HEPATIC SUPERSELECTIVE CHEMOEMBOLISATION IN HCC:
CONVENTIONAL VS. DRUG ELUTING BEADS

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Disclosure

Speaker name:
Peter Huppert, M.D.

☐ I have the following potential conflicts of interest to report:
☐ Consulting
☐ Employment in industr
☐ Stockholder of a healthcare company
☐ Owner of a healthcare company
☐ Other(s)
  x I do not have any potential conflict of interest
Rational of Transarterial Chemoembolization

- Dual blood supply with arterial tumor feeding
- Arterial drug delivery and devascularization
- $R_{art} =$ Regional advantage of arterial drug delivery ($x$-times compared to systemic delivery)

Collins 1994

<table>
<thead>
<tr>
<th>Drug</th>
<th>$R_{art}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-FU</td>
<td>80</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>60</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>4</td>
</tr>
<tr>
<td>Mitomycin</td>
<td>3</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>2</td>
</tr>
</tbody>
</table>
Conventional & DEB TACE in HCC

„conventional“ TACE

Drug(s): Doxo, Cis, Mito
Carrier: oil-in-water emulsion
Embolics: GF, particles
Conventional & DEB TACE in HCC

„conventional“ TACE
Drug(s): Doxo, Cis, Mito
Carrier: oil-in-water emulsion
Embolics: GF, particles

„Drug-eluting“ TACE
Particles preloaded with:
Doxorubicin
Microspheres
## Preparation of cTACE and DEB TACE

<table>
<thead>
<tr>
<th></th>
<th>Convent. iodized Oil TACE</th>
<th>DC-Beads</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drugs</strong></td>
<td>60-100 mg Doxo./Epirub. 6-10 cc iod. oil</td>
<td>50-150 mg Dx./Ep (37.5mg/ml) 2-4 cc Beads</td>
</tr>
<tr>
<td></td>
<td>oil-in water: 2:1-1.5:1</td>
<td>No other Beads</td>
</tr>
<tr>
<td></td>
<td>Options: MMC, Cisplatin</td>
<td></td>
</tr>
<tr>
<td><strong>Preparation time</strong></td>
<td>2-3 min</td>
<td>70-150 µm: 15 min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100-300µm: 20 min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>500-700µm: 120 min</td>
</tr>
<tr>
<td><strong>before injection</strong></td>
<td>fresh mixing</td>
<td>soft shaking</td>
</tr>
<tr>
<td><strong>Application</strong></td>
<td>Flow directed</td>
<td>1 cc/ min</td>
</tr>
<tr>
<td></td>
<td><strong>Additional particle embx.</strong></td>
<td></td>
</tr>
</tbody>
</table>
Drug eluting Systems for TACE in HCC

*DC-BEADS™

HepaSphere™

Tandem™

Material: polyvinyl alcohol, sodium acrylate, polyvinyl alcohol

Sizes: 70-150μm, 500-700μm, 200-400 (50-100) μm, 40μm, 75μm, 100μm

Loading: 37.5 mg Doxorubicin/ml, 50 mg Doxorubicin/50mg, 50 mg Doxorubicin/ml

Release t75: 9-66 min, 7 min, 49 min

Images: Biocompatibles, Biosphere/Merit Medical, Celonova

Comparable to Life Pearls™, Terumo
Drug loading and Drug release

<table>
<thead>
<tr>
<th>material</th>
<th>% drug loaded</th>
<th>% drug released</th>
<th>$t_{75%}$ [h]</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCBead™-Doxorubicin</td>
<td>98</td>
<td>27</td>
<td>2.2</td>
</tr>
<tr>
<td>HepaSphere™-Doxorubicin</td>
<td>100</td>
<td>18</td>
<td>2.2</td>
</tr>
<tr>
<td>DCBead™-Irinotecan</td>
<td>93</td>
<td>98</td>
<td>1.1</td>
</tr>
<tr>
<td>HepaSphere™-Irinotecan</td>
<td>90</td>
<td>95</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Interaction of Dx. / Irt+ with SO₃⁻ groups by an ion-exchange process displaces water from the hydration shells.
Indication for TACE in HCC

- **Stage 0**: PS 0, Child Pugh A
  - Very early stage (0)
    - Single < 2 cm
      - Single
      - Portal pressure/bilirubin
        - Increased
          - Associated diseases
          - Resection
          - Liver transplantation
          - Retreatment
          - PEI/RF
          - Liver transplantation
            - 30%-40% of patients
              - MOS > 60 mo: 5-yr survival: 50%-70%
  - Normal
  - No
  - Yes

- **Stage A-C**: PS 0-2, Child-Pugh A-B
  - Early stage (A)
    - Single or 3 nodules < 3 cm, PS 0
      - Multinodular PS 0
      - Associated diseases
      - Resection
      - Liver transplantation
      - Retreatment
      - PEI/RF
      - Chemotherapy
      - Liver transplantation
        - 30%-40% of patients
          - MOS > 60 mo: 5-yr survival: 50%-70%
  - Increased
  - Associated diseases

- **Stage D**: PS > 2, Child-Pugh C
  - Advanced stage (C)
    - Portal invasion, N1, M1, PS 1-2
      - Associated diseases
      - Resection
      - Liver transplantation
      - Retreatment
      - PEI/RF
      - Chemotherapy
      - Liver transplantation
        - 30%-40% of patients
          - MOS > 60 mo: 5-yr survival: 50%-70%
  - Terminal stage (D)

- **Chemoembolization**: Palliative treatments
  - MOS: 20 mo (45-14)

