

## Transcatheter Arterial Chemoembolisation for the Treatment of Hepatocellular Carcinoma

a report by

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Hepatocellular carcinoma (HCC) is the fifth leading cause of cancer worldwide, and its incidence is constantly increasing.<sup>1,2</sup> There are 13,000–19,000 cases per year in the US and 350,000 to one million cases per year worldwide.<sup>3–5</sup> Chronic hepatitis C (HCV) infection and improved survival of patients with cirrhosis seem to account for most of this rising incidence.<sup>6</sup>

Treatment is dependent on disease status, including size and number of lesions, patient's hepatic reserve and other co-morbidities. Partial hepatic resection with adequate margins and liver transplantation are potentially curative surgical options for selected patients. However, only 30–40% of patients with HCC qualify for surgery, leaving the rest to pursue non-surgical palliative options.<sup>7</sup> In this direction, innovative local ablative therapies for HCC have recently shown great progress and promising results. Among them, transcatheter arterial chemoembolisation is a minimally invasive approach for the palliative treatment of unresectable HCC that constantly evolves, in terms of utilized drugs, embolic materials, technical, and technological advances.

This article outlines the current status of this image-guided intervention for treatment of HCC and introduces some new concepts and advances in the era of minimally invasive therapy of HCC.

### Chemoembolisation Technique

The technique of transcatheter arterial chemoembolisation (TACE) exploits HCC preferential blood supply from the hepatic artery to deliver the anti-tumor therapy, while sparing the surrounding liver parenchyma.<sup>8,9</sup> Since TACE was introduced as a palliative treatment in patients with unresectable HCC, it has become one of the most common procedures in interventional radiology. Currently, chemoembolisation is the preferred treatment for unresectable HCC.<sup>10–12</sup> TACE is also employed as an adjunctive therapy to liver resection or as a bridge to liver transplantation, as well as prior to radiofrequency ablation (RFA).<sup>13–17</sup>

TACE involves the injection of chemotherapeutic agents, with or without lipiodol and embolic agents, into the branch of the hepatic artery that feeds the tumor.<sup>18</sup> Contraindications to this technique are constantly reviewed. The absence of hepatopedal blood flow (portal vein thrombosis), the presence of encephalopathy and biliary obstruction are currently re-evaluated as absolute contraindications, whereas relative contraindications include a variety of other factors, such as:

- serum bilirubin >2mg/dL;
- lactate dehydrogenase >425U/L;
- aspartate aminotransferase >100U/L;
- tumor burden involving >50% of the liver;
- cardiac or renal insufficiency;
- ascites;
- recent variceal bleeding; or
- significant thrombocytopenia.

Several variations of TACE protocols have been used to combat HCC; however, neither the optimal chemotherapeutic agent nor the best embolisation method has yet been established. Non-occlusive and occlusive techniques have been described and single drug therapies or combinations of agents have been used.<sup>19</sup> Several types of embolic agents have been utilized in conjunction with lipiodol for chemoembolisation, including gelfoam powder and pledgets, polyvinyl alcohol, starch, and glass microspheres.<sup>19</sup>

The most widely used single chemotherapeutic agent is doxorubicin and the combination of cisplatin, doxorubicin, and mitomycin C is the most common drug combination infused. The issue of how selectively the catheter should be placed (lobar or segmental) during chemoembolisation remains controversial. In the case of multiple tumors in a single lobe, a less selective approach is preferred, whereas a single lesion may allow a more selective engagement of the feeding vessel. The initial concept of arterial occlusion as part of the chemoembolisation procedure, which simulates surgical arterial ligation, was justified by the fact that some degree of ischemia within a tumor is likely to be synergistic in achieving a tumor response, whereas reduced inflow to tumor

extends the effective time period of drug contact with the tumor cells and achieves higher concentrations of the drug regimen. However, several recent studies have shown that tumor ischemia and hypoxia upregulate several molecular factors, such as the vascular endothelial growth factor (VEGF) and hypoxia inducible factor-1 (HIF-1), thereby preventing cell apoptosis, and stimulating tumor metabolism, growth and invasion.<sup>20,21</sup> Furthermore, improved tumor response has been shown when chemoembolisation can be repeated multiple times, and the maintenance of long-term arterial patency for repetitive treatment is highly desirable.<sup>22,23</sup>

### Assessing the Effectiveness of TACE

Assessing the effectiveness of TACE is critical in determining the success of treatment. Reduction in tumor size, according to the World Health Organization (WHO) and the Response Evaluation Criteria in Solid Tumors (RECIST),<sup>24,25</sup> is the desirable outcome for every chemoembolisation procedure. Tumor enhancement on computed tomography (CT) or magnetic resonance imaging (MRI) may additionally show treatment response, as enhancing portions of the tumor are presumed to be viable, whereas the non-enhancing ones are presumed necrotic.<sup>26–28</sup> However, CT scanning after chemoembolisation can be difficult to interpret because of the presence of lipiodol, which, due to its radiopacity, obscures tumor enhancement. Furthermore, functional MRI has recently been utilized as a new means of assessing tumor response by measuring changes in free water content within the tumor. Breakdown of cellular membranes indicate cell death and, as such, can be imaged using functional MRI. An increase in free water content within the tumor will therefore be shown as a bright signal on MRI.<sup>29</sup>

In the early post-treatment period after TACE, tumors are not expected to change in size despite the fact that they may be non-viable.<sup>30,31</sup> Shrinkage of the tumor may take six months or more to meet partial response criteria as defined by RECIST, namely, a decrease in diameter of 25%.

