TACE convenzionale e DEB-TACE

Orsola Perrone

U.O. Radiologia Interventistica
Azienda Ospedaliero Universitaria Pisana
2005: The beginning of the story

Preclinical model

Hong K et al. Clin Cancer Res 2006

Preliminary experience

Well tolerated and safe
Response rate : 75%

Varela M et al. J Hepatol 2007
Drug eluting beads

**Improved tolerability**
**Reduced toxicity**

**Prospective Randomized Study of Doxorubicin-Eluting-Bead Embolization in the Treatment of Hepatocellular Carcinoma: Results of the PRECISION V Study**
*Lammer J et al. Cardiovasc Intervent Radiol 2010*

**Survival of patients with hepatocellular carcinoma treated by transarterial chemoembolisation (TACE) using Drug Eluting Beads. Implications for clinical practice and trial design**
*Burrel M et al. J Hepatol 2012*

**Chemoembolization With Doxorubicin-Eluting Beads for Unresectable Hepatocellular Carcinoma: Five-Year Survival Analysis**
*Malagari K et al. Cardiovasc Intervent Radiol 2012*

**Median survival**
> 40 months
The “BEADS” generation
The last decade in literature

2006 2016
No difference in radiological response

DEB-TACE or Lipiodol\textsuperscript{TM}-TACE?

Lammer J et al. Cardiovasc Intervent Radiol 2010
DEB-TACE or Lipiodol\textsuperscript{TM}-TACE?

Golfieri R et al. British Journal of Cancer 2014

No difference in survival
Drug-eluting beads versus conventional chemoembolization for the treatment of unresectable hepatocellular carcinoma: A meta-analysis

**Survival**

**Obj response**

Facciorusso A et al. Dig Liver Dis 2016
TACE in Italy in 2012

- Dc-Beads: 57%
- Chemo+Lipiodol+Spongostan: 6%
- Hepasphere: 6%
- Chemo+Lipiodol+particles: 11%
- Chemo+Lipiodol: 26%
- Other: 5%

Bargellini I et al. Cardiovasc Intervent Radiol 2013
The last decade in literature
The last decade in PISA

TACE in 813 naive HCC pts
DEB-TACE or Lipiodol™-TACE?
486 naive HCC pts treated with TACE from 2006 to 2011

Mean hospitalization

- Lipiodol-TACE (n=271): 3.8±3.5 days
- DEB-TACE (n=215): 2.7±2.6 days

*P= 0.0004

Personal series
No difference in clinical outcomes but significantly lower rate of rehospitalizations for the management of TACE-related toxicities

Metanalysis on 5 RCTs and 11 observational studies, including 1860 patients

“DEB-TACE was found more cost-effective than cTACE when a minimum willingness-to-pay of about € 2000–3500/QALY was accepted, mainly depending on shorter in-hospital stay and better quality of life”

Cucchetti A et al. Dig Liver Dis 2016
1-month target tumor response after DEB-TACE in BCLC A naïve pts

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>pts (n)</td>
<td>13</td>
<td>23</td>
<td>16</td>
<td>17</td>
<td>15</td>
<td>19</td>
<td>39</td>
<td>42</td>
<td>39</td>
<td>46</td>
</tr>
<tr>
<td>CR (%)</td>
<td>38.5</td>
<td>82.6</td>
<td>81.2</td>
<td>76.5</td>
<td>33.3</td>
<td>63.1</td>
<td>51.3</td>
<td>69.1</td>
<td>69.2</td>
<td>69.6</td>
</tr>
<tr>
<td>PR (%)</td>
<td>30.8</td>
<td>13</td>
<td>12.5</td>
<td>11.8</td>
<td>33.3</td>
<td>31.6</td>
<td>28.2</td>
<td>26.1</td>
<td>25.6</td>
<td>17.4</td>
</tr>
</tbody>
</table>

Personal series
RCTs: too eager to start?

