LOCOREGIONAL TREATMENTS ON COLORECTAL CANCER LIVER METASTASES

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ABLATION TECHNIQUES
Local ablation

Radiofrequency ablation has emerged as a safe technique (2% major morbidity and <1% mortality rate) that may provide for long-term tumor control.[18-24] Radiofrequency ablation and cryosurgical ablation [25-28] remain options for patients with tumors that cannot be resected and for patients who are not candidates for liver resection.

MULTIMODALITY IMAGE FUSION IMPROVES NODULES IDENTIFICATION
ALLOWS THE TREATMENT OF MISSING METASTASIS
Before systemic CT

After 6 cycles of CT
Wait for it to come back?
COMPLETE RESPONSE OF COLORECTAL LIVER METASTASES AFTER CHEMOTHERAPY: DOES IT MEAN CURE?

66 patients: Surgical Exploration

Macroscopic residual disease: 20 LM

- 30%

No macroscopic residual disease: 46 LM

- 80%

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. J Clin Oncol 2006;24:3939-45
PD-1 blockade in mismatch repair deficient non-colorectal gastrointestinal cancers.

Dung T. Le et al.
3 months control
DRUG ELUTING BEADS INFUSION
Hepatic arterial infusion versus systemic therapy for hepatic metastases from colorectal cancer: a randomized trial of efficacy, quality of life, and molecular markers (CALGB 9481)
CALGB 9481

- 135 prospective patients
- M1 liver, non resectable
- First line
- HAI: Floxuridine (0.18 mg \cdot kg \cdot 30 \text{ mL}) + Leucovorin (4 mg \cdot m^2 \cdot 30 \text{ mL})
- Systemic: Fluorouracil (425 mg/m^2) + Leucovorin (20 mg/m^2)

<table>
<thead>
<tr>
<th></th>
<th>HAI</th>
<th>Systemic</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td>24 months</td>
<td>20 months</td>
<td>.0034</td>
</tr>
<tr>
<td>Response</td>
<td>47 %</td>
<td>24 %</td>
<td>.012</td>
</tr>
<tr>
<td>Time hepatic progression</td>
<td>9.8 months</td>
<td>7.3 months</td>
<td>.034</td>
</tr>
<tr>
<td>Time extrahepatic progression</td>
<td>7.7 months</td>
<td>14.8 months</td>
<td>.029</td>
</tr>
<tr>
<td>Neutropenia: grade &gt; 3</td>
<td>2 %</td>
<td>45 %</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>Estomatisis</td>
<td>0 %</td>
<td>24 %</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>Rise Brb</td>
<td>18.6 %</td>
<td>0 %</td>
<td>&lt; .01</td>
</tr>
</tbody>
</table>

Conclusion
HAI therapy increased overall survival, response rate, THP, and was associated with better physical functioning compared with systemic therapy. Additional studies need to address the overall benefit and cost of new chemotherapy agents versus HAI alone or the combination of HAI with new agents.

J Clin Oncol 24:1395-1403. © 2006 by American Society of Clinical Oncology
Hepatic arterial infusion combined with oral UFT/UZEL systemic chemotherapy for unresectable liver metastasis of colorectal cancer
• 16 patients
• M1 hepatic non resectable
• First line
• HAI 5-FU (1000 mg/m2) and Leucovorin (50 mg/m2)
• Together with systemic Uracil/Tegafur (UFT) (300 mg/m2) and Leucovorin (75 mg)
• Response rate: 87.5% (14 RPR and 2 DE)
• Free progression survival: 9.2 months
• Mean Survival: 22 months.
• No side effects grade > 2
Conversion to resectability using hepatic artery infusion plus systemic chemotherapy for the treatment of unresectable liver metastases from colorectal carcinoma

• 49 prospective patients
• 24 of them 1st line
• M1 liver non resectable
• HAI floxuridine (0.12 mg/kg · 30/flujo) and dexametasone (1 mg/kg · 30/flujo)
• Plus oxaliplatine (85-100mg/m2) and irinotecan (100-200mg/m2)
- 45 patients (92%): PR (84%) or CR (8%)
- 47% resectable
- Survival mean: 39.8 m
  - Among those 1st line:
    - Response rate 100%
    - Resectability 57%
    - Mean of survival 50.8 m
Comparison of Adjuvant Systemic Chemotherapy With or Without Hepatic Arterial Infusional Chemotherapy After Hepatic Resection for Metastatic Colorectal Cancer
**Results:** The median follow-up for all patients was 43 months. There were no differences in clinical risk score, disease-free interval, size of largest CRLM, number of CRLM, or prehepatectomy CEA level between the 2 groups. Adjuvant HAI-FUDR was associated with an improved overall and liver recurrence-free survival (liver RFS) and disease-specific survival (DSS). For the adjuvant HAI-FUDR group, the 5-year liver RFS, overall RFS, and DSS were 75%, 48%, and 79%, respectively, compared to 55%, 25%, and 55% for the systemic alone group ($P < 0.01$). On multivariate analysis, adjuvant treatment including HAI-FUDR was independently associated with improved liver RFS (HR = 0.34), overall RFS (HR = 0.65), and DSS (HR = 0.39), $P < 0.01$.