### Survival Benefit of Patients Treated with Chemoembolisation

The median survival of patients with inoperable HCC is four to seven months (that can be extended with maximal supportive care to approximately 10 months). Despite the widespread acceptance of TACE, some initial large randomized trials failed to demonstrate a survival advantage.<sup>10,32,33</sup> Chemoembolisation reduced

tumor growth but was not associated with significantly improved survival compared with the conservative management of patients with advanced HCC. However, skepticism was put aside when two randomized controlled trials showed a survival advantage for TACE in selected patients with preserved liver function and supportive maintenance.<sup>11,12</sup>

A meta-analysis that included seven randomized trials of arterial embolisation for unresectable HCC provided further support of the efficacy of TACE.<sup>14</sup> Compared with control (either conservative treatment or less favourable therapy, such as intravenous (IV) 5-fluorouracil), there was a statistically significant improvement in two-year survival with arterial chemoembolisation (odds ratio (OR) 0.53, 95% confidence interval (CI) 0.32–0.89).<sup>14</sup> TACE showed a median survival of more than two years and, although rarely, converted some patients into operable candidates.

### New Concepts and Future Directions

The main target of TACE is to reduce systemic toxicity, increase the therapeutic efficacy and provide a sustained release over time of chemotherapy without damaging the healthy surrounding hepatic parenchyma. Ultimately, improvements in patient quality of life and survival constitute the ideal end-points of any successful chemoembolisation procedure. To that end, intense research activity is taking place to develop new drugs, drug carriers, and imaging technology. A selection of this new field of activity follows.

#### The Introduction of Drug Carriers for Transcatheter Arterial Infusion

Currently, on-going research activity in the area of drug delivery systems has been applied for treatment of primary liver cancer. In the setting of intra-arterial infusion for HCC, these drug carriers should present some essential qualities such as precise delivery, controlled and sustained release, and high intra-tumoral concentration for a sufficient time without damaging the surrounding hepatic parenchyma. Several drug delivery systems for intra-arterial treatment of hepatic lesions have recently been tested.<sup>34–37</sup> Polyvinyl alcohol (PVA) microspheres can be loaded with a single chemotherapeutic agent, such as doxorubicin, and infused intra-arterially for selective tumor targeting.<sup>35</sup> The controlled porosity of these beads allows accurate and controlled loading of doxorubicin, thereby achieving better tumor response rates.<sup>35</sup> Recent animal studies on a model of liver cancer have shown that the concentration of doxorubicin within the tumor remains high up to 14

days post-transcatheter infusion, suggesting continuous release of doxorubicin from the microspheres, whereas systemic drug concentration is kept at a minimal level.<sup>38</sup> However, further clinical studies are needed to support this initial report of efficacy in the animals.

#### Direct Intra-arterial Injection of 3-Bromopyruvate

In the era of development of less toxic drugs for treatment of liver cancer, inhibition of cancer metabolism seems to be an appealing potent novel option. 3-Bromopyruvate (3-BrPa) is a hexokinase II-specific inhibitor that potently abolishes cell adenosine triphosphate (ATP) production via the inhibition of glycolysis.<sup>39</sup> Preliminary experiments on the rabbit VX2 tumor model for liver cancer with direct intra-arterial infusion of 3-BrPa showed very specific necrosis of the implanted lesions.<sup>39,40</sup> Additionally, intra-arterial injection did not affect the viability of surrounding normal liver tissues, and did not damage the animals' major tissues during systemic infusion.<sup>39</sup> In a recent study conducted on human hepatoma cell lines, 3-BrPa induced HCC cell apoptosis, besides inhibiting ATP production.<sup>41</sup> It should be noted that previous studies have suggested that apoptosis is an ATP-dependent process.<sup>42</sup> In another study, depletion of ATP by glycolytic inhibition induced apoptosis in multidrug-resistant cells, suggesting that deprivation of cellular energy supply may be an effective way to overcome multidrug resistance of cancerous cells.<sup>43</sup> These preliminary results show that the direct intra-arterial infusion of 3-BrPa may serve as an effective approach for

targeting liver cancer. However, further development and studies of this glycolytic inhibitor are necessary to establish its clinical therapeutic safety and efficacy.

#### Three-dimensional Rotational Angiography as an Adjunctive Tool for Successful TACE

Three-dimensional rotational angiography (3D-RA) is a relatively new modality used in endovascular procedures. The use of 3D-RA can be very useful to the interventional radiologist during TACE while the patient is on the catheterisation table. In a recent report, 3D-RA was found to help treat patients successfully, especially when complex vascular anatomy was present.<sup>44</sup> In these patients, the use of this new technology may assist in minimising procedure risks and complications and may lead to an effective treatment and improved quality of care. Further studies should be performed to assess radiation exposure and potential cost-effectiveness for the use of this technology.

#### Conclusion

Despite recent progress and research activity on chemoembolisation for the treatment of unresectable HCC, there are still unanswered questions on how to improve its efficacy and ultimately prolong patient survival. These questions may be resolved by controlled randomized trials. Parallel on-going research on the etiology, prevention, and surveillance of HCC may also contribute to a more successful therapeutic approach of this highly lethal entity. ■

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