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

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Background: Percutaneous Hepatic Perfusion (PHP, Delcath Systems Inc, New York, NY) is a non-invasive regional therapy that isolates the liver using a series of catheters, allowing infusion of high doses of chemotherapy directly into the hepatic artery. Systemic toxicity is minimized by extracorporeal hemofiltration of effluent hepatic venous blood, which is then returned to the systemic circulation. A randomized phase III study was conducted to compare PHP of high-dose melphalan with best alternative care in patients with ocular or cutaneous melanoma metastatic to the liver. A pharmacokinetic analysis, including an evaluation of filter extraction efficiency, was performed in a subset of patients from this study. **Methods:** Melphalan was perfused into the liver over 30 minutes via PHP at a maximum dose of 3.0 mg/kg of ideal body weight (maximum 220 mg/treatment). Extracorporeal hemofiltration was performed during and for 30 minutes after melphalan infusion. PHP was performed with patients under general anesthesia. Blood samples (7 mL) were collected during the first cycle of PHP melphalan simultaneously from the periphery (arterial line) and extracorporeal circuit (both pre- and post-filter). Sample collections were made at: baseline (peripheral only); 15 minutes after the start of the infusion; immediately post-infusion; 5, 10, 15, and 30 minutes post-infusion. Plasma concentrations of melphalan were determined by high-pressure liquid chromatography with ultraviolet detection. 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 location (i.e. three profiles/patient). Pharmacokinetic parameters were: maximum plasma concentration (C_{max}); area under the concentration-time curve from time zero to final sample (AUC_{last}) calculated using the linear trapezoidal method; and filter efficiency [defined as: (pre-filter AUC_{last}) minus (post-filter AUC_{last}) divided by (pre-filter AUC_{last})]. **Results:** Plasma samples were available from 48 patients, of which 40 were evaluable. Mean absolute melphalan dose was 191 mg (range, 137–220 mg) and duration of perfusion was 30 minutes (range, 16–52 minutes). Mean prefilter, postfilter and systemic C_{max} values were 8726 ng/mL, 2330 ng/mL and 1429 ng/mL, respectively. Mean prefilter AUC_{last} was 264,652 min*ng/mL, mean postfilter AUC_{last} was 74,146 min*ng/mL and mean systemic AUC_{last} was 50,777 min*ng/mL; individual patient data for AUC_{last} are shown in the Figure. Mean filter extraction efficiency was 71.2% ± 10.4%. Filter efficiency did not change significantly with absolute melphalan dose (p=0.86, Spearman) or theoretical rate of perfusion (p=0.064, Spearman). **Conclusions:** The mean filter extraction efficiency of the PHP filtration system is 71%, and results appear to be consistent across patients (narrow 95% CI intervals). These findings indicate that the filter removes most of the melphalan administered via PHP.

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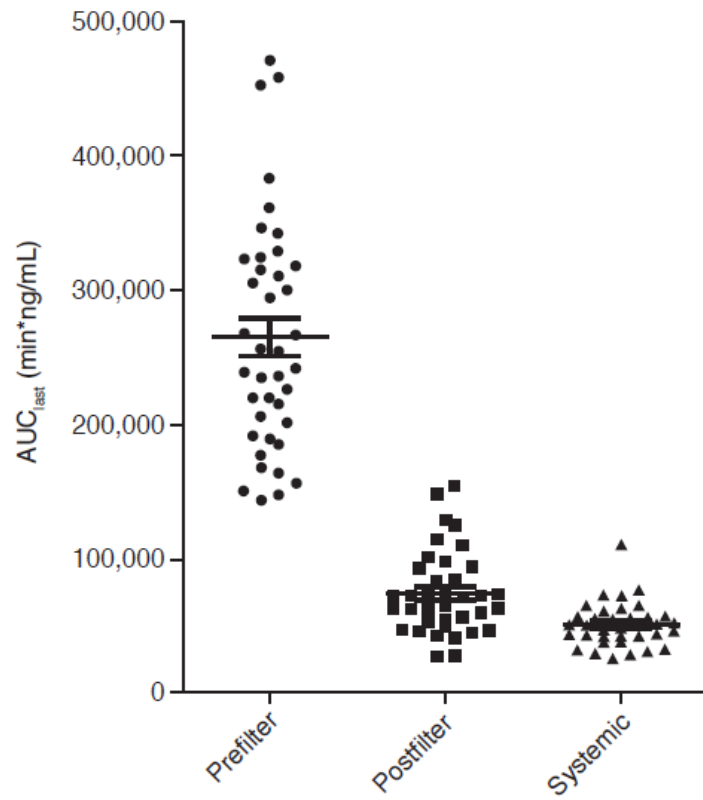
Figure. Individual AUC_{last} by site, after 3.0 mg/kg (ideal body weight) melphalan

Horizontal bars represent mean and 95% CIs