Analysis of Clinical Toxicity in Patients Undergoing Percutaneous Intra-Arterial Hepatic Perfusion (PHP) with Melphalan for Unresectable Hepatic Malignancies

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Rationale for Regional Therapy

Regional therapy allows **dose escalation** to the cancer-bearing region or organ of the body while minimizing systemic exposure and toxicity, via complete separation of the regional and systemic circulation.

Eliminates or significantly **reduces systemic toxicity**, and dose escalation of therapeutic agents is limited largely by the tissue tolerance of the perfused organ/limb.

- Improved efficacy/tumor response

Based on its unique **vascular anatomy**, the liver is a favorable site for delivery of regional therapy.

- Established tumors in liver derive the majority of blood flow from the arterial tree (tumors: 100% versus normal liver: 25%)

Potential for delivery of clinically relevant levels of **hyperthermia** or **biologic agents**

Allows treatment of the **entire tumor burdened organ**

- Versus local ablative or selective embolization procedures
Treatment of Hepatic Metastases
Rationale for Regional Therapy

Unresectable cancers (primary or metastases) confined to liver are a significant clinical problem:

Colorectal cancer: 30,000/yr
Hepatocellular carcinoma: 16,000/yr
Ocular melanoma: 2,000/yr
Neuroendocrine tumors: 2,000/yr
Other histologies: ?

Therapeutic options are limited and survival after diagnosis of liver metastases is short.

Morbidity and mortality in this setting is invariably secondary to disease progression in the liver.
Background: Isolated Hepatic Perfusion

Colorectal Metastases  
- n=120 pts  
- RR: 60%, Median OS: 17.4m

Ocular Melanoma Metastases  
- n=29 pts  
- RR: 62%, Median OS: 12.1m

Neuroendocrine Metastases  
- n=13 pts  
- RR: 50%, Median OS: 48m
Delcath Systems double balloon IVC catheter
Percutaneous Hepatic Perfusion
Protocol Schema

On Study Evaluation

- **Treatments 1 and 2**
  - Melphalan
  - Angiogram (Celiac, SMA)
  - GDA assessment (Treatment #1)

  - 4 Weeks

Interval Evaluation

- **Treatments 3 and 4**
  - Melphalan
  - Angiogram (Celiac, SMA)
  - GDA assessment

  - 4 Weeks

Post Treatment Evaluation

- 4 Weeks
- 4 Weeks

16 weeks
Chemotherapy Levels During Therapy

Hepatic Arterial Infusion with Venous Filtration
(Patient: Hemberger B, 5/23/03, 3.5 mg/kg, 178 mg)

Time (min)
0 10 20 30 40 50 60 70
Melphalan Concentration (µg/ml)
0 5 10 15 20
Periphery Artery
Pre-filter
Post-filter

Infusion

Hepatic Arterial Infusion with Venous Filtration
(Patient: William A, 3/4/03, 3 mg/kg, 178 mg)

Time (min)
0 10 20 30 40 50 60 70
Melphalan Concentration (µg/ml)
0 5 10 15 20
Periphery Artery
Pre-filter
Post-filter

Infusion

Hepatic Arterial Infusion with Venous Filtration
(Patient: Russo, 4/16/02, 2 mg/kg)

Time (min)
0 10 20 30 40 50 60 70
Melphalan Concentration (µg/ml)
0 2 4 6 8
Periphery Artery
Pre-filter
Post-filter

Infusion

Hepatic Arterial Infusion with Venous Filtration
(Patient: Hannigan MP, 12/10/02, 2.5 mg/kg)

Time (min)
0 10 20 30 40 50 60 70
Melphalan Concentration (µg/ml)
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Pre-filter
Post-filter

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Infusion
Results: Toxicity
(198 Treatments)

Mean Melphalan Dose at 3.0 mg/kg: 180 mg (126-220)

Unsuccessful Therapy
- Hepatic artery dissection (n=2)
- Sclerotic hepatic artery (n=3)
- Hepatic venous anomaly (n=3)

Toxicity (Grade III/IV)
- Neutropenia: 120 (60.6%)
- Thrombocytopenia: 96 (48.5%)
- Anemia: 36 (18%)
- Hepatic (LFTs, Bili): 31 (15.7 %)

Median Length of Stay: 3 days
Results: Patient Demographics

Patients: 76
Number of Treatments: 198
Unsuccessful Treatments: 8
Histology:
  Melanoma: 26
  Neuroendocrine: 19
Results: Complications
(198 Treatments)

Arterial or Venous Catheters
  Hepatic Artery Dissection (n=2)
  Cervical Hematoma (n=1)
  Pneumothorax (n=1)

Bleeding
  Intrahepatic (Tumor) Hemorrhage (n=1)
  Excessive Menstrual Bleeding (n=2)
  Gross Hematuria (n=1)

Other
  Heparin Induced Thrombocytopenia (n=1)
  Transient Ascites (n=1)
  Protamine Reaction (n=1)
  Melphalan Anaphylaxis (n=1)
  Hepatorenal Syndrome (n=1)
### PHP for Patients with Metastatic Melanoma

#### Radiographic Treatment Response

(n=16)

<table>
<thead>
<tr>
<th>Response</th>
<th>n</th>
<th>%</th>
<th>Duration</th>
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</thead>
<tbody>
<tr>
<td>Overall</td>
<td>8</td>
<td>50</td>
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</tr>
<tr>
<td>Complete</td>
<td>2</td>
<td>13</td>
<td>10, 15</td>
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<tr>
<td>Partial</td>
<td>6</td>
<td>37.5</td>
<td>2+, 8, 8, 12, 15, 16</td>
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<tr>
<td>Stable Disease</td>
<td>4</td>
<td>25</td>
<td>7, 7, 8, 8+</td>
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<tr>
<td>Progressive Disease</td>
<td>4</td>
<td>25</td>
<td></td>
</tr>
</tbody>
</table>

#### Follow-up Status

- AWD\(^{b}\): 1, 6
- DOD: 15, 94

#### Site of Disease Recurrence/Progression (n=11 responders)

- Hepatic: 6, 50
- Systemic: 4, 33
- Both: 2, 17

\(^{a}\) + censored with stable or responding hepatic disease with systemic progression

\(^{b}\) AWD, alive with disease; DOD, dead of disease
Metastatic Glucagonoma

54 year-old female
Metastatic pancreatic neuroendocrine tumor
Primary in place, treated post PHP with XRT

Glucagon.
Metastatic Glucagonoma

Pre-Treatment
April 2003

Post-PHP x 2
November 2003

Follow-up (22m)
March 2005
Conclusions

This strategy allows for the delivery of high-dose, intra-arterial cytotoxic chemotherapy with manageable regional and systemic toxicity.

Regional delivery of chemotherapy paired with hemofiltration allows for an increased therapeutic index for cytotoxic agents such as melphalan.

PHP with Melphalan is effective in patients with hepatic metastases from melanoma and gastrointestinal neuroendocrine metastases.
Future Directions

Metastatic Ocular Melanoma
   Phase III random-assignment trial vs. Best alternative care
   Primary endpoint: Hepatic DFS (cross-over permitted)
   Conversion to multi-center trial

Metastatic Neuroendocrine Tumors
   Phase II trial, completion of second stage, expand to multicenter phase II

Hepatocellular Carcinoma
   Completion of Phase II study

Metastatic Colorectal Cancer
   Phase I trial with Oxaliplatin post completion of pre-clinical animal studies
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