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EDITORIAL

Anti-angiogenesis in hepatocellular carcinoma treatment: Current evidence and future perspectives

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Abstract

Hepatocellular carcinoma (HCC) is among the most common cancer diseases worldwide. Arterial hypervascularisation is an essential step for HCC tumorigenesis and can be targeted by transarterial chemoembolization (TACE). This interventional method is the standard treatment for patients with intermediate stage HCC, but is also applied as "bridging" therapy for patients awaiting liver transplantation in many centers worldwide. Usually the devascularization effect induced by TACE is transient, consequently resulting in repeated cycles of TACE every 4-8 wk. Despite documented survival benefits, TACE can also induce the up-regulation of proangiogenic and growth factors, which might contribute to accelerated progression in patients with incomplete response. In 2007, sorafenib, a multi-tyrosine kinase and angiogenesis inhibitor, was approved as the first systemic treatment for advanced stage HCC. Other active targeted compounds, either inhibitors of angiogenesis and/or growth factors, are currently being investigated in numerous clinical trials. To overcome revascularisation or tumor progression under TACE treatment it seems therefore attractive to combine TACE with systemic targeted agents, which might theoretically block the effects of proangiogenic and growth factors. Over the last 12 mo, several retrospective or prospective cohort studies combining TACE and sorafenib have been published. Nevertheless, robust results of the efficacy and tolerability of such combination strategies as proven by randomized, controlled trials are awaited in the next two years.

Key words: Hepatocellular carcinoma; Sorafenib; Anti-angiogenesis; Transarterial chemoembolization

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INTRODUCTION

The incidence of hepatocellular carcinoma (HCC) is rising with a world-wide annual incidence above 600 000[1]. Treatment of HCC is challenging because HCC mainly occurs within liver cirrhosis[1], and therapy options and prognosis are determined by tumor biology as well as impaired liver function. Several clinical staging systems have been proposed[2]. However, the most commonly used in Western countries is the Barcelona Clinic Liver Cancer (BCLC) system[3,4]. According to this algorithm, treatment is stratified according to tumor stage, liver function, and performance status. Intermediate stage HCC (BCLC stage B) without options for surgical treatment or ablation is treated by transarterial chemoembolization (TACE). TACE has been shown to expand median survival from 16 to 19-20 mo[5,6]. In patients with advanced (BCLC stage C) and especially end-stage HCC (BCLC stage D), survival depends not only on progression of

tumor disease but depends incremental on accompanying liver dysfunction, also. Without intervention, survival of patients with advanced HCC rarely exceeds 6 mo, and median survival in patients with end-stage HCC (BCLC stage D, Okuda stage Ⅲ, performance status 3-4) is commonly below 3-4 mo[4,7-9]. According to the modified BCLC system, the dual kinase inhibitor sorafenib is considered the standard of care for patients with advanced HCC[10]. However, the survival benefit is limited to approximately 3 mo, whereas disease stabilization can be achieved in 27%-78% as shown in prospective trials[11-14].

Typically, HCC is a hypervascularized tumor with characteristic early arterial enhancement during dynamic imaging, which is the rational for TACE. By TACE, however, mainly central vessels of a tumor nodule are occluded, while progression may occur via neovascularization in the tumor periphery. In theory, this might be prevented or at least attenuated by concomitant systemic treatment with anti-angiogenic agents (Figure 1).

ANGIOGENESIS IN PATHOGENESIS OF HEPATOCELLULAR CARCINOMA

Chronic hepatitis and hepatic fibrogenesis are closely connected to angiogenesis[15]. Different cytokines, growth factors, and metalloproteinases are involved in these processes. Vascular endothelial growth factor (VEGF) was shown to be crucially involved in angiogenesis as well as fibrogenesis[15]. Despite other factors, hepatic tissue hypoxia seems to be a relevant trigger for angiogenesis in necroinflammatory liver disease, especially by induction of VEGF, resulting in increasing arterial contribution to hepatic perfusion[16,17]. At this stage, the majority of neo-vessels originate from the portal vein, supporting short-circuits between the portal vein system and the hepatic veins[16,18]. Despite the predominant occurrence of HCC in liver cirrhosis rather than in non-cirrhotic liver disease[1], it is still unknown whether HCC arises from hepatic stem cells or from hepatocytes *via* malignant transformation. The latter concept is supported by the observation that development of HCC from dysplastic nodules has been described[19,20]. Arterial hypervascularization seems to be pathognomonic for established HCC, and HCC nodules larger than 2 cm regularly show arterial enhancement[21,22]. Therefore, neovascularization seems to be crucial for HCC tumorigenesis.

