IS THERE A ROLE FOR INTRA-ARTERIAL THERAPY OR ISOLATED LIVER PERFUSION?

Pr Olivier Detry
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YES!

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Disclosure statement

• No financial relationships to disclose !
CRC Liver Mets

- 25% of patients with CRC have synchronous liver Mets at time of diagnosis
- 50% of patients will develop metachronous Mets
- R0 resection remains the standard of treatment and the only hope for cure and long-term survival
- Survival after resection: 25 to 50% at 5 years
- 50% of recurrences within 2 years
- 25 to 50% of recurrences are intrahepatic only
Liver vascularisation:
66 % Portal vein
33 % Hepatic artery

MTST vascularisation:
> 80 % Hepatic artery

CRC Liver Mets
CRC Liver Mets
and intraarterial therapy

• Intra arterial chemotherapy
• Radioembolisation Yttrium
• Isolated liver perfusion
Intra-arterial chemotherapy

- Adjuvant IA chemotherapy
- Irresectable MTST
  - palliative (1\textsuperscript{st} or 2\textsuperscript{nd} line)

- Better compared to old style chemotherapy
- Discussed compared to modern iv therapy
Intérêt d’une chimiothérapie intra-artérielle adjuvante chez les patients à risque élevé de récidive hépatique


Résultats
2000-2009

121 patients, MH > 3

CIAH + : 55 pts

8 pts
• 3 décès postopératoires
• 1 neuropathie grade IV
• 2 thrombose du KT
• 2 progressions précoces

CIAH 47 pts

CIAH - : 66 pts

IV + : 62 pts

4 pts pas de CT

6 pts 5FU IV

FOLFOX ou FOLFIRI IV 56 pts
Résultats

Chimiothérapie intra-artérielle

• Nombre de cures
  • 29 (61%) ≥ 6 cures
  • 18 (38%) < 6 cures
  
  Moyenne 8 ± 1,7
  Moyenne 3,2 ± 1,5

• Causes arrêt CIAH avant 6 cures
  • Toxicité systémique : 6 (13%)
  • Dysfonction KT : 6 (13%)
  • Récidive précoce : 5 (10%) (2 hépatique, 3 extra-hépatique)
  • Demande du patient : 1 (2%)
Résultats
Survie globale

54% à 5 ans
40% à 5 ans

logrank : chi2 à 1 ddl = 1.843, p = 0.1747

At risk
- 56 53 39 22 16 13 9 4 3
- 47 42 33 17 11 7 6 5 4

p NS
Résultats
Survie sans récidive

logrank : chi² à 1 ddl = 15.781, p < 0.0001

36% à 3 ans
5% à 3 ans

p < 0.0001
Résultats

Survie sans récidive hépatique

Logrank : chi2 à 1 ddl = 7.468, p = 0.0063

43% à 3ans
20% à 3ans

p=0.0063

At risk

- 56 25 12 7 5 4 4 2 1
- 47 30 16 9 7 5 5 3 3
Palliative IA chemotherapy

Original Articles

Prolonged Survival of Initially Unresectable Hepatic Colorectal Cancer Patients Treated With Hepatic Arterial Infusion of Oxaliplatin Followed by Radical Surgery of Metastases

Diane Goéré, MD,* Isabelle Deshaies, MD,* Thierry de Baere, MD, PhD,† Valérie Boige, MD,‡ David Malka, MD, PhD,‡ Frédéric Dumont, MD,* Clarisse Dromain, MD,† Michel Ducreux, MD, PhD,‡ and Dominique Elias, MD, PhD*

Annals of Surgery • Volume 251, Number 4, April 2010

FIGURE 1. Overall survival of nonoperated (n = 64) and operated (n = 23) patients calculated from the date of diagnosis of liver metastases.
Intra-arterial chemotherapy

• ideal for multiple CRC MTST isolated to the liver
  - irresectable
  - after resection > 4 lesions
• Technically challenging
  - thrombosis
  - infection
• Placement: surgical or radiological
Surgical placement
Intra-arterial chemotherapy

- Need for better prospective studies comparing modern IV and IA chemotherapy both in palliative and postoperative conditions
Yttrium-90 radioembolization