Prospective Randomized Study of Doxorubicin-Eluting-Bead Embolization in the Treatment of Hepatocellular Carcinoma: Results of the PRECISION V Study

Johannes Lammer · Katarina Malagari · Thomas Vogl · Frank Pilleul · Alban Denys · Anthony Watkinson · Michael Pitton · Geraldine Sergent · Thomas Pfammatter · Sylvain Terraz · Yves Benhamou · Yves Avajou · Thomas Gruenberger · Maria Pomoni · Herbert Langenberger · Marcus Schuchmann · Jerome Dumortier · Christian Mueller · Patrick Chevalier · Riccardo Lenzi · On Behalf of the PRECISION V Investigators

Enrollment period:
November 2005 - June 2007

Randomised controlled trial of doxorubicin-eluting beads vs conventional chemoembolisation for hepatocellular carcinoma

R Colliati1, E Giampalma2, M Renaud1,1, R Cioni1, I Bargellini1, C Bartolozzi2, A D Bresolin3, I Gandini2, R Nano1, D Gazzerini1, A Cuccioni1, L Bolondi1 and F. Trovato1 on behalf of the PRECISION ITALIA STUDY GROUP

Enrollment period:
March 2008 - December 2010
TACE in 2016: are we missing something?

Poor tumor response

Lammer J et al. Cardiovasc Intervent Radiol 2010
TACE in 2016: are we missing something?

Tumor response affects survival

EASL

Survival Functions

mRECIST

Log rank P
CR vs. PR <0.001
PR vs. SD 0.002
SD vs. PD 0.023

Overall survival

CR
PR
SD
PD

Malagari K et al.
Cardiovasc Intervent Radiol 2012

Shim JH et al.
Radiology 2012
TACE: the next generation...

- Balloon-occluded TACE (BO-TACE)
- Smaller size particles
- Degradable starch microspheres (DSM)
- Radiopaque particles
- Loading with new agents
Balloon-occluded TACE

Micro-balloon

The reduced intravascular pressure may increase drug flow into cancer nodules by reducing portal vein uptake

Irie T et al. CVIR 2013
Increased drug dose

Better tumor response

### Drug-eluting beads platforms

**smaller sizes, higher doses**

<table>
<thead>
<tr>
<th>Size (μm)</th>
<th>45-700</th>
<th>120-800</th>
<th>100-400</th>
<th>40-100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loading (mg/mL)</td>
<td>37.5</td>
<td>37.5</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>

*Modified from Namur J.
Presented at ECIO 2016*
**Drug-eluting beads platforms** smaller sizes

**Hepasphere 120-240 μm**

<table>
<thead>
<tr>
<th>mRECIST</th>
<th>Overall response n (%)</th>
<th>Target lesion response n (%)</th>
<th>Nontarget lesion response n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>8 (17.8)</td>
<td>10 (22.2)</td>
<td>5 (12.5)</td>
</tr>
<tr>
<td>PR</td>
<td>23 (51.1)</td>
<td>21 (46.6)</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>9 (20)</td>
<td>10 (22.2)</td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>5 (11.1)</td>
<td>4 (8.8)</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Non-PD</td>
<td></td>
<td></td>
<td>32 (80)</td>
</tr>
</tbody>
</table>

45 pts

OR: 68.9 %
Safe and well tolerated

Malagari K et al. CVIR 2014

**DCBeads M1 75-150 μm**

<table>
<thead>
<tr>
<th>Diameter of nodules</th>
<th>No. of modules</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3 cm</td>
<td>72</td>
<td>31</td>
<td>25</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>3-5 cm</td>
<td>21</td>
<td>10</td>
<td>7</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>&gt;5 cm</td>
<td>10</td>
<td>2</td>
<td>5</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Overall response</td>
<td>103</td>
<td>42</td>
<td>36</td>
<td>18</td>
<td>4</td>
</tr>
</tbody>
</table>

45 pts

OR: 77.7 %
Safe and well tolerated

Spreatico C et al. CVIR 2015
Degradable starch microspheres

The starch microspheres consist of a three-dimensional, cross linked hydrophilic starch matrix, which swells heavily in a water suspension environment and are completely degradable by amylase.

Potential advantages:
- No embolization-related side effects
- Preserved arterial access to the tumor (repeated treatments)
- No stimulation of neoangiogenesis (reduced recurrence rate)
- Combination with different agents (chemotherapeutics, cytokines, gene therapy products)
DSM-TACE MULTICENTER STUDY IN HCC TREATMENT, PLACED IN THE TRIVENETO AREA (North-East Italy)

Silvia Dal Bello
Castelfranco Veneto

Cesari Stefano(1), Biscosi Mauro(2), Romanzi Francesco(3), Berletti Riccardo(4), Avventi Paolo(1), Dal Bello Silvia(1), Sponza Massimo(5), Vit Alessandro (5), Iurilli Vincenzo(6), Miotto Diego(6)

Presented at
ECIO 2016

This trial started June, 1, 2013 in 5 Interventional Radiology Centers, situated in the Triveneto Area (North-East, Italy).