Consistently, increased expression of angiopoietin-1/-2 mRNA in tumor tissue was reported, suggesting a critical role of neo-vascularisation for HCC pathogenesis[23]. Moreover, augmented expression of VEGF was found in HCC, and higher serum VEGF levels were associated with poor prognosis of patients with HCC[24-29]. In contrast, a recent study showed that neither VEGF-A nor VEGFR were up-regulated in HCC tissue, and angiotensin-1/-2 expression were only modestly changed[30]. Of note, sinusoidal capillarization suggesting vascular remodeling was observed within the same study[30]. These inconsistent data further highlight that tumor angiogenesis is a complex process and most likely heterogeneous. The angiopoietin/VEGF system seems to play an important role in angiogenesis of HCC, but other, yet incompletely understood pathways may also be involved.

THERAPEUTIC INHIBITION OF ANGIOGENESIS IN HEPATOCELLULAR CARCINOMA

Inhibition of angiogenesis is an established and successful treatment strategy in a variety of malignant diseases. The liver is predominantly supplied by the portal venous system, whereas HCC nodules are characterized by typical arterial hypervascularization. This accounts for the rationale for use of hypervascularization as a diagnostic criterion as well as development of angiogenesis inhibition treatment strategies. In the absence of targeted agents, embolization of arterial tumor vessels was established in the 1980s. Currently, TACE is commonly used in patients with HCC BCLC stage 0/A as bridging therapy until liver transplantation and as non-curative therapy in patients with HCC BCLC stage B and C[6].

Indeed, TACE may lead to reduction of tumor vascularization and viable tumor volume[6]. Recently, this has also been confirmed for a modified TACE technique using doxorubicin eluting beads (DEB)[31]. Furthermore, VEGF levels as a surrogate marker for angiogenesis were shown to correlate with therapeutic outcome after TACE. Pretreatment VEGF levels were significantly higher in patients not responding to TACE compared to patients with disease stabilization. Moreover, pretreatment VEGF serum levels > 240 pg/mL were an independent prognostic factor for survival[32].

It has been suggested that tumor progression after TACE may be caused by activation of angiogenesis due to TACE-induced hypoxemia[33]. Plasma VEGF levels were shown to increase shortly after TACE, reaching a peak value one day after TACE[34-37]. Additionally, increase of plasma VEGF levels after TACE was correlated with the development of metastasis and a reduced progression free survival[35,37]. Unfortunately, reliable biomarkers predicting response to TACE are missing. Nevertheless, a median survival of 35 mo has been reported in patients with complete tumor response[38]. In this study low VEGF levels were associated with a longer survival, while higher VEGF levels were detectable in patients without tumor response. Of note, prior TACE was reported to induce angiogenesis in surgical specimens, whereas patients who underwent surgery without prior TACE had no induction of angiogenesis[39]. Whether the use of DEB-TACE, which can induce higher rates of tumor response, also leads to upregulation of proangiogenic factors is under debate[40,41].

Sorafenib, the first systemically agent approved for HCC, is a multikinase inhibitor with activity against VEGFR2, PDGFR, c-Kit receptors, b-RAF, and p38[42], signal transduction pathways which seem to be involved in pathogenesis of HCC[43]. However, there are limita-

Table 1 Efficacy of systemic targeted monotherapy in hepatocellular carcinoma according to current phase Ⅰ-Ⅲ studies