- TheraSpheres (20-30 microns)
- SIRSpheres (20-60 microns)
- First line therapy
- Second or third line chemotherapy
- Salvage for chemorefractory patients
### First-Line

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Treatment Details</th>
<th>Type</th>
<th>ORR</th>
<th>DCR</th>
<th>CR</th>
<th>PR</th>
<th>PD</th>
<th>PFS</th>
<th>OS</th>
<th>2-Year OS</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gray</td>
<td>74</td>
<td>SIR-Spheres† + FUDR HAC vs. FUDR HAC</td>
<td>LO</td>
<td>44%</td>
<td>18%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>15.9 mo</td>
<td>39% at 2 yr</td>
</tr>
<tr>
<td>van Hazel</td>
<td>21</td>
<td>SIR-Spheres† + 5FU/LV vs. 5FU/LV</td>
<td>LD</td>
<td>90.1%*</td>
<td>0%</td>
<td>9.9%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>18.6 mo</td>
<td>29.4 mo</td>
</tr>
<tr>
<td>Sharma</td>
<td>20</td>
<td>SIR-Spheres† + FOLFOX4</td>
<td>LO</td>
<td>90%</td>
<td>10%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9.3 mo</td>
<td>nr</td>
</tr>
<tr>
<td>Kosmider</td>
<td>19</td>
<td>SIR-Spheres† + FOLFOX4 or 5FU/LV</td>
<td>LO</td>
<td>84%</td>
<td>5%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10.4 mo</td>
<td>29.4 mo</td>
</tr>
<tr>
<td>Tie</td>
<td>31</td>
<td>SIR-Spheres† + FOLFOX4 or 5FU/LV</td>
<td>LO</td>
<td>91%</td>
<td>9%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>13.2 mo</td>
<td>30.7 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>phase II/III studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>16.4 mo</td>
<td></td>
</tr>
</tbody>
</table>

### Consolidation of First-Line

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Treatment Details</th>
<th>Type</th>
<th>ORR</th>
<th>DCR</th>
<th>CR</th>
<th>PR</th>
<th>PD</th>
<th>PFS</th>
<th>OS</th>
<th>2-Year OS</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sangro</td>
<td>23</td>
<td>SIR-Spheres†</td>
<td>LD</td>
<td>nr</td>
<td>nr</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6.3 / 11.2 months</td>
<td>16.8 / 23.6 months</td>
</tr>
</tbody>
</table>

### Second- or Third-Line

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Treatment Details</th>
<th>Type</th>
<th>ORR</th>
<th>DCR</th>
<th>CR</th>
<th>PR</th>
<th>PD</th>
<th>PFS</th>
<th>OS</th>
<th>2-Year OS</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lim</td>
<td>30</td>
<td>SIR-Spheres† (+ 5FU)70%</td>
<td>LD</td>
<td>33%</td>
<td></td>
<td>27%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5.3 mo</td>
<td>nr</td>
</tr>
<tr>
<td>van Hazel</td>
<td>25</td>
<td>SIR-Spheres† + irinotecan</td>
<td>LD</td>
<td>48%</td>
<td></td>
<td>39%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6.0 mo</td>
<td>12.2 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>phase II/III studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9.2 mo</td>
<td></td>
</tr>
</tbody>
</table>

