience from a real-life cohort: outcome of patients with hepatocellular carcinoma following transarterial chemoembolization. Scand J Gastroenterol:1–22

Lammer J, Malagari K, Vogl T, Pilleul F, Denys A, Watkinson A, Pitton M et al (2010) Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. Cardiovasc Intervent Radiol 33:41–52

Lencioni R, de Baere T, Soulen MC, Rilling WS, Geschwind JFH (2016a) Lipiodol transarterial chemoembolization for hepatocellular carcinoma: a systematic review of efficacy and safety data. Hepatology 64:106–116

Lencioni R, Llovet JM, Han G, Tak WY, Yang J, Guglielmi A, Paik SW et al (2016b) Sorafenib or placebo plus TACE with doxorubicin-eluting beads for intermediate stage HCC: the SPACE trial. J Hepatol 64:1090–1098

Lencioni R, Marrero J, Venook A, Ye SL, Kudo M (2010) Design and rationale for the non-interventional global investigation of therapeutic DEcisions in hepatocellular carcinoma and of its treatment with Sorafenib (GIDEON) study. Int J Clin Pract 64:1034–1041

Llovet JM, Burroughs A, Bruix J (2003) Hepatocellular carcinoma. Lancet 362:1907–1917

Llovet JM, Decaens T, Raoul JL, Boucher E, Kudo M, Chang C, Kang YK et al (2013) Brivanib in patients with advanced hepatocellular carcinoma who were intolerant to sorafenib or for whom sorafenib failed: results from the randomized phase III BRISK-PS study. J Clin Oncol 31:3509–3516

Llovet JM, Pena CEA, Lathia CD, Shan M, Meinhardt G, Bruix J, Grp SIS (2012) Plasma biomarkers as predictors of outcome in patients with advanced hepatocellular carcinoma. Clin Cancer Res 18:2290–2300

Llovet JM, Real MI, Montana X, Planas R, Coll S, Aponte J, Ayuso C et al (2002) Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet 359:1734–1739

Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC et al (2008) Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 359:378–390

Lo CM, Ngan H, Tso WK, Liu CL, Lam CM, Poon RT, Fan ST et al (2002) Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology 35:1164–1171

Malek NP, Schmidt S, Huber P, Manns MP, Greten TF (2014) The diagnosis and treatment of hepatocellular carcinoma. Dtsch Arztebl Int 111:101–106

Meyer T, Kirkwood A, Roughton M, Beare S, Tsochatzis E, Yu D, Davies N et al (2013) A randomised phase II/III trial of 3-weekly cisplatin-based sequential transarterial chemoembolisation vs embolisation alone for hepatocellular carcinoma. Br J Cancer 108:1252–1259

Park JW, Chen M, Colombo M, Roberts LR, Schwartz M, Chen PJ, Kudo M et al (2015) Global patterns of hepatocellular carcinoma management from diagnosis to death: the BRIDGE study. Liver Int 35:2155–2166

Park Y, Kim SU, Kim BK, Park JY, Kim do Y, Ahn SH, Park YE et al (2016) Addition of tumor multiplicity improves the prognostic performance of the hepatoma arterial-embolization prognostic score. Liver Int 36:100–107

Ravi S, Singal AK (2014) Regorafenib: an evidence-based review of its potential in patients with advanced liver cancer. Core Evid 9:81–87

Raymond E, Faivre S, Douillard J, Boucher E, Lim H, Kim J, Lanzalone S et al (2007) Phase II trial of the efficacy and safety of sunitinib malate monotherapy in unresectable hepatocellular carcinoma. Ann Oncol 18: Vii15–Vii15

Santoro A, Rimassa L, Borbath I, Daniele B, Salvagni S, Van Laethem JL, Van Vlierberghe H et al (2013) Tivantinib for second-line treatment of advanced hepatocellular carcinoma: a randomised, placebo-controlled phase 2 study. Lancet Oncol 14:55–63

Shim JH, Park JW, Kim JH, An M, Kong SY, Nam BH, Choi JI et al (2008) Association between increment of serum VEGF level and prognosis after transcatheter arterial chemoembolization in hepatocellular carcinoma patients. Cancer Sci 99:2037–2044

Sieghart W, Hucke F, Pinter M, Graziadei I, Vogel W, Muller C, Heinzl H et al (2013) The ART of decision making: retreatment with transarterial chemoembolization in patients with hepatocellular carcinoma. Hepatology 57:2261–2273

Verslype C, Cohn AL, Kelley RK, Yang TS, Su WC, Ramies DA, Lee Y et al (2012) Activity of cabozantinib (XL184) in hepatocellular carcinoma: results from a phase II randomized discontinuation trial (RDT). J Clin Oncol 30

Wang G, Liu Y, Zhou SF, Qiu P, Xu L, Wen P, Wen J et al (2016) Sorafenib combined with transarterial chemoembolization in patients with hepatocellular carcinoma: a meta-analysis and systematic review. Hepatol Int 10:501–510

Zeng J, Lv L, Mei ZC (2016) Efficacy and safety of transarterial chemoembolization plus sorafenib for early or intermediate stage hepatocellular carcinoma:

a systematic review and meta-analysis of randomized controlled trials. Clin Res Hepatol Gastroenterol 40(6):688–697

Zhu AX, Finn RS, Mulcahy M, Gurtler J, Sun W, Schwartz JD, Dalal RP et al (2013) A phase II and biomarker study of ramucirumab, a human monoclonal antibody targeting the VEGF receptor-2, as first-line monotherapy in patients with advanced hepatocellular cancer. Clin Cancer Res 19:6614–6623

Zhu AX, Kang YK, Rosmorduc O, Evans TR, Santoro A, Ross P, Gane E et al (2016a) Biomarker analyses of clinical outcomes in patients with advanced hepatocellular carcinoma treated with Sorafenib with or without Erlotinib in the SEARCH trial. Clin Cancer Res 22:4870–4879

Zhu AX, Baron AD, Malfertheiner P, Kudo M, Kawazoe S, Pezet D, Weissinger F, et al. (2016b) Ramucirumab as second-line treatment in patients with advanced hepatocellular carcinoma: analysis of REACH trial results by child-pugh score. JAMA Oncol

Zhu AX, Sahani DV, Duda DG, di Tomaso E, Ancukiewicz M, Catalano OA, Sindhwani V et al (2009) Efficacy, safety, and potential biomarkers of sunitinib monotherapy in advanced hepatocellular carcinoma: a phase II study. J Clin Oncol 27:3027–3035