#476

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

E.R. Gardner,[1] William D. Figg,[1] Marybeth S. Hughes[2] and James F. Pingpank[2]

[1]Clinical Pharmacology Program and [2]Surgery Branch, Center for Cancer Research, National Cancer Institute, Bethesda, MD, USA

Background

- Chemosaturation therapy with percutaneous hepatic perfusions (Chemosat®*; CS-PHP) is a minimally invasive, repeatable regional therapy which:
  - allows percutaneous inter-arterial administration of a chemotherapeutic agent to the liver
  - subsequently filters the regional (hepatic) venous blood by extracorporeal filtration[1]
  - lowers the concentration of chemotherapeutic agent in the blood before returning it to the systemic venous circulation.
- Clinical implementation of CS-PHP is ongoing.

*Delcath Systems, Inc., NY, NY, USA

Purpose

- A randomized phase III study compared CS-PHP of high-dose melphalan with best alternative care (BAC) in patients with ocular or cutaneous melanoma metastatic to the liver:[2]
  - a statistically significant improvement in hepatic progression-free survival, the primary endpoint, was seen with a hazard ratio of 0.36 (95% CI 0.23–0.54; p<0.0001) with CS-PHP melphalan versus BAC.[3]
- A pharmacokinetic analysis of CS-PHP melphalan, including an evaluation of filter extraction efficiency, was performed in a subset of patients from this study.

Study design

- Randomized, open-label, multicenter phase 3 study.

Patients

- Ocular or cutaneous metastatic melanoma predominantly in the liver parenchyma with limited extra-hepatic disease.

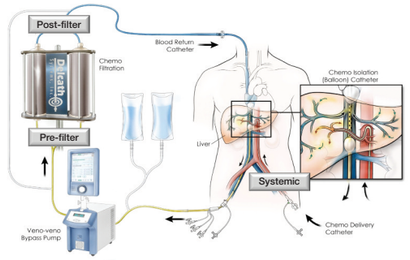
Treatment

- Melphalan CS-PHP:
  - 3.0 mg/kg as a 30-minute hepatic intra-arterial infusion
  - an additional 30 minutes of extracorporeal filtration at end of infusion (washout)
  - under general anesthesia
  - allowed up to 6 treatments, repeated every 4–8 weeks.

Pharmacokinetic sampling

- Blood samples were collected during cycle 1 of CS-PHP melphalan.
- Samples (7 mL) were collected from 3 sites at each timepoint:
  - systemic (arterial line)
  - extracorporeal circuit (pre-filter)
  - extracorporeal circuit (post-filter).
- Sample collection times: baseline; 15 minutes after infusion start; immediately 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:
  - the assay was validated, sensitive and accurate.

CS-PHP circuit and sampling sites



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 location (i.e. three 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 = $\frac{\text{(pre-filter AUC}_{last}\text{)} - \text{(post-filter AUC}_{last}\text{)}}{\text{(pre-filter AUC}_{last}\text{)}}$

Results

Patients

- Plasma samples were available from 48 patients:
  - 40 patients from 7 different centers were evaluable
  - 8 patients were excluded because of incorrect/ambiguous sample labeling (n=5), or early termination of sampling or drug delivery (n=3).

Baseline characteristics

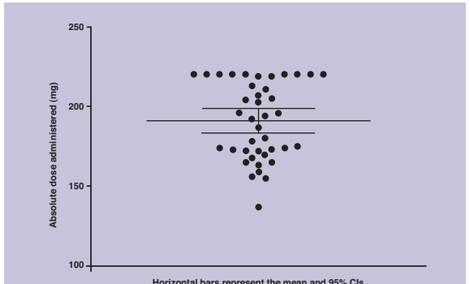
Characteristics	CS-PHP ITT population (n=44)	CS-PHP PK population (n=40)
Median age, years	55	50
Gender, %		
Male	52	50
Female	48	50
Ideal body weight, kg	–	64.7 (45.6–86.2)
Actual body weight, kg	–	80.6 (42.6–133.3)
Primary tumor site, %		
Ocular	86	80
Cutaneous	11	20
Unknown	2	0