### Phase II/III Studies

- irinotecan 14–17
- FOLFIRI 18, 19
- irinotecan + cetuximab 15, 20–22
- panitumumab 23–26
## Salvage Therapy of Treatment-Refractory Disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Treatment</th>
<th>Response Rates</th>
<th>OS (Months)</th>
<th>P-Value</th>
<th>OS (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hendlisz(^{27}) 44</td>
<td>SIR-Spheres(^{†}) + SFU vs. 5FU ( &gt; SIR-Spheres(^{†}) at PD)</td>
<td>LO 10%</td>
<td>76%</td>
<td>5.5 months(^{\Delta L})</td>
<td>P = 0.001</td>
<td>10.0 months</td>
</tr>
<tr>
<td>Seidensticker(^{28}) 29</td>
<td>SIR-Spheres(^{†}) vs. BSC matched pairs</td>
<td>LD 41.4%</td>
<td>17.2%</td>
<td>5.5 months(^{†})</td>
<td>P = 0.003</td>
<td>8.3 months</td>
</tr>
<tr>
<td>Bester(^{29}) 224</td>
<td>SIR-Spheres(^{†}) vs. conventional therapy or BSC</td>
<td>LD nr</td>
<td>nr</td>
<td>2.1 months(^{†})</td>
<td>3.5 months</td>
<td></td>
</tr>
<tr>
<td>Cosimelli(^{30}) 50</td>
<td>SIR-Spheres(^{†})</td>
<td>LD 24%</td>
<td>24%</td>
<td>4 months(^{†})</td>
<td>11.9 months</td>
<td></td>
</tr>
<tr>
<td>Sofocleous(^{31}) 19</td>
<td>SIR-Spheres(^{†})</td>
<td>LD 70.6%(^{OCR})</td>
<td>6 months(^{†})</td>
<td>12.6 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kennedy(^{32}) 606(^{†})</td>
<td>SIR-Spheres(^{†})</td>
<td>LD nr</td>
<td>nr</td>
<td>9.6 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sofocleous(^{33}) 18(^{†})</td>
<td>SIR-Spheres(^{†})</td>
<td>LD 40.0%(^{OCR})</td>
<td>5.1 months(^{†})</td>
<td>7.4 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leoni(^{34}) 51(^{\Delta})</td>
<td>SIR-Spheres(^{†})</td>
<td>LD 24%(^{c})</td>
<td>nr</td>
<td>8.0 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nace(^{35}) 51(^{\Delta})</td>
<td>SIR-Spheres(^{†}) (+ FUDR HAC)(^{139}%)</td>
<td>LD 12.9%</td>
<td>64.5%</td>
<td>10.2 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cianni(^{36}) 41(^{\Delta})</td>
<td>SIR-Spheres(^{†})</td>
<td>LD 46%</td>
<td>36%</td>
<td>9.3 months(^{†})</td>
<td>11.8 months</td>
<td></td>
</tr>
<tr>
<td>Jakobs(^{37}) 41(^{\Delta})</td>
<td>SIR-Spheres(^{†})</td>
<td>LD 17%</td>
<td>61%</td>
<td>5.9 months(^{\Delta L})</td>
<td>10.5 months</td>
<td></td>
</tr>
<tr>
<td>Kennedy(^{38}) 208(^{\Delta})</td>
<td>SIR-Spheres(^{†}) responders &amp; non-responders &amp; historical controls</td>
<td>LD 35.5%(^{W})</td>
<td>55%</td>
<td>10.5 months</td>
<td>P = 0.0001</td>
<td>4.5 months</td>
</tr>
</tbody>
</table>
Selective treatment of the right liver MTST
Isolated liver perfusion

- High concentration of chemotherapy
- High temperature
- melphalan + TNF-α
- oxaliplatin
<table>
<thead>
<tr>
<th><strong>Duration</strong></th>
<th>1 h</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hepatic tissue temp</strong></td>
<td>39.5–40°C</td>
</tr>
<tr>
<td><strong>Tumor necrosis factor</strong></td>
<td>1.0 mg</td>
</tr>
<tr>
<td><strong>Melphalan</strong></td>
<td>1.5 mg/kg</td>
</tr>
<tr>
<td><strong>Flow rate</strong></td>
<td>600–1200 ml/min</td>
</tr>
<tr>
<td><strong>Arterial line pressure</strong></td>
<td>110–200 mmHg*</td>
</tr>
<tr>
<td><strong>Veno-venous bypass flow</strong></td>
<td>1.8–2.0 l/min</td>
</tr>
<tr>
<td><strong>Perfusate volume</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Perfusate composition</strong></td>
<td></td>
</tr>
<tr>
<td>700 cm³ crystalloid</td>
<td></td>
</tr>
<tr>
<td>300 cm³ packed red blood cells</td>
<td></td>
</tr>
<tr>
<td>2000 U heparin</td>
<td></td>
</tr>
<tr>
<td>20–40 meq NaHCO₃</td>
<td></td>
</tr>
<tr>
<td><strong>Post perfusion flush</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Hepatic artery</strong></td>
<td>1.5 l crystalloid</td>
</tr>
<tr>
<td><strong>Portal vein</strong></td>
<td>1.0 l crystalloid</td>
</tr>
</tbody>
</table>