**Conclusions:** Adjuvant HAI-FUDR combined with modern systemic chemotherapy is independently associated with improved survival compared to adjuvant systemic chemotherapy alone. A randomized clinical trial between these 2 regimens is justified.

*(Ann Surg 2011;00:1–6)*
SYSTEMIC CHEMOTHERAPY LIMITATIONS

• Do not reach the target site in optimal quantities

• Not effective enough in tumour microenvironment

• Non functioning lymphatic system allows drug escaping

Reddy LH et al. J. Pharm. Pharmacology, 2005, 57, 1231-1242
Several reasons contribute to this failures:

• Unfavourable pharmacokinetics of drugs (rapid clearance and biodegradation determining a short plasma life)
• Large biodistribution and non-intended extravasation of chemotherapy agents induce severe toxicity in non-targeted lesion
• Poor tumour selectivity
• Susceptibility to induce drug resistance in tumour cells
• Unfavourable physiological properties (ex: hydrophobicity) promotes unsuccessful drug accumulation at desired region

Possible solutions:

• Biodegradable polymeric particles
• **Hydrogels**
• Vesicular systems: liposomes and niosomes
• Magnetic drug delivery systems
• Lipoproteins
• Clay minerals and anionic clays
• Metals
• Ion exchange resins
IA DEB ADVANTAGES

1. Lesion/organ targeting (tumour selectivity)
2. Anoxia to the tumor
3. Prolonged chemotherapy release
   (high exposure and high drug dose to metastases)
4. Low systemic exposure
NON DESIRED EFFECTS OF TACE

- Increased circulating cells and metastases
- Increased HIF 1α
- Increased release of factors promoting angiogenesis
- Increased interstitial pressure
- Low pH environment
- Hypoxia
WHAT DO YOU PREFER? NORMOXIA, HYPOXIA OR ANOXIA?
HYPOXIA AND ANOXIA

HYPOXIA AND ANOXIA

• Murono K et al. **SN-38 overcomes chemoresistance of colorectal cancer cells induced by hypoxia, through HIF1alpha.** Anticancer Res. 2012 Mar;32(3):865-72

• Jones RP et al. **Hepatic activation of irinotecan predicts tumour response in patients with colorectal liver metastases treated with DEBIRI: exploratory findings from a phase II study.** Cancer Chemother Pharmacol. 2013 Aug;72(2):359-68
100 mg irinotecan en LHD
100 mg irinotecan en LHI
SEGMENTAL OR LOBAR DEB TACE FOR METASTASES?
SEGMENTAL OR LOBAR

SEGMENTAL OR LOBAR

Vessel co-option

• Unresponsive to VEGF family blocking
• Perfect target for DEB-TACE while controlling angiogenesis?
December 2011 - April 2013: 22 DEBIRI en 9 patients

Mean time from diagnosis to 1st DEBIRI: 17 months

Response: RECIST 1.1

Toxicity: CTCAE v3.0 and VAS
<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median)</td>
<td>62 years (range 42-67)</td>
</tr>
<tr>
<td>Sex male/female</td>
<td>7 (78%)/2 (22%)</td>
</tr>
<tr>
<td>ECOG PS 0/1</td>
<td>8 (89%)/1 (11%)</td>
</tr>
<tr>
<td>KRAS mutated/native</td>
<td>5 (56%)/4 (44%)</td>
</tr>
<tr>
<td>Primary tumor Colon/Recto</td>
<td>8 (89%)/1 (11%)</td>
</tr>
<tr>
<td>Metastasis chronology synchronic/methacrhonous</td>
<td>8 (89%)/1 (11%)</td>
</tr>
<tr>
<td>Previous metastasectomy</td>
<td>6 (67%)</td>
</tr>
<tr>
<td>CEA pre-DEBIRI (mean)</td>
<td>65 ng/mL</td>
</tr>
<tr>
<td>CEA post-DEBIRI (mean)</td>
<td>22 ng/mL</td>
</tr>
<tr>
<td>Patients characteristics</td>
<td>Frecuency</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Lines of CT before (mean)</td>
<td>2 (range 1-4)</td>
</tr>
<tr>
<td>DEBIRI 2nd line CT</td>
<td>2 (22%)</td>
</tr>
<tr>
<td>DEBIRI en 3rd line CT</td>
<td>6 (67%)</td>
</tr>
<tr>
<td>DEBIRI en 4th line CT</td>
<td>1 (11%)</td>
</tr>
<tr>
<td>Administration Bevacizumab</td>
<td>8 (89%)</td>
</tr>
<tr>
<td>Nº cycles Bevacizumab (mean)</td>
<td>8 (range 4-24)</td>
</tr>
<tr>
<td>Anti-EGFR</td>
<td></td>
</tr>
<tr>
<td>- Cetuximab</td>
<td>4 (44,4%)</td>
</tr>
<tr>
<td>- Panitumumab</td>
<td>2 (22,2%)</td>
</tr>
<tr>
<td>Mean cycles anti-EGFR</td>
<td>8 (range 1-16)</td>
</tr>
</tbody>
</table>
RESULTS