- Castelfranco Veneto
- Tolmezzo
- Vittorio Veneto
- Trento
- Udine
- Padova
Degradable starch microspheres

BCLB B patients, with HCC in at least 4 liver segments

<table>
<thead>
<tr>
<th>PATIENTS</th>
<th>63</th>
</tr>
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<tbody>
<tr>
<td>dsm-TACE</td>
<td>177</td>
</tr>
<tr>
<td>TACE per patient (average)</td>
<td>2.8</td>
</tr>
<tr>
<td>TACE per patient (min/max)</td>
<td>1-8</td>
</tr>
</tbody>
</table>
Degradable starch microspheres

**Safety**

<table>
<thead>
<tr>
<th>Side Effects</th>
<th>N</th>
<th>%</th>
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<tbody>
<tr>
<td>post-ischemic syndrome</td>
<td>2</td>
<td>1.13</td>
</tr>
<tr>
<td>gangrenous cholecystitis</td>
<td>1</td>
<td>0.56</td>
</tr>
<tr>
<td>pancytopenia</td>
<td>1</td>
<td>0.56</td>
</tr>
<tr>
<td>Pain (6-8 h)</td>
<td>109</td>
<td>61.58</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>18</td>
<td>10.17</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>10</td>
<td>5.65</td>
</tr>
<tr>
<td>Liver enzyme alteration (24h)</td>
<td>4</td>
<td>2.26</td>
</tr>
</tbody>
</table>

**mRECIST**

<table>
<thead>
<tr>
<th>Objective Response</th>
<th>n.(63)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>21</td>
<td>37.50</td>
</tr>
<tr>
<td>Partial response</td>
<td>23</td>
<td>41.07</td>
</tr>
<tr>
<td><strong>OBJECTIVE RESPONSE</strong></td>
<td><strong>44</strong></td>
<td><strong>78.57</strong></td>
</tr>
<tr>
<td>Complete + partial response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-responders (stable disease or progression)</td>
<td>12</td>
<td>21.43</td>
</tr>
<tr>
<td>Waiting for the follow-up</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>

*Dal Bello S et al. Presented at ECIO 2016*
Preparation of Radiopaque Drug-Eluting Beads for Transcatheter Chemoembolization

\[ y = 2.39x + 22.0 \]
\[ R^2 = 0.99 \]

Newer platforms for newer drugs

Idarubicin-loaded beads for chemoembolisation of hepatocellular carcinoma: results of the IDASPHERE phase I trial
M. Boulin1, P. Hilton1, J. P. Cerqueira1, F. Bonnetain1, S. Dabakaru2, A. Mirullo1, J. L. Jouet1, C. Lepage1, M. Bardeau1, M. Winteremain2, P. Guizard1, D. Demy1, A. Grandjean1, L. Bedenne1, L. B. Gueux1

Sunitinib-eluting beads for chemoembolization: Methods for in vitro evaluation of drug release
Katrin Fuchs1,*, Pierre E. Bize1, Alban Denys1, Gerrit Borchard1, Olivier Jordan1

Preparation and structure of drug-carrying biodegradable microspheres designed for transarterial chemoembolization therapy.
Wang Y1, Benzina A, Molin DG, Akker Ny, Gagliardi M, Koole LH

Targeting glucose metabolism in cancer: new class of agents for loco-regional and systemic therapy of liver cancer and beyond?
Lynn Jeanette Savic1,2, Julius Chapiro1,2, Gregor Duwe2, and Jean-François Geschwind1,1

Acidic pH-Triggered Drug Eluting Nanocomposites for MRI Monitored Intra-Arterial Drug Delivery to Hepatocellular Carcinoma.
Park W, Chen J, Cho S, Park SJ, Larson AC, Na K, Kim DH

The dark side of the guidelines

2nd Interventional Radiologist under 40 Meeting
Interventional Oncology
Lipiodol-TACE or DEB-TACE: which and when

Yesterday, I didn’t know,
Today, I know I don’t know,
Tomorrow, who knows?!