Author	Year	Phase	Investigational drug	*n*	RR	DS	PFS/TTP	PFS-6m	OS
O'Neil *et al*[59][1]	2009	Ⅱ	AZD 6244	16	0	37.5	NR	NR	NR
Malka *et al*[60]	2007	Ⅱ	Bevacizumab	30	12.5	54	3.5/NR	17	NR
Schwartz *et al*[61]	2006	Ⅱ	Bevacizumab	30	6.7	57	NR/6.4	NR	NR
Siegel *et al*[58]	2008	Ⅱ	Bevacizumab	46	13	NR	6.9/NR	NR	12.4
Raoul *et al*[62]	2009	Ⅱ	Brivanib	55	11	10	NR/2.8	NR	10
Gruenwald *et al*[63]	2007	Ⅱ	Cetuximab	27	0	44	2.0/1.9	22.2	NR
Zhu *et al*[64]	2007	Ⅱ	Cetuximab	30	0	17	1.4/NR	NR	9.6
Philip *et al*[65]	2005	Ⅱ	Erlotinib	38	9	50	3.2/NR	32	13
Thomas *et al*[66]	2007	Ⅱ	Erlotinib	40	0	43	3.1/NR	NR	6.25 (10.75)[2]
Blaszkowsky *et al*[67]	2010	Ⅲ	Everolimus	25	4	44	3.8/3.9	8%	8.4
O'Dwyer *et al*[68]	2006	Ⅱ	Gefitinib	31	3	22.5	2.8/NR	NR	6.5
Lin *et al*[69]	2008	Ⅱ	Imatinib	15	0	13.3	NR/NR	NR	NR
Ramanathan *et al*[70]	2006	Ⅱ	Lapatinib	37	5	35	2.3/NR	2.3	6.2
Rizell *et al*[71]	2008	Ⅱ	Sirolimus	21	4.8	23.8	NR/NR	NR	6.5
Abou-Alfa *et al*[12]	2006	Ⅱ	Sorafenib	137	2.2	33.6	NR/4.2	NR	9.2
Cheng *et al*[72]	2009	Ⅲ	Sorafenib	226 (150 treated)	3.3	54	NR/2.8	NR	6.5
Furuse *et al*[13]	2008	Ⅰ	Sorafenib	27	4	83	NR/4.9	46.2	15.6
Llovet *et al*[11]	2008	Ⅲ	Sorafenib	602 (299 treated)	2	71	NR/5.5	NR	10.7
Yau *et al*[14]	2009	Ⅱ	Sorafenib	51	8	18	3.0/NR	NR	5
Zhu *et al*[73]	2009	Ⅱ	Sunitinib	34	2.9	47	3.9/4.1	NR	9.8
Faivre *et al*[74]	2009	Ⅱ	Sunitinib	37	2.7	35	3.7/5.3	NR	8
Hoda *et al*[75]	2008	Ⅱ	Sunitinib	23	6	35	NR/NR	NR	NR
Koeberle *et al*[54]	2010	Ⅱ	Sunitinib	45	2	40	2.8/2.8	NR	9.3
Kanai *et al*[57]	2010	Ⅰ/Ⅱ	TSU-68	35	8.6	42.8	NR/2.1	NR	13.1

[1]Trial stopped; [2]Recorded from therapy start (recorded from diagnosis). DS: Disease stabilization (%); NR: Not reported; OS: Overall survival (mo); PFS/TTP: Progression free survival/time to progression (mo); PFS-6m: Progression free survival rate at 6 mo (%); RR: Response rate [complete + partial response (%)].