- **Sorafenib**: Symptomatic treatment
  - MOS: 11 mo (6-14)
  - MOS < 3 mo
Indication: Bridging to Ltx

- 67-years old male
- Child-Pugh Score 9
- 4.7 cm subcapsular nodulat type
- 1 arterial feeder
- listed for Ltx. 5/2010
- MELD score 8
- survival 36 mo.
Negative Predictors & Contraindications

diffuse type of HCC
compact type of HCC
infiltrative type of HCC
arterioportal shunts
cTACE in case of PV Infiltration

- 72 years old male
- Child-Pugh-Score 6
- 8 cm HCC infiltrating right PV
- 5 x TACE (Intervals: 3-5 mo.)
- Survival 63 months

In case of good liver function
PV infiltr. is no contraindication for selective TACE
Superelektive cTACE & Grading of iodized oil uptake

Uptake of iodized oil
Grade 1-3 (Maki-classification)

conventional TACE
60-100 mg Anthracyclin
6-10 (20) ml iodized oil particles for embolization

grade 1b

grade 3

28.7.99

28.7.99

8.11.99

15.11.99
Conv. TACE vs. BSC in HCC: Phase III-Studies
(Random effects model pooled OR, 95% CI)

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Pooled OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>GETCH</td>
<td>1995</td>
<td>0.6</td>
</tr>
<tr>
<td>Pelletier</td>
<td>1998</td>
<td>0.4</td>
</tr>
<tr>
<td>Lo</td>
<td>2000</td>
<td>0.3</td>
</tr>
<tr>
<td>Llovet</td>
<td>2002</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Pooled OR: 0.6

Adapted from: Llovet et al 2003, Hepatology 37; 429-42
Conv. TACE vs. BSC in HCC: Phase III-Studies
(Random effects model pooled OR, 95% CI)

Survival benefit: 6-10 months

GETCH 1995
Pelletier 1998
Lo 2000
Llovet 2002
Pooled OR

Lo et al. Hepatology (2002), 35; 1164-71
Patients: 40
TACE: Cis 1-30 mg, iodized oil 1-30 cc, GF

307 / 387 (79%) excluded

Llovet et al. Lancet (2002), 359; 1734-39
Patients: 40
TACE: Doxo 25-75 mg/m², 10 cc iodized oil, GF

791 / 903 (88%) excluded

Adapted from: Llovet et al 2003, Hepatology 37; 429-42
Advantages of drug eluting Beads

- Delayed drug delivery
- Enhanced local necrosis
- Favourable toxicity profile
- Reduced systemic effects
- Better pts. tolerance
- Improved detection of recurrencies
Advantages of conventional TACE

• Proven survival benefit in comparison to BSC

• Clear feed back by iodized oil uptake in CT

• Limited serious side effects even in multinodular and huge tumors

• Cost/procedure 1/3 compared to DEB TACE
Conventional TACE vs. DEB TACE: RCT PRECISION V-Studie

Lammer et al. 2010 Cardiovasc Intervent Radiol 33:41-52
Conventional TACE vs. DEB TACE: RCT PRECISION V-Studie

Subgroup analysis
- Child B
- ECOG 1
- Bilobar or recurrent disease

Objective response in favor of DEB p=0.038
Conventional TACE vs. DEB TACE: RCT PRECISION V-Studie

Doxorubicin-Related Side Effects

- A significant reduction in drug-related toxicity is seen in patients receiving PRECISION TACE™ with DC Bead™
- There is a near complete absence of alopecia in PRECISION TACE with DC Bead patients
Conventional TACE vs. DEB TACE: PRECISION V-Studie

**Toxicity profile**

<table>
<thead>
<tr>
<th></th>
<th>konv. TACE</th>
<th>DC-BEADS</th>
</tr>
</thead>
<tbody>
<tr>
<td>max. peripheral level of Doxorubicin</td>
<td>2.341 ng/mL</td>
<td>79 ng/mL</td>
</tr>
<tr>
<td>AUC</td>
<td>1.812 ng/mL min</td>
<td>663 ng/mL min</td>
</tr>
</tbody>
</table>

Varela et al. 2007
J Hepatol 46;474-81
# Metaanalyses

**DEB DOX TACE vs. c LIP TACE**

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Studies</th>
<th>Patients</th>
<th>Odds ratio Objective response</th>
<th>Odds ratio Overall survival</th>
<th>Odds ratio Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gao</td>
<td>2013</td>
<td>7</td>
<td>693</td>
<td>1.4</td>
<td>n.e.</td>
<td>n.e.</td>
</tr>
<tr>
<td>Huang</td>
<td>2014</td>
<td>7</td>
<td>700</td>
<td>1.9</td>
<td>0.6</td>
<td>0.8</td>
</tr>
<tr>
<td>Facciorusso</td>
<td>2016</td>
<td>12</td>
<td>1.449</td>
<td>1.2</td>
<td>0.6</td>
<td>0.85</td>
</tr>
<tr>
<td>Zou</td>
<td>2016</td>
<td>13</td>
<td>1.560</td>
<td>1.2</td>
<td>0.7</td>
<td>0.6</td>
</tr>
</tbody>
</table>

**Population heterogeneity**
- ECOG PS
- Child-Pugh Class
- etiology of cirrhosis
- tumor stages
- postinterventional imaging
- response criteria
- study design

Odds ratios in favor of DEB DOX TACE, however no statistical significant differences

Weak evidence
Summary

- Conventional TACE using iodized oil emulsified with drugs and additional particle embolization is associated with proven survival benefit of 6-12 months in selected cases.

- TACE using Drug-eluting particles reduces toxic side effects with better patient tolerance and increases local tumor necrosis.
Thank You for Attention!
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