Transarterial chemoembolisation with degradable starch microspheres (DSM-TACE): an alternative option for advanced HCC patients?

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Aims and objectives

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third leading cause of cancer-related deaths in the world. [1, 2]

The Barcelona clinic liver cancer (BCLC) classification is the current standard classification system for clinical management of patients with HCC and divides HCC patients in 5 stages (0 - very early stage, A - early stage, B - intermediate stage, C - advanced stage and D - end stage). [3, 4]

Advanced HCC patients (BCLC stage C) with cancer related symptoms (symptomatic tumors, ECOG 1-2), macrovascular invasion (either segmental or portal invasion) or extrahepatic spread (lymph node involvement or metastases) bear a dismal prognosis, with expected median survival times of 6 months, or 25% at 1 year. [5, 6] In this group of patients, in case of well-preserved liver function (Child-Pugh A class), the only therapy that demonstrated survival benefits is represented by Sorafenib, a raf-, vascular endothelial growth factor (VEGF) receptor-, platelet-derived growth factor (PDGF) receptor-blocking multikinase tyrosine kinase inhibitor (TKI).

In 2008 the SHARP Investigators Study Group, and thereafter the Asia Pacific trial, demonstrated that sorafenib prolongs time to progression (SHARP trial: sorafenib group 5.5 months vs placebo group 2.8 months, p<0.001; Asia-Pacific trial: sorafenib 2.8 months vs placebo 1.4 months, p<0.001), but no significant differences in terms of median time to symptomatic progression were observed. Moreover, the SHARP Investigators Study Group observed an overall incidence of treatment-related adverse events of 80% in the sorafenib group (predominantly grading 1 or 2 in severity and gastrointestinal, constitutional, or dermatologic in nature -diarrhea, weight loss, hand-foot skin reaction, alopecia, anorexia, and voice changes- heading for permanent treatment discontinuation in 11% of cases. However, to date, there is no approved alternative in patients dismissing or ineligible for Sorafenib. [4-9, 11-14]

Based on this background, it would be useful to find an acceptable and adequate alternative treatment option. It could be achieved due to the development of degradable starch microspheres (EmboCept®S 50µm, 450mg/7.5ml Pharmacept). In detail, Embocept consists of a suspension of starch microspheres rapidly and completely degradable by liver #-amylase in 25-40 minutes from the infusion, allowing a temporally occlusion of the smaller arterial vessels, improving the therapeutic effect, leading to a lower risk of systemic toxicity and post-embolic syndrome potentially eligible also for advanced patients. [10, 15, 16]

The aim of this pilot study was to evaluate the feasibility, safety, tolerance, and efficacy of DSM-TACE loaded with doxorubicin in the treatment of patients with advanced HCC ineligible for sorafenib administration for clinical contraindication or due to unbearable side effects.
Methods and materials

Study design/Study population

This is a prospective single-center multidisciplinary phase II pilot study to test the feasibility, safety, reproducibility and effectiveness of transarterial chemoembolisation with degradable-starch-microspheres (DSM-TACE). All enrolled patients were affected by advanced HCC, ineligible for sorafenib administration or dismissing it due to unbearable side effects. The study was conducted according to the protocol and the principles laid down in the Declaration of Helsinki, in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guideline for Good Clinical Practice (GCP). The study was approved by our Ethics Committee and informed consent was obtained from all subjects prior to any treatment.

All patients were evaluated by a tumor board (HepatoCatt group) composed by all medical specialists involved in HCC patients’ management (hepatologist, oncologist, hepatic and transplant surgeon, nuclear physician, radiotherapist, radiologist and interventional radiologist), based on the clinical-laboratoristic and radiological exams evaluation (CT-MR).

Requirements for inclusion were: (a) advanced HCC in patients dismissing or ineligible to sorafenib administration, (b) liver cirrhosis classified as Child-Pugh score A5-6 or B7. The exclusion criteria were: (a) Child-Pugh score B #8 or class C, (b) performance status (ECOG) # 2, (c) platelet count < 40,000/µL and/or international normalized ratio >1.5, (d) severe renal impairment or serum creatinine levels # 2 mg/dl, (e) doxorubicin administration contraindications, (e) total bilirubin levels # 3mg/dl.

Primary endpoints were: overall disease control (ODC), calculated as the sum of objective responses and stable diseases, and safety, evaluated as the occurrence of adverse events.

Treatment

DSM-TACE was always performed in an angiography suite with the structural characteristics of an operating room, with monitoring of vital signs and anesthesia care, by an interventional radiologist with 10 years of experience in interventional procedures at the time of beginning of this study. The treatment was performed under local anesthetics through a femoral approach, with a Seldinger needle, by using a 5F 12-cm arterial introducer sheath (Terumo, UK, Ltd.). The selective celiac catheterization and the cannulation of common hepatic artery were performed with a 5F diagnostic catheter (Cobra, Simmons). An hepatic angiography was then obtained to identify the appropriate anatomy of the hepatic artery and of any possible branches related to non-
target structures, and exclude any arteriovenous fistulae. After diagnostic angiography, a superselective lobar catheterization was performed with a coaxial technique, placing a 2.7-Fr microcatheter (Progreat; Terumo, Tokyo, Japan) in the right or left hepatic artery that was feeding the tumor lesions. A superselective lobar angiography was then performed to confirm the correct position of microcatheter, to identify/protect non-hepatic arteries and limit any possible extrahepatic perfusion of the treatment. In particular, identification of cystic artery was recommended to ensure that the catheter tip would bypass this anatomical point to avoid extrahepatic infusion into the gallbladder.

