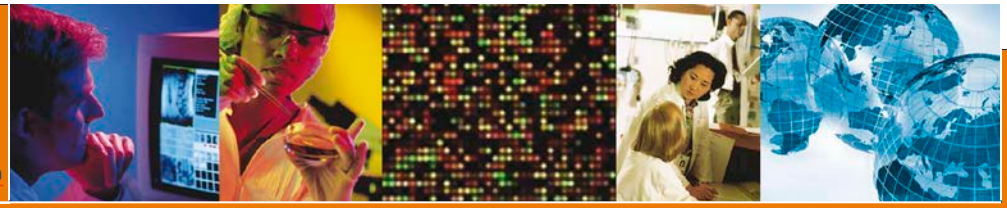
P-143

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

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

ILCA
International Liver Cancer Association



Background

- Chemosaturation therapy with percutaneous hepatic perfusions (CS-PHP; CHEMOSAT®; Delcath Systems, Inc, NY, USA) is a minimally invasive, repeatable regional therapy[1]
- 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[2]
- 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

ILCA
International Liver Cancer Association

1. Pingpank JF, et al. JCO 2005;23:3465-74
2. Pingpank JF, et al. JCO 2010;28:18s (suppl; abstr LBA8512)

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_{max})
  - area under the concentration-time curve from time zero to final sample (AUC_{last}) calculated using the linear trapezoidal method
  - filter efficiency = $\frac{(\text{pre-filter } AUC_{last}) - (\text{post-filter } AUC_{last})}{(\text{pre-filter } AUC_{last})}$

Melphalan dose

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

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

*Amount of drug administered divided by duration of perfusion assuming a constant rate of perfusion

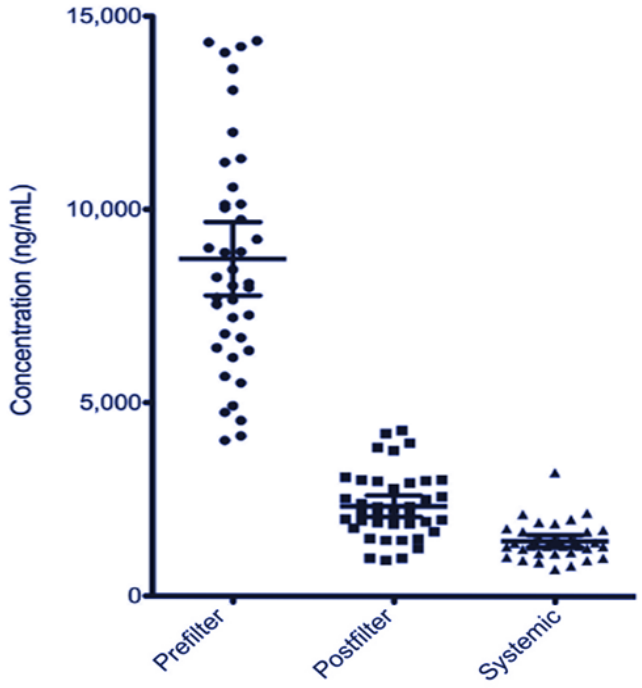
Melphalan exposure

Sample site	N	C_{max} (ng/mL)		AUC_{last} (min • ng/mL)	
		Mean	Range	Mean	Range
Pre-filter	40	8728	4026–14,367	264,652	143,441–470,501
Post-filter	40	2330	930–4292	74,146	27,333–154,049
Systemic	37	1429	701–3203	50,777	25,566–111,362

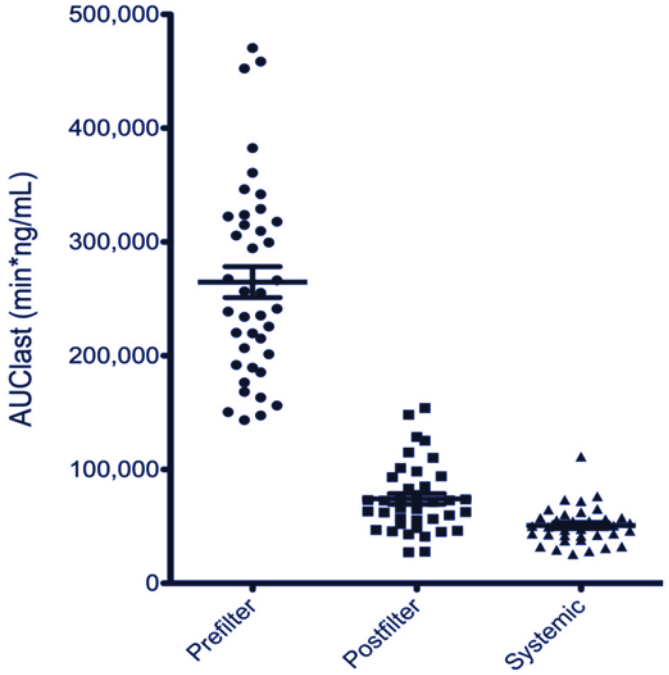
- Mean filter efficiency was 71.2% (range 26.4–86.8%)
- Filter efficiency did not appear to be influenced by melphalan dose

