A Phase I Feasibility Study of Hepatic Arterial Melphalan Infusion with Hepatic Venous Hemofiltration using Percutaneously Placed Catheters in Patients with Unresectable Hepatic Malignancies

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Abstract

Primary and metastatic cancer confined to the liver represents a significant clinical problem, often representing the life-limiting component of disease even in the presence of extra-hepatic spread. The use of systemic chemotherapy for unresectable primary hepatocellular carcinoma (HCC) and extensive metastases from colorectal (CRC), ocular (OM), cutaneous melanoma (CM), and neuroendocrine (NE) tumors is limited by low response rates mostly of limited duration. We initiated a Phase I feasibility study of a 30 min hepatic artery (HA) infusion of melphalan via a percutaneously placed catheter with hepatic venous hemofiltration using a double balloon catheter positioned in the retrohepatic inferior vena cava to shunt hepatic venous effluent (HVE) through an activated charcoal filter (Delcath Systems, Inc.) then to the systemic circulation. Drug levels were assessed at regular intervals in the HA, the HVE before (HVE-U) and after (HVE-F) hemofiltration, and in systemic blood (SYS). Levels were analyzed at 0, 15, 30 min during infusion and 5, 10, 15, and 30 min after ("hepatic wash-out"). Total hepatic drug delivery (AUC) as well SYS levels were determined. Percent filter efficiency (FE) was defined as (HVE-U-HVE-F)/HVE-U. Patients were assessed for hepatic and systemic toxicity. Twelve patients (mean age: 51, M: 7, F: 5) with primary and metastatic hepatic tumors received 28 treatments (mean 2.3/pt) under an IRB approved protocol at an initial melphalan dose of 2.0 mg/kg. Primary tumors were OM (n=5), CM (n=2), biliary (n=2), NE (n=1), sarcoma (n=1), and breast (n=1). Mean AUC was 4.36 mcg/ml (+/- 1.65), and FE was 83.3% (+/- 8%). Transient grade III/IV hepatic and systemic toxicity (NCI CTC) was seen in 18% and 57% of treatments, respectively. Antitumor activity was observed in 5 of 12 patients (CR, n=1; PR, n=1; Minor Response, n=1; Disease Stabilization, n=2). Delivery of melphalan via this system is possible with limited, manageable toxicity. At this initial dose, anti-tumor activity was observed in 5 of 12 patients. Dose escalation studies are warranted.

Background

Primary and metastatic liver cancer is a widespread clinical problem without effective therapies for the vast majority of patients. There are approximately 530,000 new cases of hepatocellular carcinoma (HCC) each year worldwide. The liver is also a common site of metastases including ocular melanoma, gastrointestinal adenocarcinoma, sarcoma, and neuroendocrine tumors. Liver metastases will occur in approximately 25% of the 140,000 Americans diagnosed with colorectal cancer each year. The vast majority of these are unresectable and even with modern intravenous chemotherapy regimens, the median survival is only 12 to 18 months. Seventy to 90% of patients with metastatic ocular melanoma will develop disease confined to the liver and even with treatment, survival is less than a year.

The prevalence, morbidity, and lack of effective treatments for hepatic malignancies have spawned efforts to establish more organ-specific techniques to minimize systemic toxicity while maximizing targeted delivery. Such local or regional techniques take advantage of the steep dose-response curves of modern chemotherapies. Since systemic toxicities are dose limiting in traditional strategies, these techniques allow for higher dosing of chemotherapy to the affected organ while minimizing systemic exposure, providing a potential therapeutic advantage. Hepatic arterial infusion takes advantage of the fact that most hepatic tumors parasitize the majority of their blood flow from the hepatic artery. However, with HAI, drugs such as doxorubicin that are not easily extracted by the liver still create systemic exposure and can thereby limit treatment.

In isolated hepatic perfusion (IHP), the vascular supply to the liver is isolated, and systemic blood is shunted using a veno-veno bypass circuit in the operating room. The liver is then attached to a re-circulating perfusion circuit containing chemotherapy. Using this technique, overall objective response rates as high as 76% with median response durations of 10.5 months have been observed. The major disadvantages of this approach are that only a single treatment can be applied and it requires open surgery with associated morbidity. Further treatments are prevented by postoperative adhesions around the vena cava and portal structures and lack of a suitable cannulation site for arterial infusion.

