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 transcatheter arterial 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.

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[2], and therapy options and prognosis are determined by tumor biology as well as impaired liver function. Several clinical staging systems have been proposed[3]. However, the most commonly used in Western countries is the Barcelona Clinic Liver Cancer (BCLC) system[4-6]. 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 transcatheter chemoembolization (TACE). TACE has been shown to expand median survival from 16 to 19-20 mo[7,8]. 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\(^{1,5,6}\). According to the modified BCLC system, the dual kinase inhibitor sorafenib is considered the standard of care for patients with advanced HCC\(^{19}\). 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\(^{13}\). 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\(^{15,19}\). 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\(^{10,17}\). 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\(^{11}\), 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 angiotopoietin-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\(^{30}\).

Indeed, TACE may lead to reduction of tumor vascularization and viable tumor volume\(^{31}\). 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\(^{38,39}\). 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\(^{15}\). However, there are limita-
tions on the therapy with sorafenib, founded on re-
stricted efficacy and potential side effects, mainly fatigue,
diarrhea and hand-food syndrome. In comparison to 
TACE valid predictive biomarkers are missing, also[11].

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Phase</th>
<th>Investigational drug</th>
<th>n</th>
<th>RR</th>
<th>DS</th>
<th>PFS/TTP</th>
<th>PFS-6m</th>
<th>OS</th>
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<tbody>
<tr>
<td>O’Neil et al[59]</td>
<td>2009</td>
<td>Ⅱ</td>
<td>AZD 6244</td>
<td>16</td>
<td>0</td>
<td>37.5</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Malka et al[60]</td>
<td>2007</td>
<td>Ⅱ</td>
<td>Bevacizumab</td>
<td>30</td>
<td>12.5</td>
<td>54</td>
<td>3.5/NR</td>
<td>17</td>
<td>NR</td>
</tr>
<tr>
<td>Schwartz et al[61]</td>
<td>2006</td>
<td>Ⅱ</td>
<td>Bevacizumab</td>
<td>30</td>
<td>6.7</td>
<td>57</td>
<td>6.4/NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Siegel et al[62]</td>
<td>2008</td>
<td>Ⅱ</td>
<td>Bevacizumab</td>
<td>46</td>
<td>13</td>
<td>NR</td>
<td>6.9/NR</td>
<td>NR</td>
<td>12.4</td>
</tr>
<tr>
<td>Raoul et al[63]</td>
<td>2009</td>
<td>Ⅱ</td>
<td>Brivanib</td>
<td>55</td>
<td>11</td>
<td>10</td>
<td>NR/2.8</td>
<td>NR</td>
<td>10</td>
</tr>
<tr>
<td>Gruenwald et al[64]</td>
<td>2007</td>
<td>Ⅱ</td>
<td>Cetuximab</td>
<td>27</td>
<td>0</td>
<td>44</td>
<td>2.0/1.9</td>
<td>22.2</td>
<td>NR</td>
</tr>
<tr>
<td>Schwartz et al[65]</td>
<td>2006</td>
<td>Ⅱ</td>
<td>Cetuximab</td>
<td>30</td>
<td>0</td>
<td>17</td>
<td>1.4/NR</td>
<td>NR</td>
<td>9.6</td>
</tr>
<tr>
<td>Philip et al[66]</td>
<td>2005</td>
<td>Ⅱ</td>
<td>Erlotinib</td>
<td>38</td>
<td>9</td>
<td>50</td>
<td>3.2/NR</td>
<td>32</td>