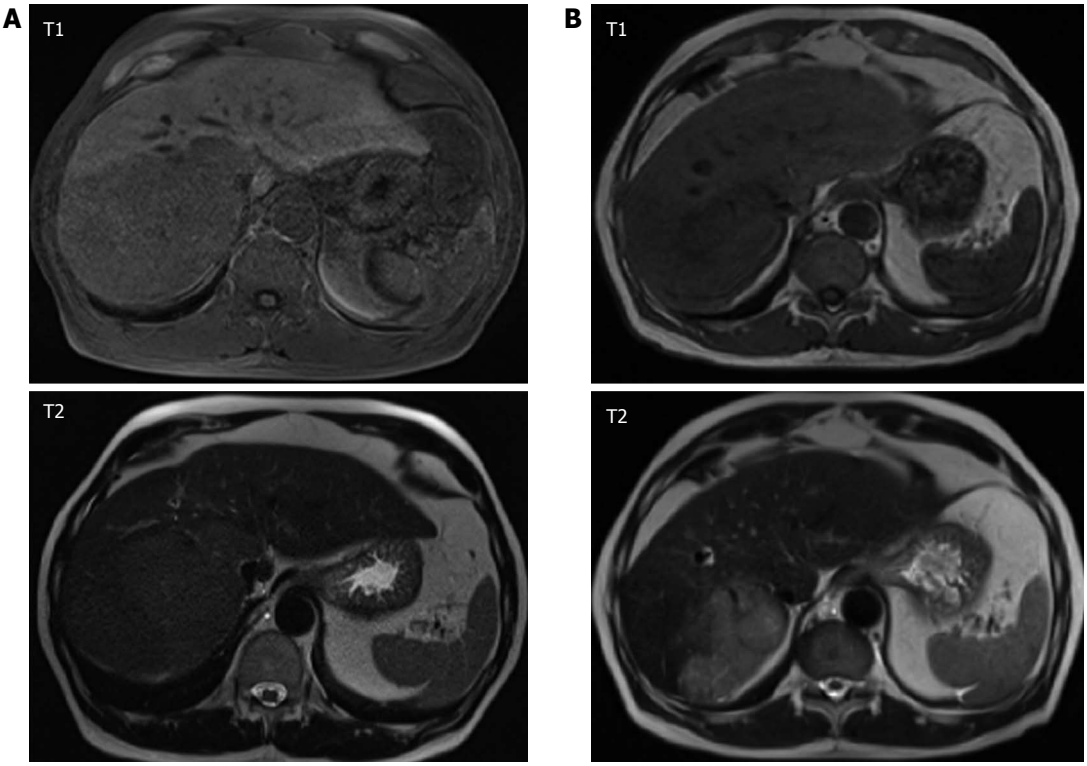

Figure 1 Dynamic gadolinium-enhanced magnetic resonance imaging (MRI; T1, T2 weighting), in a 67 year old patient with hepatocellular carcinoma evolved from liver cirrhosis due to hemochromatosis (A) before initiation of anti-angiogenic therapy and (B) after 70 d or three cycles of transarterial chemoembolization and continuous administration of sorafenib, respectively. Patient showed partial response according to RECIST criteria. Serum alfa-fetoprotein level decreased from 276 to 115 ng/mL.

tions on the therapy with sorafenib, founded on restricted efficacy and potential side effects, mainly fatigue, diarrhea and hand-food syndrome. In comparison to TACE valid predictive biomarkers are missing, also[11].

Table 2 Efficacy of combination therapy with systemic acting agents and targeted therapy in hepatocellular carcinoma according to current phase Ⅰ-Ⅱ studies

Author	Year	Phase	Investigational drug	*n*	RR	DS	PFS/TTP	PFS-6m (%)	OS
Sun *et al*[76]	2007	Ⅱ	Bevacizumab/CapOx	30	11	78	4.5/NR	40	NR
Thomas *et al*[55]	2009	Ⅱ	Bevacizumab/erlotinib	40	25	42.5	9.0/NR	NR	15.7
Hsu *et al*[77]	2008	Ⅱ	Bevacizumab/capecitabine	45	9	42	4.1/NR	NR	10.7
Zhu *et al*[78]	2006	Ⅱ	Bevacizumab/GemOX	33	20	27	5.3/NR	NR	9.6
Berlin *et al*[79]	2008	Ⅱ	Bortezomib/doxorubicin	39	2.3	25.6	2.4/NR	NR	5.7
Asnacios *et al*[80][1]	2008	Ⅱ	Cetuximab/GemOx	45	20	40	4.7/NR	NR	9.5
Louafi *et al*[81][1]	2007	Ⅱ	Cetuximab/GemOx	35	24	4.5	NR/NR	40	9.2
Knox *et al*[82][2]	2008	Ⅱ	G3139/doxorubicin	17	0	35	NR/1.8	17.2	5.4
Abou-Alfa *et al*[83][3]	2010	Ⅱ	Sorafenib/doxorubicin	96	4	77	6.9/8.6	2.7	13.7
Richly *et al*[84]	2009	Ⅰ	Sorafenib/doxorubicin	18	6.3	69	4.0[4]/NR	NR	NR

[1]Overlap of patient cohorts cannot be excluded from information provided in the abstracts; [2]Trial stopped due to lack of efficacy; [3]Trial stopped due to superiority of sorafenib; [4]Calculated from a median duration of disease control rate (combined endpoint for complete and partial response as well as stable disease) of 17.4 wk. CapOx: Capecitabine and oxaliplatin; DS: Disease stabilization (%); GemOx: Gemcitabine and oxaliplatin; NR: Not reported; OS: Overall survival (mo); PFS/TTP: Progression free survival/time to progression (mo); PFS-6m: Progression free survival rate at 6 mo (%); RR: Response rate [complete + partial response (%)].

