„Beyond permanent particles: Rationale to use biodegradable particles for HCC“

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Disclosure

Speaker name: ...........................................................................................................................................

I have the following potential conflicts of interest to report:

☑  Consulting
☐  Employment in industry
☐  Stockholder of a healthcare company
☐  Owner of a healthcare company
☐  Other(s)

☐  I do not have any potential conflict of interest
Importance of particles size & drug loading

Our goal: Anoxia
HCC: Anoxia vs. Hypoxia

HCC in cell cultures:

- **4h Anoxia**: minimal growth reduction
- **8h Anoxia**: cell doubling 2-3 time slowed
- **12h Anoxia**: growth stopped for days
- **>24h Anoxia**: cell death in 100%

Götz Richter et al. UKL Freiburg 1984
TACE produces tumor anoxia and inflammatory reaction, which may promote angiogenesis and tumor growth.

- HIF-1α increased by hypoxemia (after infarct)
- VEGF mediator for neovascularization (growth and permeability)

HIF = hypoxia inducible factor; HRE = hypoxia response element
Ang-2 = angiopoietin-2; NOS = nitric oxide synthase
PDGF-β = platelet-derived growth factor-β

Courtesy of P. Pereira

HCC: Anoxia vs. Hypoxia

Hypoxia and hepatocellular carcinoma: The therapeutic target for hepatocellular carcinoma
⇒“Hypoxia enhances proliferation, angiogenesis ... of HCC“

Transcatheter arterial chemoembolization (TACE) in hepatocellular carcinoma (HCC): the role of angiogenesis and invasiveness
Sergio A. et al. AM J Gastroenterol 2008 Apr;103(4):914-21
Evaluation von Angiogenesefaktoren (VGEF, b-FGF) und Tumorvaskularisation
⇒“When TACE is not totally effective, it may induce a significant neoangiogenetic reaction“
Plasma VEGF levels increase significantly after cTACE

Mean plasma VEGF levels increases with disease stage in patients with HCC.
VEGF-Level correlates with response rate and OSR after cTACE

[Graph showing VEGF levels over time for responders, total, and non-responders with survival probability over months for VEGF under and over median value of 43.65 pg/dL.]


Courtesy of P. Pereira
Impact of Different Embolic Agents for Transarterial Chemoembolization (TACE) Procedures on Systemic Vascular Endothelial Growth Factor (VEGF) Levels

**Background and Aims:** Intermediate stage hepatocellular carcinoma (HCC) can be treated by transarterial chemoembolization (TACE). However, there appear to be side effects, such as induction of proangiogenic factors, e.g. vascular endothelial growth factor (VEGF), which have been shown to be associated with a poor prognosis. This prospective study was designed to compare serum VEGF level response after TACE with different embolic agents in patients with HCC.

**Methods:** Patients were assigned to one of three different TACE regimens: degradable starch microspheres (DSM) TACE, drug-eluting bead (DEBDOX) TACE or Lipiodol TACE (cTACE). All patients received 50 mg doxorubicin/m² body surface area (BSA) during TACE. Serum VEGF levels were assessed before TACE treatment, 24 h post-treatment and 4 weeks later.

**Results:** Twenty-two patients with 30 TACE treatments were enrolled. Compared to baseline VEGF levels, a marked increase was observed for 24 h post-TACE (164% of baseline level) and during the 4-week follow-up (170% of baseline level) only for the cTACE arm (p < 0.05). In contrast, the increase of serum VEGF levels were only 114% and 123% for DEBDOX and 121% and 124% for DSM, respectively.

**Conclusions:** Conventional TACE using Lipiodol shows marked increase in blood levels of the proangiogenic factor VEGF, while DEBDOX and DSM TACE induce only a moderate VEGF response.
Plasma VEGF levels increase after cTACE, not after DSM or DEB.
Biodegradable TACE: ... to obtain a chemotherapeutic effect, but to avoid the permanent embolization-related side effects

1. to preserve the arterial access to the tumor ➔ higher repetition rate

2. to avoid a permanent embolization for lower inflammation ➔ better local recurrence (?)

3. to avoid the stimulation of neoangeonesis ➔ lower recurrence rate

4. to avoid & reduce the PES & complications ➔ better patient comfort and less complications
Portal pressure/bilirubin

Stage 0
PST 0, Child–Pugh A

Very early stage (0)
1 HCC < 2 cm
Carcinoma in situ

Early stage (A)
1 HCC or 3 nodules < 3 cm, PST 0

Intermediate stage (B)
Multinodular, PST 0

Advanced stage (C)
Portal invasion, N1, M1, PST 1–2

End stage (D)
PST > 2, Child–Pugh C

HCC

Resection
Liver transplantation (CLT/LDLT)
RF/PEI

Curative treatments (30–40%)
Median OS > 60 months; 5-year survival 40–70%

TACE
Sorafenib
Best supportive care

Target 20%
OS: 20 months (45–14)

Target 40%
OS: 11 months (6–14)

Target 10%
OS: < 3 months

CLT, cadaveric liver transplantation; EASL, European Association for the Study of the Liver; EORTC, European Organisation for Research and Treatment of Cancer; LDLT, living donor liver transplantation

Downstaging strategy with DSM-TACE (EmboCept® S) in HCC patients

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Patient characteristic

- Mono-center study: from November 2013 to August 2014

- 22 multifocal HCC patients (BCLC B- intermediate stage)
  - Gender [Male] n (%) 20 (87%)
  - Mean Age (years) ± SD 59 ± 6
  - HCC side (bilobal/monolobal) 9/13 (40.9/59.1 %)
  - Mean Nodules Number ± SD 3.2 ± 1.6
  - Mean diameter (mm) ± SD 21.1 ± 11.7
  - Mean AFP (UI/mL) ± SD 14.9 ± 21.4
  - 6 patients with ascites
  - No main portal vein thrombosis
  - Previous (> 6 months) HCC treatment n.8 pts. (34.8%)
    - Chemoembolization e/or thermal ablation