Locoregional drug infusion was preceded by atropine (0.5 mg/ml), intra-arterial administration of dexamethasone (1 mg/kg in 30 ml) and transcatheter intra-arterial infusion of 2-4mL of lidocaine (1%).

Under fluoroscopic guidance, a solution of 7.5ml of Embocept (EmboCept®S 50µm, 450mg/7.5ml - PharmaCept) loaded with 50mg of Adriblastin, followed by 2.5ml of unloaded Embocept was slowly infused until a slow flow or near stasis was observed.

All the patients received antibiotic to prevent infection before and after treatment for seven days; we used ciprofloxacin, a second-generation fluoroquinolone at dosage of 500 mg/day.

On the basis of extent and distribution of the disease, it was decided to carry out a single lobe or a bilobar treatment with 1 treatment session for every lobe involved, with a 2 week interval in case of bilobar disease up to a maximum of 4 sessions. [17]

**Post-treatment and Follow-up Studies**

Perioperative morbidity and mortality included major/minor complications and death occurring within 7 days from treatment were registered.

Procedural safety was evaluated using liver function peri-procedural laboratoristic exams and multiphasic CT study performed at 4 ± 1 weeks after complete treatment, also to plan a new treatment session, if necessary.

Treatment efficacy based on #-fetoprotein dosage and mRECIST criteria, in terms of complete response (CR), partial response (PR), stability disease (SD) and local tumor progression (LTP), was evaluated on Multiphasic CT exam performed every 3 months thereafter. [17]

**Results**

**Study population**
Between November 2013 and March 2014, 10 consecutive patients with advanced HCC dismissing or ineligible for sorafenib administration were enrolled. The main features of patients and tumors are reported in Table I.

**Intraprocedural/post-treatment results**

A total of 18 treatments were performed. Technical success was achieved in all patients. No major complications were registered. Minor complications were increased serum level of transaminases compared to basal value (2 patients, 20%), and transient cholecystitis (1 patients, 10%).

Based on m-RECIST criteria, at 1-month follow-up, six partial responses (60%) and 2 stable disease (20%) with an overall disease control of 80% were observed. In these patients with ODC, a repeated DSM-TACE schedule treatment was performed.

During the mean follow-up of 7 months (range: 4 -10 months), a ODC of 70% was obtained (PR: 20%; SD: 50%).

**Images for this section:**
<table>
<thead>
<tr>
<th>Male</th>
<th>10</th>
<th>100%</th>
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<tbody>
<tr>
<td>Female</td>
<td>0</td>
<td>0%</td>
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<tr>
<td>Age (ys)</td>
<td>68.5 ± 10.4</td>
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**Cirrhosis Etiology**

| Hepatitis B | 0 | 0% |
| Hepatitis C | 5 | 50% |
| Alcohol-related | 3 | 30% |
| Cryptogenic | 2 | 2% |

**Extension Disease**

| Unilobar | 2 | 20% |
| Bilobar | 8 | 80% |

**Child-Pugh score**

| A | 7 | 70% |
| B7 | 3 | 30% |

**Previous Surgery**

| No | 9 | 90% |
| Yes (right epatectomy) | 1 | 10% |

**Vascular Invasion**

| Yes | 4 | 40% |
| No | 6 | 60% |

Sorafenib administration dismissing for
Fig. 2: C.G.G, #, 52aa. Patient with advanced multinodular HCC ineligible for sorafenib administration because of clinical conditions: pre-treatment CT exam demonstrated a main nodule of HCC, 3.7cm in diameter, in the V hepatic segment (a), one nodule of 1cm in the VII segment (b) and partial neoplastic portal vein thrombosis (c).
**Fig. 3:** 6-months CT control demonstrated the partial response of disease in terms of complete necrosis of the main nodule in the V segment (d) and stability of the lesion in the VII hepatic segment (e) and of the portal vein thrombosis (f).
Conclusion

Sorafenib administration is considered the only treatment option available for patients with well-preserved liver function (Child-Pugh A class), advanced HCC - BCLC C - or with tumor progressing on loco-regional therapies; the SHARP Investigators Group and the Asia-Pacific trials demonstrated a significant effectiveness of sorafenib in terms of overall survival and disease time to progression, but no significant differences in terms of symptomatic time to progression were observed.

Moreover a consistent number of patients experiences treatment-related adverse events, costitutional, dermatological and gastrointestinal in nature (80% patients) and about 11% heads for permanent treatment discontinuation (11%). [4-9, 16-18]

Our study demonstrates that DSM-TACE could be a safe, reproducible and effective promising alternative treatment option for advanced HCC patients ineligible for sorafenib administration or dismissing it due to unbearable side effects, allowing a high rate of overall disease local control.

Personal information

References


