Evolving role of DEBIRI™ with DC Bead® - TACE in mCRC

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Colorectal Liver Metastases

- The liver is the major site of spread for colorectal cancer
- Patients without treatment have poor survival
- Liver resection for colorectal liver metastases (CRLM) may significantly improve survival
Five-year survival of colorectal cancer patients


Liver resection n=3116

Stage III, no liver resection

Stage IV, no liver resection

Overall

Survival probability

Years

0 0.5 1 1.5 2 2.5 3 3.5 4 4.5 5

0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1

Overall  Stage III, no liver resection  Stage IV, no liver resection  Patients with resected liver metastases

Modern approach

- Resect all visible hepatic and localized extra hepatic (lung, nodal, localized peritoneal disease)
- Use of PVE to allow two stage resections
- Combination of resection and ablative techniques
- Vascular resections
Role of pre-operative chemotherapy

• Borderline operable disease

• In-operative disease
Secondary liver resection rates of metastases and tumour response

Jones et al (in press)
Significant improvement in response rates in Phase III trials in 1st line mCRC

- **FOLFIRI + Erbitux**: 57% vs 40%
- **FOLFOXIRI**: 60% vs 34%
- **Ox-CT + Erbitux**: 59% vs 50%

**Response rates (%)**

- **BSC**: 0%
- **Fluoropyrimidine**: 15–25%
- **Irinotecan**: 31–39%
- **Oxaliplatin**: 45–54%
- **FLOX**: 46%
- **IFL + bev**: 43% vs 35%
- **IFL**: 31–39%

**Cancer Type**

- **Capecitabine**: 19–25%

**Gene Mutations**

- **KRAS wt**: 50%
- **5FU**: 15%

**References**

Borderline operable disease
In-operable disease
Caval replacement with Bovine pericardial patch
Problems with pre-operative chemotherapy in liver surgery
Liver after prolonged chemotherapy (not observed after ≤6 cycles)

We used to call this ‘chemotherapy associated steato-hepatosis’ (CASH)

Steatosis and steatohepatitis

Steatohepatitis causes increased post-operative liver failure and death within 90 days

Sinusoidal Obstruction Syndrome

Causes increased peri-operative bleeding*

*Courtesy of Professor Gilles Mentha, University of Geneva
Complete response

Surgical exploration

Macroscopic residual disease: 20 LM

- 30%

No macroscopic residual disease: 46 LM

- 66 metastases disappeared on imaging after CT

15 initial sites resected

Viable tumour cells in 12 sites

- 80%

31 initial sites left in liver

In situ recurrence: 23

- 74%

55/66 (83%) LM non-cured

Benoist et al. JCO 2006;24:3939-45
Macroscopic CR after chemotherapy:
~20% of cells in periphery are viable

Courtesy of Professor Gilles Mentha, University of Geneva
Too much pre-surgery chemotherapy

The liver surgeon’s nightmare

Excessive oxaliplatin:
excessive bleeding at surgery

Excessive irinotecan:
increased risk of post-operative liver failure and 90 day death

“Disappearing” tumours
Targeted chemotherapy?

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Response rate</th>
<th>Secondary resection rate</th>
<th>Survival</th>
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</thead>
<tbody>
<tr>
<td>DEBIRI™ with DC Bead® TACE</td>
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What would be the advantages of DEBIRI™ with DC Bead®- TACE over conventional therapy?

- Single administration, so reduced hepatic and systemic toxicity?
- Targeted, so protecting ‘normal’ liver?
- Could be combined with metal filings to radio-locate disappearing lesions?
- Cheaper?
- Faster action, so possibly shorter delay from treatment to surgery?
Study to evaluate safety/toxicity of targeted neoadjuvant DEBIRI™ with DC Bead® in patients with resectable colorectal liver metastases
Study Design

- Multi-centre, open label, single arm phase II study

- Primary endpoint – tumour resectability at surgery (% with R0 resection)