Melphalan dosage

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

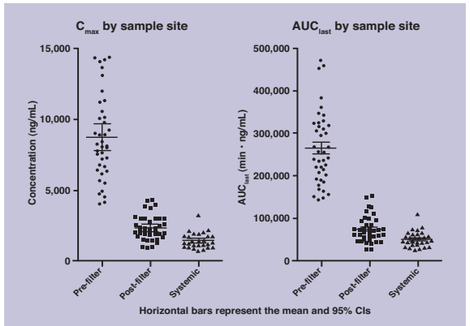
	Mean ± SD	Range
Absolute dose, mg	191 ± 24	137–220
Duration of perfusion, min	30 ± 7	16–52
Theoretical rate of perfusion,* mg/kg/min	0.10 ± 0.02	0.06–0.19
Theoretical rate of perfusion,* mg/min	6.6 ± 1.7	4.2–12.9

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



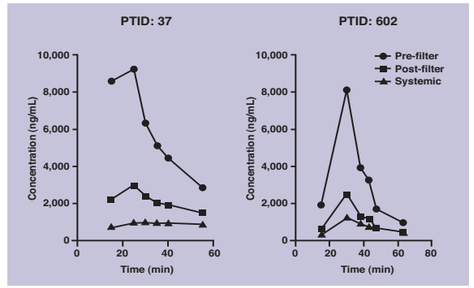
Melphalan exposure

Sample site	N	C_{max}(ng/mL) Mean	C_{max}(ng/mL) Range	AUC_{last}(min • ng/mL) Mean	AUC_{last}(min • ng/mL) 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



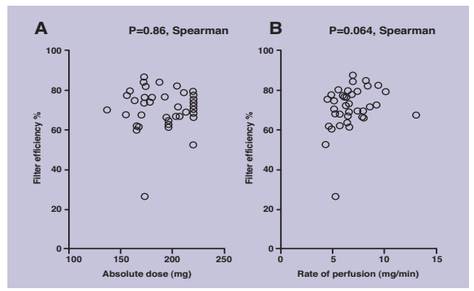
Sample concentration-time profiles

- Concentration-time profiles from two patients who received melphalan 3.0 mg/kg over 25 and 30 minutes, respectively:

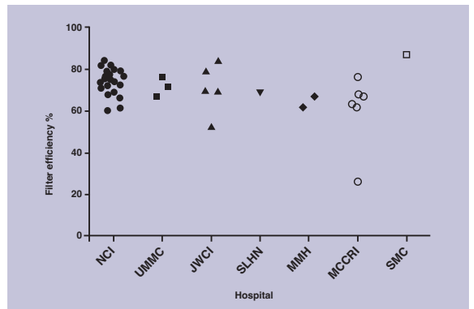


Filter efficiency

- Mean filter efficiency was 71.2% (range 26.4–86.8%).
- Filter efficiency did not appear to be influenced by absolute dose (A) or theoretical rate of perfusion (B):



- Filter efficiency did not appear to vary by hospital site:



Most common peri-procedural* grade 3/4 AEs

Percentage of patients	CS-PHP (n=40)
Platelet count decreased	73
Hemoglobin decreased	63
aPTT prolonged	30
AST increased	30
Blood calcium decreased	20
ALT increased	10
Blood bilirubin increased	10
Back pain	10

*Day of treatment through to day 3 post-treatment; Safety population.

Most common in-cycle* grade 3/4 AEs

Percentage of patients	CS-PHP (n=40)
Neutrophil count decreased	93
Platelet count decreased	83
White blood cell count decreased	58
Hemoglobin decreased	55
Blood bilirubin increased	18
Febrile neutropenia	15
AST increased	13
Blood alkaline phosphatase increased	13
ALT increased	10
Blood albumin decreased	8

*Day 4 post-treatment through to end of treatment cycle; Safety population.

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% CI intervals) and is unaffected by melphalan dose and rate of infusion.
- These findings indicate that the filter consistently removes most of the melphalan administered via CS-PHP.
- Clinical development of a high-efficiency (> 95%) second generation filter is under way.
- Safety profile of CS-PHP is manageable and is consistent with systemic exposure to melphalan.

References

1. Pingpank JF, et al. J Clin Oncol 2005;23:3465–74.
2. Pingpank JF, et al. J Clin Oncol 2010;28:18s, (suppl; abstr LBA8512).
3. Pingpank JF, et al. ECCO-ESMO 2011:abstract E16–1113.

Support for third-party medical writing assistance was provided by Delcath Systems Inc.

Presented at the 14th World Congress on Gastrointestinal Cancer, June 27–30 2012, Barcelona, Spain.