Although several different chemotherapies have been used with IHP, the success of isolated limb perfusion using melphalan to treat melanoma, sarcoma, and other histologies has suggested its use in IHP as well. Studies examining the use of melphalan in IHP to treat hepatic metastases from colorectal cancer have shown promising results.

This ongoing study was performed to evaluate a percutaneous isolated liver perfusion technique using melphalan that could be administered repeatedly and would allow the benefits of IHP without the complications of a surgical procedure.

Methods and Materials

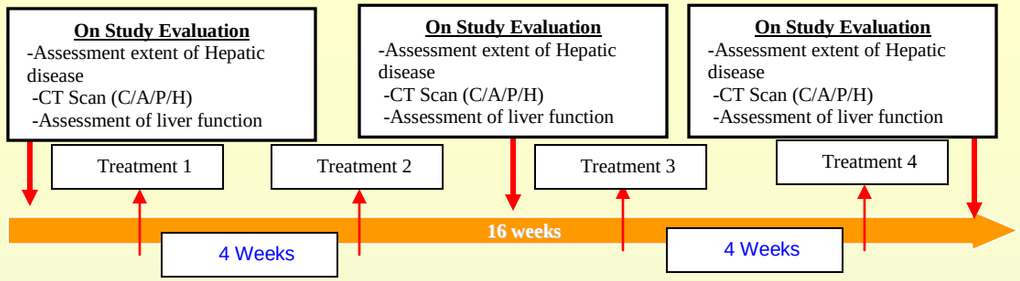
Percutaneous hepatic perfusion (PHP) uses a percutaneous, double balloon, inferior vena cava (IVC) catheter system (Delcath System, Delcath Inc., Stamford, CT) to isolate hepatic venous outflow and allow high dose infusion of chemotherapy to the liver. The main component of the system is a 16F, polyethylene double balloon catheter with one large lumen and three accessory lumina. The two low-pressure occlusion balloons are inflated independently through separate lumina. The cephalic balloon blocks the IVC superior to the hepatic veins, while the caudal balloon obstructs the IVC inferior to the hepatic veins, allowing complete isolation of hepatic venous outflow. The span between the two occlusion balloons consists of a fenestrated segment that feeds into the large, central lumen which exits the catheter from the proximal end. The additional lumen enters the catheter at a point inferior to the caudal balloon and exits at the distal tip. This lumen serves as a channel for a guidewire and also allows some systemic blood to bypass the IVC blockage, enabling some flow from the lower IVC to the right atrium. In the procedure, melphalan is infused through a separate catheter inserted into the hepatic artery. The melphalan perfuses the liver and exits the organ through the hepatic veins. Hepatic venous flow is isolated using the occlusion balloon catheter and melphalan-dosed blood from the central lumen is pumped through an extracorporeal circuit consisting of a centrifugal pump (Biomedicus, Eden Prairie, MN) and hemoperfusion drug filtration cartridges (Hemosorba, Asahi Medical Co, Tokyo, Japan). Melphalan flowing through the circuit is removed from the blood by binding to the two activated-carbon filter cartridges arranged in parallel. The filtered blood is added back to systemic circulation via a venous return sheath inserted into the internal jugular vein.

Treatments are administered with patients under general anesthesia. Bilateral internal jugular veins and one common femoral vein are accessed, as well as bilateral common femoral arteries, with ultrasound guidance. The extracorporeal circuit is assembled and primed with 0.9% Sodium Chloride Injection. The hepatic arterial catheter is positioned in the proper hepatic artery using the Seldinger technique and standard fluoroscopic and arteriographic techniques. A complete visceral angiogram is performed and the arterial supply to the liver is completely identified. In some cases, arteries need to be embolized to ensure that the infused chemotherapy is administered only to the liver. Gastroduodenal artery embolization has been used to treat duodenal bleeding and is usually well tolerated. If an isolated administration is impossible or unsafe, the patient is taken off study.