- Secondary endpoints
  - Adverse events
  - Tumour response on imaging
  - Residual tumour on pathological review of resected tissue
  - Correlation of tumour response on imaging and pathology
  - Survival
<table>
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<tr>
<th>Participating Centres</th>
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<tbody>
<tr>
<td>University Hospital</td>
</tr>
<tr>
<td>Aintree, Liverpool, UK</td>
</tr>
<tr>
<td>Hopital Paul Brousse, Villejuif, France</td>
</tr>
<tr>
<td>Basingstoke Hospital, Basingstoke, UK</td>
</tr>
<tr>
<td>Fundacio Privada de Girona, Spain</td>
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<tr>
<td>Medical University</td>
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<tr>
<td>Vienna, Austria</td>
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<td>Pathology review at a single centre</td>
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</table>
40 patients with easily resectable colorectal liver metastases

One DEBIRI™ with DC Bead® - TACE (Irinotecan loaded beads)

Liver resection 4 weeks later
Trial Design

100-300micron DC Bead® preloaded with irinotecan during manufacture

Aim to give 200mg irinotecan

Selective embolisation to segmental administration
Baseline (PET)CT within 1 month of procedure

DEBIRI™ with DC Bead® - TACE

4 weeks

CT followed by liver resection

Follow up CT at 3, 6, 9 & 12 months.
Technical considerations

Preloaded DC Bead® are easy to use

4 hour “life”

Small tumours more difficulty to localise

Contrast enhanced US C arm CT
Post embolisation procedure

Pain and nausea expected

- Pre procedure NSAIDs
- Manage with IV anti-emetics at time of embolisation
- Post procedure IV Narcotics, Morphine via PCA, IV paracetemol, NSAIs, and occasionally Entonox (inhaled Nitrous oxide)
- Potential benefit of lidocaine

Usual length of stay 24 hours post procedure, maximum 48 hours
Recruited October 2011  
n=49

- TACE performed  
  n=40
  - 1 pancreatitis (2.5%)  
  - 4 post-embolic syndrome (10%)

- TACE not performed  
  n=9
  - 2 arterial access problems  
  - 2 progressive disease  
  - 2 bilobar disease  
  - 1 HCC  
  - 1 allergic to contrast  
  - 1 infection
Results - 2

- 38 (95%) resected
  - 2 had disease progression

- 63% R0 resection rate (clear margins)
  - 37% R1 (margins contain tumour)

- 2 (5%) patients died within 30 days
  - Neither death related to DEBIRI™ with DC Bead® - TACE
    - Aspiration pneumonia
    - Pneumomediastinum after CVC
Radiological response to DEBIRI™ with DC Bead® - TACE

Pre-TACE

4-week post TACE

Progression by RECIST criteria
Pathological Response Rates after Treatment

**Pathological response rates:**
- **Complete response**
- **Major response**
- **Minor response**

<table>
<thead>
<tr>
<th>Pathological response</th>
<th>% lesions</th>
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<tbody>
<tr>
<td>None</td>
<td>2</td>
</tr>
<tr>
<td>Minor</td>
<td>22</td>
</tr>
<tr>
<td>Major</td>
<td>59</td>
</tr>
<tr>
<td>Complete</td>
<td>17</td>
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**Treatment:**
- **DEBIRI™-TACE**
Pathological Response Rates after Treatment

Blazer et al JCO 2008

- Complete response
- Major response
- Minor response

Pathological response:
- None: 2
- Minor: 22
- Major: 59
- Complete: 17

DEBIRI™-TACE
FOLFOX/FOLFIRI
Assessing tumour response
Patient 6 histopathology

Treated metastasis

Untreated metastasis
Subsequent studies in CRLM?

Randomised Phase III

to demonstrate equivalence in safety and 3 yr DFS between DEBIRI™ with DC Bead® - TACE and systemic chemotherapy in the neoadjuvant setting for resectable CRLM

Randomised Phase II/III

to assess the impact of DEBIRI™ with DC Bead® - TACE in addition to systemic chemotherapy in non-resectable CRLM with primary end point being secondary resection
Target recruitment is 180 patients to show a doubling in resection rates

9 UK Centres

Positive review from NCRN liver subgroup

Currently with CTACC re badging – funding secured

Translational research planned
Conclusion

• Neoadjuvant DEBIRI™ with DC Bead® - TACE appears to be safe and R0 liver resections are feasible

• Tumour necrosis rates are encouraging and comparable to systemic chemotherapy

• Phase III study is in preparation