Melphalan exposure

C_{max} by sample site

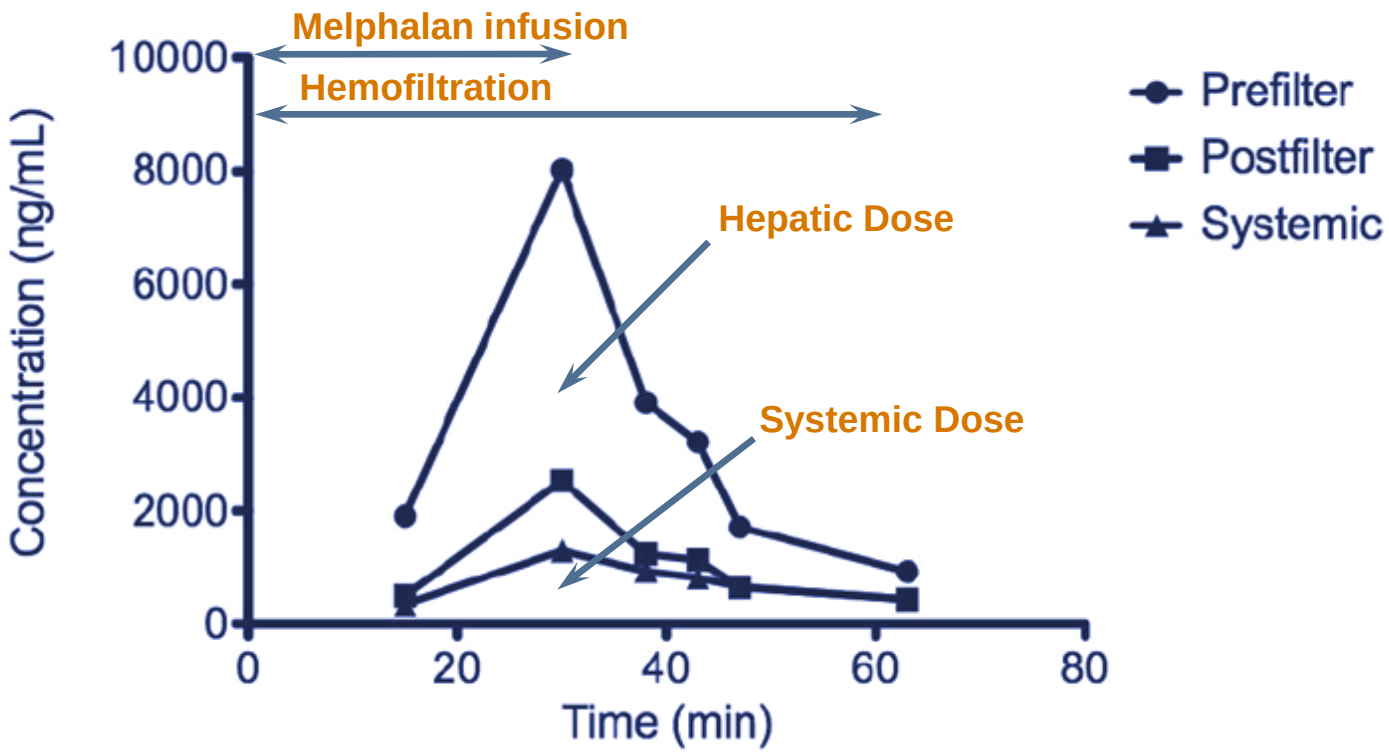


AUC_{last} by sample site



Horizontal bars represent the mean and 95% CIs

Concentration-time profile



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