*Not used currently
*Measured pressure in circuit, actual delivered pressure into hepatic artery is lower.
• Ocular melanoma MTST
• Neuro-endocrine MTST
• CRC MTST

Figure 4. Actuarial overall survival in 120 patients with diffuse colorectal cancer liver metastases who underwent isolated hepatic perfusion (IHP) based on baseline carcinoembryonic antigen (CEA) level (top panel) or with or without hepatic artery infusion (HAI) therapy (bottom panel) following IHP. Tx, treatment.
Figure 6. Diagram of the Delcath Catheter System. Melphalan is administered directly into the hepatic artery through an infusion catheter placed percutaneously via the femoral artery. Hepatic venous outflow is isolated via a double balloon catheter in the retrohepatic inferior vena cava (IVC) (shown top right). Blood is drawn out of the retrohepatic IVC through multiple fenestrations located along the length of the catheter between the cranial and caudal balloons. The blood is then pumped through a pair of activated charcoal filters prior to return to the systemic circulation via an internal jugular vein catheter. Fluoroscopic image of the isolated, retrohepatic IVC segment obtained by retrograde injection of contrast through the intraballoon fenestrations to confirm the absence of systemic leak is shown in the middle right.
Isolated Hypoxic Hepatic Perfusion with Retrograde Outflow in Patients with Irresectable Liver Metastases; A New Simplified Technique in Isolated Hepatic Perfusion

Cornelis Verhoef, MD,1 Johannes H. W. deWilt, MD, PhD,1 Flavia Brunstein, MD, PhD,1 Andreas W. K. S. Marinelli, MD, PhD,1 Boudewijn vanEtten, MD, PhD,1 Maarten Vermaas, MD,1 Gunther Guetens, PhD,2 Gert de Boeck, PhD,2 Ernst A. de Bruijn, PhD,2 and Alexander M. M. Eggermont, MD, PhD1

1Department of Surgical Oncology, Erasmus University Medical Centre—Daniel den Hoed Cancer Centre, PO Box 5201, 3008 AE, Rotterdam, The Netherlands
2Laboratory of Experimental Oncology, University of Leuven—UZ Gasthuisberg, CDG building, Herestraat 49, B-3000, Leuven, Belgium
Isolated liver perfusion
A Phase I Study of Hyperthermic Isolated Hepatic Perfusion with Oxaliplatin in the Treatment of Unresectable Liver Metastases from Colorectal Cancer

Herbert J. Zeh III, MD¹, Charles K. Brown, MD, PhD¹, Matthew P. Holtzman, MD¹, Merrill J. Egorin, MD²,³, Julianne L. Holleran, BS², Douglas M. Potter, PhD⁴, and David L. Bartlett, MD¹

¹Division of Surgical Oncology, Department of Surgery, University of Pittsburgh School of Medicine, Suite 417 UPMC Cancer Pavilion, 5150 Center Ave., Pittsburgh, PA 15232, USA; ²Molecular Therapeutics/Drug Discovery Program, University of Pittsburgh Cancer Institute, Pittsburgh, PA 15232, USA; ³Division of Hematology/Oncology, Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA 15232, USA; ⁴Biostatistics Department, Graduate School of Public Health and Biostatistics Facility, University of Pittsburgh Cancer Institute, University of Pittsburgh, Pittsburgh, PA 15213, USA

TABLE 1 Oxaliplatin dose escalation scheme

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Oxaliplatin dose (mg/m²)</th>
<th>Planned number of patients</th>
<th>Actual number of patients enrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>40⁴</td>
<td>3–6</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>60</td>
<td>3–6</td>
<td>1⁵</td>
</tr>
<tr>
<td>6</td>
<td>90</td>
<td>3–6</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>120</td>
<td>3–6</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>150</td>
<td>3–6</td>
<td>0</td>
</tr>
</tbody>
</table>

¹ MTD
² DLT of grade V VOD and fulminant hepatic failure
IS THERE A ROLE FOR INTRA-ARTERIAL THERAPY OR ISOLATED LIVER PERFUSION?

YES!

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Thanks!