

Percutaneous Hepatic Perfusion (CHEMOSAT® or CS-PHP) of Melphalan in Patients (pts) with Hepatic Metastases from Melanoma: Phase III Pharmacokinetic Analysis

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Background: CS-PHP (Chemostat®; Delcath Systems Inc, New York, NY) is a regional therapy which: i) isolates the liver using a system of percutaneously positioned catheters; ii) delivers high-dose chemotherapy directly into the hepatic artery; and iii) minimizes systemic toxicity by hemofiltration of hepatic venous blood. **Methods:** A randomized phase III study compared CS-PHP delivery melphalan with best alternative care in pts with liver metastases from melanoma. A pharmacokinetic analysis was performed in a subset of pts from this study. Pts received melphalan 3.0 mg/kg ideal body weight via CS-PHP over 30 min with 60 min of hemofiltration starting at the time of perfusion. Blood samples (7 mL) were collected during cycle 1. Sample collection sites: arterial line; prefilter (extracorporeal circuit); postfilter (extracorporeal circuit). Sampling times: baseline; mid-infusion; immediate post-infusion; 5, 10, 15, 30 min post-infusion. Melphalan plasma concentrations were determined by HPLC with UV detection. Data were analyzed using a non-compartmental approach. Pharmacokinetic parameters: maximum plasma concentration (C_{max}); area under concentration-time curve from t_0 to final sample (AUC_{last}); filter efficiency [(pre-filter AUC_{last}) minus (post-filter AUC_{last}) divided by (pre-filter AUC_{last})]. **Results:** Plasma samples were available from 48 pts, of which 40 were evaluable. Mean absolute melphalan dose was 191mg (range 137-220mg) and duration of perfusion was 30 min (range 16-52 min). Mean filter extraction efficiency was 71.2%±10.4%. Filter efficiency did not change significantly with absolute melphalan dose ($p=0.86$, Spearman) or rate of perfusion ($p=0.064$, Spearman). **Conclusions:** CS-PHP exposes the liver to high concentrations of melphalan. Filter extraction efficiency is consistent among pts and does not appear to be influenced by melphalan dose or rate of perfusion.

| Sample site | N | C_{max} (ng/mL) | | AUC_{last} (min.ng/mL) | |
|-------------|----|-------------------|-------------|--------------------------|-----------------|
| | | mean | range | mean | range |
| Prefilter | 40 | 8728 | 4026-14,367 | 264,652 | 143,441-470,501 |
| Postfilter | 40 | 2330 | 930-4292 | 74,146 | 27,333-154,049 |
| Systemic | 37 | 1429 | 701-3203 | 50,777 | 25,566-111,362 |

Key words: melphalan; pharmacokinetics; hepatic perfusion; filtration

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