- Median DEBIRIs: 3 (range: 1-6)
- Irinotecan dose: 255.5 mg (range: 100-600 mg)
- Follow-up: 17.5 months
- PFS: 5 months (IC 95%= 3-6)
- 12 months OS: 89%
TASA DE RESPUESTA

- RESPUESTA COMPLETA: 66,7%
- RESPUESTA PARCIAL: 22,2%
- ESTABILIZACIÓN ENFERMEDAD: 11,1%
### Acute Toxicity (24h): n=22

<table>
<thead>
<tr>
<th>Effect</th>
<th>G3</th>
<th>G1-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperbilirubinemia</td>
<td>2 (9%)</td>
<td>0</td>
</tr>
<tr>
<td>Emesis</td>
<td>1 (4.5%)</td>
<td>2 (9%)</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>0</td>
<td>1 (4.5%)</td>
</tr>
<tr>
<td>Pain</td>
<td>1 (4.5%)</td>
<td>8 (36.3%)</td>
</tr>
</tbody>
</table>
Dolor - Puntuación media en la Escala Visual Analógica (EVA) = 3’78

Escala visual analógica

0 1 2 3 4 5 6 7 8 9 10

X

No dolor

1 cm

El peor dolor imaginable
Late toxicity (30 days): n=22

<table>
<thead>
<tr>
<th>Effect</th>
<th>G3</th>
<th>G1-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertransaminasemia</td>
<td>0</td>
<td>1 (4.5%)</td>
</tr>
<tr>
<td>Liver failure</td>
<td>1 (4.5%)</td>
<td>0</td>
</tr>
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</table>
NEOADJUVANT DEBIRI FOR RFA?
NEOADJUVANT DEBIRI FOR RFA?
NEOADJUVANT DEBIRI FOR RFA?
DEBIRI IN OTHER LOCATIONS
DEBIRI IN OTHER LOCATIONS
DEBIRI IN OTHER LOCATIONS
DEBIRI IN OTHER LOCATIONS
INTRA-ARTERIAL RADIATION THERAPY ($^{90}\text{Y}$)
Study Design

• A phase III, open label, prospective, multi-center, randomized clinical trial

• 24 months accrual and 12 months additional follow-up (with up to a maximum of 33 months accrual based on sample size re-estimation)

• 340 patients with up to a maximum of 500 patients based on sample size re-estimation

• 100 sites in US, Canada, EU and Asia
Randomization 1: 1 between treatment and control group

Stratified according to:
- unilobar or bilobar disease
- first-line chemotherapy
- KRAS status
Study Objective:
To evaluate the efficacy and safety of TheraSphere® in patients with metastatic colorectal cancer of the liver scheduled to receive second line chemotherapy

Primary Endpoint:
Progression-Free Survival (PFS) according to RECIST Criteria v1.1 from time of randomization
Overall Survival (OS) Time
Calculated from randomization to death

Hepatic Progression-Free Survival (HPFS):
The time from randomization to the date of disease progression in the liver according to RECIST 1.1

Time to symptomatic progression (TTSP)
• From the time of randomization to assessment of ECOG performance status >2
• Deterioration in performance status is to be confirmed at one subsequent evaluation 8 weeks later
TS-102 EPOCH
SECONDARY ENDPOINTS

Disease Control Rate
Per RECIST criteria v1.1 for all targeted [liver] tumors

Quality of Life
Functional Assessment of Cancer Therapy colorectal cancer (FACT-c)

Adverse events and reportable serious adverse events
Defined by the study protocol (NCI Common Toxicity Criteria for Adverse Events; CTCAE v. 4.0)
**TS-102 EPOCH**

**Treatment Arm**

Initiate 2nd line CTX ≥14 days from last administration of all first line agents

Randomization (Takes place ≥14 days from end of 1st line CTX and anti-VEGF therapy)

Patients with metastatic CRC of the liver

14 day screening period

Administer TS to both lobes (pts with bilobar disease) or single lobe (pts with unilobar disease) on the same treatment day in place of 2nd cycle of chemo.

Study Visit Q 8 weeks until progression

Continue 2nd line CTX

Primary Endpoint PFS

Secondary Endpoint OS

Hepatic Progression: Subsequent TS work-up and administration

TS treatment replaces 1 cycle of CTX; anti-VEGF/EGFR washout required

Study Visit Q 8 weeks until death

Hepatic Progression: Best Alternative Care

**Control Arm**

Initiate 2nd line CTX ≥14 days from last administration of all first line agents

Continue 2nd line CTX

**Progression**

*Note – one cycle of chemotherapy is given prior to treatment with TheraSphere*

Version date 06-Jun-2013 (protocol V 5.1 30-May-2014)