- Chil-Pugh A/B/C 14/6/2
  - Mean CPT ± SD 6.6 ± 1.7

- MELD mean score 10.6 ± 3.5

- Aetiology HCV/HBV/Alcohol/Virus+alcohol 10/2/8/2
Study design / Procedure

- DSM: 225 – 450 mg EmboCept® S
- 50 – 150 mg Doxorubicin
- 3 x DSM-TACE every 4-6 weeks

- CT-control before each next DSM-TACE (mRECIST)
- Decision of site of chemoembolization based on CT, MRI and DSA
  - 4 F Cobra C1 or Simmons 1 catheters for common hepatic catheterization
  - Coaxial 2.7 F microcatheter Selective for right or left hepatic catheterization
## Results 1

<table>
<thead>
<tr>
<th>mRECIST</th>
<th>1st DSM-TACE (n=22)</th>
<th>2nd DSM-TACE (n=15)</th>
<th>3rd DSM-TACE (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response</td>
<td>4 (18.2%)</td>
<td>5 (33.3%)</td>
<td>4 (44.5%)</td>
</tr>
<tr>
<td>Partial Response</td>
<td>15 (68.2%)</td>
<td>9 (60%)</td>
<td>5 (55.5%)</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>3 (13.6%)</td>
<td>1 (6.7%)</td>
<td>-</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>-</td>
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</table>

Overall response rate after 1 treatment: 86.4% (4 complete - 15 partial)
Results 3

Tolerability:

• **Major complications**
  – 1 case of cholecystitis

• **Minor complications**
  – PES was observed in 9 patients
  – Abdominal pain mostly in all patients (without pre-medications!)

**Decision:** 80 mg pantoprazole 3 days before + 5 days following TACE

• 7 new patients developed ascites
AIM: To evaluate the downstaging rates in hepatitis C virus-patients with hepatocellular carcinoma (HCC), treated with degradable starch microspheres transcatheter arterial chemoembolization (DSM-TACE), to reach new-Milan-criteria (nMC) for transplantation.

METHODS: This study was approved by the Ethics Committee of our institution. From September 2013 to March 2014 eight patients (5 men and 3 women) with liver cirrhosis and multinodular HCC, that did not meet nMC at baseline, were enrolled in this study. Patients who received any other type of treatment such as ternal ablation or percutaneous ethanol injection were excluded. DSM-TACE was performed in all patients using EmboCept® S and doxorubicin. Baseline and follow-up computed tomography or magnetic resonance imaging was assessed measuring the longest enhancing axial dimension of each tumor according to the modified Response Evaluation Criteria In Solid Tumors measurements, and medical records were reviewed.

RESULTS: DSM-TACE was successfully performed in all patients without major complication. We treated 35 lesions (mean 4.3 per patient). Six of eight patients (75%) had their HCC downstaged to meet nMC. Every patient whose disease was downstaged eventually underwent transplantation. The six patients who received transplant were still living at the time of this writing, without recurrence of HCC. Baseline age ($P = 0.25$), Model for End-stage Liver Disease score ($P = 0.77$), and α-fetoprotein level ($P = 1.00$) were similar between patients with and without downstaged HCC.

CONCLUSION: DSM-TACE represents a safely and effective treatment option with similar safety and efficacy of conventional chemoembolization and could be successfully performed also for downstaging disease in patients without nMC, allowing them to reach liver transplantation.
Background: Hepatocellular carcinoma (HCC) is the 3rd leading cause of cancer-related death worldwide. The majority of HCCs are diagnosed in a stage that is not eligible for curative resection. For intermediate stage HCC, transarterial chemoembolization (TACE) is the recommended treatment. We evaluated the safety and efficacy of DSM (degradable starch microspheres) as embolic agent in transarterial chemoembolization (TACE) for the treatment of intermediate stage, non-resectable hepatocellular carcinoma (HCC).

Methods and Findings: A national, multi-center observational study on the safety and efficacy of DSM-TACE for the treatment of intermediate HCC was conducted. The recruitment period for the study was from January 2010 to June 2014. The primary endpoints were safety and treatment response according to the mRECIST criteria.

A total of 179 DSM-TACE procedures in 50 patients were included in the analysis. The therapeutic efficacy assessed with mRECIST was as follows: complete response (n=1; 2 %), 21 partial response (42 %), 13 stable disease (26 %), 9 progressive disease (18 %), and 6 incomplete data (12 %). Thus, the objective response rate was 44% (n=22) and disease control rate was 70% (n=35).

A total of 76 immediate adverse events (AE) and 2 severe adverse events (SAE) were recorded. Forty-eight percent of patients (n=24) did not encounter any immediate AE/SAE. Between treatments, a total of 66 AE and one SAE were recorded. Twenty-four patients (48 %) did not encounter any AE/SAE in between treatments.

Conclusion: The use of DSM as a TACE embolic agent appears to be safe for the treatment of HCC and has promising efficacy.
Summary

Biodegradable TACE:

- induce a lower VGEF rise compared to cTACE and DEB-TACE
- a safe & effective treatment option for HCC (survival >20 mo.)
- an option even in Child C and PV-Thrombosis

- new options: high dosage Cisplatin (first or second line TACE)
Welcome in Frankonia

Prof. Dr. med. Boris Radeleff | Sana Klinikum Hof GmbH
Beyond permanent particles: Rationale to use biodegradable particles for HCC