Pharmacokinetic Analysis of Percutaneous Hepatic Perfusion of Melphalan in Patients with Hepatic Metastases from Melanoma

Erin R. Gardner,¹ William D. Figg,¹ H. Richard Alexander Jr.,² and Daniel S. Johnston,³ on behalf of phase 3 Investigators

¹Clinical Pharmacology Program, Center for Cancer Research, National Cancer Institute, Bethesda, MD; ²Department of Medicine, University of Maryland School of Medicine, Baltimore, MD; ³Delcath Systems, Inc., Queensbury, NY, USA
Background

- Chemosaturation therapy with percutaneous hepatic perfusions (CS-PHP; CHEMOSAT®; Delcath Systems, Inc, NY, USA) is a minimally invasive, repeatable regional therapy.
- It is available in the EU and is currently undergoing FDA review.
- A randomized phase 3 study (n=93) showed that CS-PHP using high-dose melphalan significantly prolonged hepatic progression-free survival versus best alternative care (BAC) in patients with ocular or cutaneous melanoma metastatic to the liver.
- A pharmacokinetic analysis of CS-PHP delivery of melphalan, including an evaluation of filter extraction efficiency, was performed in a subset of patients from the phase 3 study.
Study design

Patients

- Plasma samples were available from 40 evaluable patients

Treatment

- Melphalan 3.0 mg/kg as a 30-minute hepatic intra-arterial infusion via CS-PHP
- Extracorporeal filtration performed during infusion and for an additional 30 minutes after end of infusion (washout)
- Performed under general anesthesia
Pharmacokinetic sampling

- Blood samples were collected during cycle 1
- Samples (7 mL) were collected from 3 sites:
  - systemic (arterial line in the arm)
  - extracorporeal circuit (pre-filter)
  - extracorporeal circuit (post-filter)
- Sample collection times: baseline; mid-infusion; immediate post-infusion; and 5, 10, 15, and 30 minutes post-infusion
- Plasma concentrations of melphalan were determined by high-pressure liquid chromatography with ultraviolet detection using a validated assay
Pharmacokinetic analysis

- Data were analyzed using a non-compartmental approach with WinNonlin v5.2 (Pharsight Corporation, Mountain View, CA).
- Concentration-time profiles were constructed for each sampling site (i.e. 3 profiles/patient).
- Pharmacokinetic parameters:
  - maximum plasma concentration ($C_{\text{max}}$)
  - area under the concentration-time curve from time zero to final sample ($AUC_{\text{last}}$) calculated using the linear trapezoidal method
  - filter efficiency = $\frac{(\text{pre-filter } AUC_{\text{last}}) - (\text{post-filter } AUC_{\text{last}})}{(\text{pre-filter } AUC_{\text{last}})}$
# Melphalan dose

## Doses and perfusion rates during cycle 1 (n=40)

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute dose, mg</td>
<td>191 ± 24</td>
<td>137–220</td>
</tr>
<tr>
<td>Duration of perfusion, min</td>
<td>30 ± 7</td>
<td>16–52</td>
</tr>
<tr>
<td>Theoretical rate of perfusion,* mg/kg/min</td>
<td>0.10 ± 0.02</td>
<td>0.06–0.19</td>
</tr>
<tr>
<td>Theoretical rate of perfusion,* mg/min</td>
<td>6.6 ± 1.7</td>
<td>4.2–12.9</td>
</tr>
</tbody>
</table>

*Amount of drug administered divided by duration of perfusion assuming a constant rate of perfusion.
# Melphalan exposure

<table>
<thead>
<tr>
<th>Sample site</th>
<th>N</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</th>
<th>AUC&lt;sub&gt;last&lt;/sub&gt; (min • ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean</td>
<td>Range</td>
</tr>
<tr>
<td>Pre-filter</td>
<td>40</td>
<td>8728</td>
<td>4026–14,367</td>
</tr>
<tr>
<td>Post-filter</td>
<td>40</td>
<td>2330</td>
<td>930–4292</td>
</tr>
<tr>
<td>Systemic</td>
<td>37</td>
<td>1429</td>
<td>701–3203</td>
</tr>
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</table>

- Mean filter efficiency was 71.2% (range 26.4–86.8%)
- Filter efficiency did not appear to be influenced by melphalan dose
Melphalan exposure

$C_{\text{max}}$ by sample site

$\text{AUC}_{\text{last}}$ by sample site

Horizontal bars represent the mean and 95% CIs

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Concentration-time profile

- Melphalan infusion
- Hemofiltration
- Hepatic Dose
- Systemic Dose

Concentration (ng/mL)

Time (min)
Conclusions

- CS-PHP effectively exposes the liver to high concentrations of melphalan
- The mean filter extraction efficiency of the first-generation CS-PHP filtration system is 71%
- Filter extraction efficiency appears to be consistent across patients (narrow 95% confidence intervals)
- The filter consistently removes most of the melphalan administered via CS-PHP
- The PK and filter extraction efficiency data support the clinical evidence of substantial regional efficacy of CS-PHP in controlling liver-dominant metastases with a manageable safety profile