<td>13</td>
</tr>
<tr>
<td>Thomas et al[67]</td>
<td>2007</td>
<td>Ⅱ</td>
<td>Erlotinib</td>
<td>40</td>
<td>0</td>
<td>43</td>
<td>3.1/NR</td>
<td>NR</td>
<td>6.25 (10.75)</td>
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<tr>
<td>Blaszkowsky et al[68]</td>
<td>2010</td>
<td>Ⅲ</td>
<td>Everolimus</td>
<td>25</td>
<td>4</td>
<td>44</td>
<td>3.8/3.9</td>
<td>8%</td>
<td>8.4</td>
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<tr>
<td>O’Dwyer et al[69]</td>
<td>2006</td>
<td>Ⅱ</td>
<td>Gefitinib</td>
<td>31</td>
<td>3</td>
<td>22.5</td>
<td>2.8/NR</td>
<td>NR</td>
<td>6.5</td>
</tr>
<tr>
<td>Lin et al[70]</td>
<td>2008</td>
<td>Ⅱ</td>
<td>Imatinib</td>
<td>15</td>
<td>0</td>
<td>13.3</td>
<td>NR/NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Ramanathan et al[71]</td>
<td>2006</td>
<td>Ⅱ</td>
<td>Lapatinib</td>
<td>37</td>
<td>5</td>
<td>35</td>
<td>2.3/NR</td>
<td>2.3</td>
<td>6.2</td>
</tr>
<tr>
<td>Rixe et al[72]</td>
<td>2008</td>
<td>Ⅱ</td>
<td>Sirolimus</td>
<td>21</td>
<td>4.8</td>
<td>23.8</td>
<td>NR/NR</td>
<td>NR</td>
<td>6.5</td>
</tr>
<tr>
<td>Abou-Alfa et al[73]</td>
<td>2009</td>
<td>Ⅱ</td>
<td>Sorafenib</td>
<td>137</td>
<td>2.2</td>
<td>33.6</td>
<td>NR/4.2</td>
<td>NR</td>
<td>9.2</td>
</tr>
<tr>
<td>Cheng et al[74]</td>
<td>2009</td>
<td>Ⅲ</td>
<td>Sorafenib</td>
<td>226 (150 treated)</td>
<td>3.3</td>
<td>54</td>
<td>NR/2.8</td>
<td>NR</td>
<td>6.5</td>
</tr>
<tr>
<td>Furuse et al[75]</td>
<td>2008</td>
<td>Ⅰ</td>
<td>Sorafenib</td>
<td>27</td>
<td>4</td>
<td>83</td>
<td>NR/4.9</td>
<td>46.2</td>
<td>15.6</td>
</tr>
<tr>
<td>Llovet et al[76]</td>
<td>2008</td>
<td>Ⅱ</td>
<td>Sorafenib</td>
<td>27</td>
<td>4</td>
<td>83</td>
<td>NR/4.9</td>
<td>46.2</td>
<td>15.6</td>
</tr>
<tr>
<td>Yau et al[77]</td>
<td>2009</td>
<td>Ⅱ</td>
<td>Sorafenib</td>
<td>602 (299 treated)</td>
<td>2</td>
<td>71</td>
<td>NR/5.5</td>
<td>NR</td>
<td>10.7</td>
</tr>
<tr>
<td>Zhang et al[78]</td>
<td>2009</td>
<td>Ⅱ</td>
<td>Sunitinib</td>
<td>33</td>
<td>2.9</td>
<td>47</td>
<td>3.9/4.1</td>
<td>NR</td>
<td>9.8</td>
</tr>
<tr>
<td>Fazli et al[79]</td>
<td>2009</td>
<td>Ⅱ</td>
<td>Sunitinib</td>
<td>37</td>
<td>2.7</td>
<td>35</td>
<td>3.7/5.3</td>
<td>NR</td>
<td>8</td>
</tr>
<tr>
<td>Hida et al[80]</td>
<td>2008</td>
<td>Ⅱ</td>
<td>Sunitinib</td>
<td>23</td>
<td>6</td>
<td>35</td>
<td>NR/NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Kooberle et al[81]</td>
<td>2010</td>
<td>Ⅱ</td>
<td>Sunitinib</td>
<td>45</td>
<td>2</td>
<td>40</td>
<td>2.8/2.8</td>
<td>NR</td>
<td>9.3</td>
</tr>
<tr>
<td>Kanai et al[82]</td>
<td>2010</td>
<td>Ⅰ/Ⅱ</td>
<td>TSU-68</td>
<td>35</td>
<td>8.6</td>
<td>42.8</td>
<td>NR/2.1</td>
<td>NR</td>
<td>13.1</td>
</tr>
</tbody>
</table>

1Trial stopped; 2Recorded 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 che-
moembolization 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.
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\[45-49\]. 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\[50-54\]. 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\[55\]. 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.

REFERENCES

34. Li X, Feng GS, Zheng CS, Zhuo CK, Liu X. Expression of