The double balloon catheter is then inserted into the IVC using the Seldinger technique and is positioned under fluoroscopic guidance. The catheter is then attached to the extracorporeal circuit tubing and the outflow line of the filtration circuit is connected to the venous return sheath. Under fluoroscopy, the cephalad balloon is inflated with dilute contrast medium until the shape of the balloon is no longer round, indicating that it is maximally inflated and free floating in the right atrium. The balloon is then manipulated with gentle traction until indentation of the diaphragmatic hiatus is visible at the inferior margin. Under fluoroscopy the caudal balloon is inflated with dilute contrast medium until the lateral edges of the balloon deform to the walls of the IVC. Contrast medium is injected through the fenestrated portion of the catheter to ensure that the balloon catheter is properly placed and the hepatic venous outflow is isolated and without leakage into the right atrium. The main lumen is flushed and the filters are brought on-line.

Once all systems are functioning properly, melphalan is administered as a 30-minute infusion infusion via the hepatic artery.Following infusion, the extracorporeal circuit is continued for an additional 30 minutes to ensure the complete removal of residual melphalan that may be released into the blood from the liver parenchyma. Once completed, the pumps are shut down, the balloons are deflated, and the catheters are removed. The patient is kept at bedrest and monitored for 12 hours.

Heparin is administered during the procedure to maintain the activated clotting time (ACT) at therapeutic levels. Protamine or fresh frozen plasma may be given following the procedure to facilitate early catheter and sheath removal. Coordination with anesthesiologists experienced in the effects of IVC occlusion is important. When the balloons are inflated, pressors are usually required to maintain hemodynamic stability, as venous return is compromised. Additionally, at the time of filter activation, systemic catecholamine levels decrease due to filtration effects.



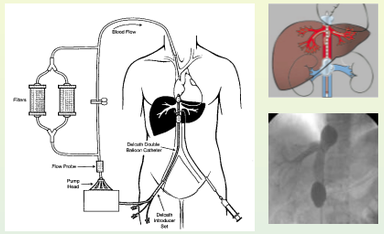


Figure 1A: Diagram of the Delcath® Catheter System: Melphalan is administered directly into the hepatic artery through an infusion catheter placed percutaneously via the femoral artery. Hepatic venous outflow is isolated via a double balloon catheter in the retro-hepatic inferior vena cava. Blood is drawn out of the retro-hepatic IVC through multiple fenestrations located along the length of the catheter between the cranial and caudal balloons. The blood is then run through a pair of activated charcoal filters prior to return to the systemic circulation via an internal jugular vein catheter. Melphalan levels are monitored at regular intervals throughout the treatment (see below) from blood drawn from the infusion line, the pre- and post-filter circuit, and a peripheral arterial line.

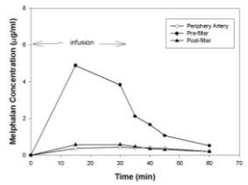
Figure 1B: Depiction of the Isolated Retro-Hepatic IVC: Hepatic venous outflow is isolated by inflating two balloons in the IVC. The cranial balloon is inflated in the right atrium (RA) and the pulled down into the IVC above the hepatic vein, until occlusive. Subsequently, a caudal balloon is inflated above the renal veins, to complete the segment isolation.

Figure 1C: Flouroscopic image of the isolated, retrohepatic IVC segment obtained by retrograde injection of contrast through the intra-balloon fenestrations, to confirm the absence of systemic leak.