Table 3 Efficacy of sorafenib and transarterial chemoembolization in hepatocellular carcinoma (sequential therapy not included) according to current phase Ⅰ-Ⅱ studies

Author	Year	Phase	Investigational drug	*n*	RR	DS	PFS/TTP	OS
Chow *et al*[45]	2010	Ⅱ	Sorafenib + SIRT	35	31.4	77.1	NR/NR	10.8
Chung *et al*[47][1]	2010	Ⅱ	Sorafenib + TACE	50	NR[2]	96	NR/NR	NR
Dufour *et al*[48]	2010	Ⅰ	Sorafenib + TACE	14	NR[3]	NR[3]	NR[3]	NR[3]
Erhardt *et al*[46][1]	2009	Ⅱ	Sorafenib + TACE	44	NR[4]	63.6	8.0/16.1	11.7
Reyes *et al*[49][1]	2009	Ⅱ	Sorafenib + DEB-TACE	50	NR[5]	NR	NR/NR	NR

[1]Interim analysis; [2]20/50 patients received 2 cycles of transarterial chemoembolization (TACE), only, and 18 of these 20 patients achieved complete response compared to 2 patients with progressive disease. 30/50 patients received more than 2 cycles of TACE and achieved partial response or stable disease; [3]Primary objective of this prospective trial was evaluation of safety and tolerability of a continuous regimen of sorafenib combined with TACE; [4]According to 31 patients who received at least 1 cycle of TACE, 2/31 (6.5%) showed complete response, 15/31 (48.4%) showed partial response, and 11/31 (35.5%) showed stable disease. PFS, TTP, and OS are given for all 44 patients enrolled at time point of interim analysis; [5]Patients who completed DEB-TACE showed 100% objective tumor response and 100% partial response or stable disease according to EASL or RECIST criteria, respectively. DEB-TACE: (Drug eluting beads)-transarterial chemoembolization; NR: Not reported; DS: Disease stabilization (%); OS: Overall survival (mo); PFS/TTP: Progression free survival/time to progression (mo); PFS-6m: Progression free survival rate at 6 mo (%); RR: Response rate [complete + partial response (%)]; SIRT: Selective internal radio therapy.

STRATEGIES FOR COMBINATION OF TACE AND TARGETED AGENTS IN HCC

Combination of local and systemic inhibition of angiogenesis seems to be a consequential step to improve outcome in intermediate and advanced stage HCC[44]. Tolerability of combination therapy with sorafenib and conventional TACE as well as DEB-TACE was shown within different trials[45-49]. Currently, the combination of conventional TACE and sorafenib as well as combination of sorafenib and DEB-TACE (SPACE trial) is being evaluated in phase Ⅱ and Ⅲ trials[50]. Moreover, sorafenib was combined with selective internal radiation therapy within a multicenter phase Ⅱ study showing good efficacy in patients with advanced HCC but without extra-hepatic metastasis[45]. So far, no increased toxicity has been reported. The combination of brivanib, a dual VEGFR and fibroblast growth factor inhibitor[51], and TACE is currently evaluated within the multicenter phase Ⅲ BRISK TA Study.

Another interesting approach could be the inhibition of VEGF driven angiogenesis by targeting VEGF with siRNA as shown in a proof-of-concept study recently[52]. Furthermore, promising results were reported for other agents alone or in combination with TACE, e.g. tegafur/uracil, the multi-tyrosine kinase inhibitor TSU-68, sunitinib, erlotinib, and the VEGF antibody bevacizumab[53-57]. However, none of these agents is approved for HCC. Of these, bevacizumab is the currently most commonly clinical used VEGF inhibitor in a variety of malignant entities. However, despite encouraging results in earlier trials, even as single agent treatment, bleeding complications were reported in up to 11% of patients treated with bevacizumab[58]. For the combination of bevacizumab with TACE, severe bleeding and septic complications have been reported in 25% of patients, and the AVATACE-1 trial investigating TACE in combination with bevacizumab has been terminated due to safety concerns in the treatment arm, which does not justify a further clinical development of bevacizumab in this indication. This highlights that large phase Ⅲ trials are required for new agents in HCC, which seems challenging given the increasing number of phase Ⅰ and Ⅱ studies addressing HCC in the last years (Tables 1-3).

In summary, inhibition of angiogenesis in HCC seems a very promising approach for future treatment

of HCC. Multimodal approaches with combination of local and systemic therapy may further improve survival in intermediate and advanced stage HCC.

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