Melphalan Concentrations (μg/ml) During Perfusion and Washout

	During Infusion			Post Infusion Washout				AUC(0-6 0min)	Cmax
	0	15"	30"	5"	10"	15"	30"	(μg/ml hr)	(μg/ml)
Infusion Catheter	45.8	45.1	44.8						
Pre-filter	0.00	4.88	3.83	2.12	1.66	1.07	0.52	1.72	4.88
Post-filter	0.00	0.57	0.58	0.47	0.35	0.30	0.20	0.38	0.58
% Post/Pre	0.00	11.7	15.2	22.0	21.1	28.1	38.5	22.1	11.9
Arterial	0.00	0.37	0.45	0.40	0.39	0.37	0.20	0.32	0.40

AUC During Infusion (0-60m)



Treatment Parameters

Patients Enrolled/Treated: 15/12
Number of Treatments: 30
Melphalan Dose: 2.0 mg/kg
Median Length of Stay (range): 2 d (2-6)
Median Procedure Length (range): 270min (205-420)
Median Bypass Pump Time (range): 72 min (51-109)
Mean Bypass Flow Rate (range): 683ml/min (300-1000)

Grade III/IV Toxicity (30 Procedures)

Hepatic (n=5)
↑ LFT's 5 pts (16.6%)
↑ Bili 1 pt (3.3%)
↑PT/PTT 0 pts

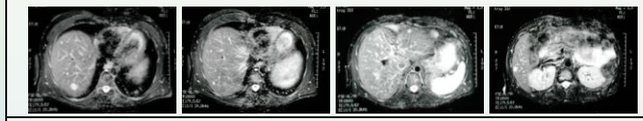
Systemic (n=21)
Neutropenia 17pts (57%)
Anemia 3 pts (10%)
Thrombocyt 11pts (37%)
Nausea (II) 3 pts (10%)
Fatigue (II) 3 pts (10%)

Melphalan AUC and Cmax in 12 Patients

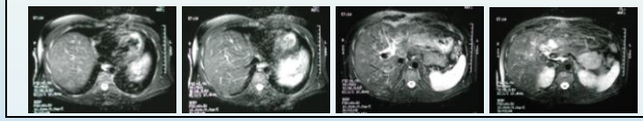
Patient	Dose (mg)	AUC (μg/ml hr) Pre-filter	AUC (μg/ml hr) Post-filter	AUC (μg/ml hr) Arterial	Extraction (Pre-Post)/Pre	Cmax (μg/ml) Pre-filter	Cmax (μg/ml) Post-filter	Cmax (μg/ml) Arterial
1	150	4	1.08	0.98	73.0	6.32	1.88	1.79
2	120	3.34	0.38	0.63	88.6	5.93	0.6	1.03
3	128	3.11	0.65	1.13	79.1	6.17	0.98	1.97
4	126	4.1	0.40	1.50	90.2	7.63	0.78	2.5
5	114	2.66	0.85	0.55	68.0	8.57	2.17	1.13
6	90	3.62	0.46	1.64	87.3	8.91	0.74	2.91
7	120	5.3	0.50	1.00	90.8	8.05	0.90	1.50
8	110	1.72	0.40	0.30	77.9	4.88	0.60	0.40
9	147	4.3	1.2	0.70	72.8	8.11	2.3	1.20
10	144	3.48	0.6	0.6	83.6	10.5	1.0	0.82
11	144	5.8	1.17	0.59	79.8	11.8	2.03	1.00
12	144	5.32	0.48	0.49	91.0	11.4	0.84	0.72
Mean		3.90	0.67	0.88	81.8	8.19	1.23	1.51
SD		1.18	0.31	0.42	7.9	2.20	0.65	0.81
Median		3.81	0.53	0.66	81.7	8.08	0.93	1.16

Pharmacokinectics of melphalan administered via Delcath® system. All patients were treated with 2 mg/kg of melphalan (IBW). AUC measurements, via HPLC, reveal consistent delivery throughout the 30-minute infusion, with rapid subsequent washout of drug during the following 30-minute filter period. Low systemic (Arterial) melphalan levels measured peripherally, verify the calculated filter efficiency of 81.8 % (mean).

Pre-Treatment MRI: Ocular Melanoma



Post-Treatment MRI: Ocular Melanoma



Treatment Response: 38-year old male with ocular melanoma with metastatic disease confined to the liver, 13 months after a complete response (CR) to operative isolated hepatic perfusion with melphalan, treated with 4 Delcath hepatic perfusions with melphalan. A CR was observed, and was maintained for 10 months after treatment, at which time recurrent hepatic metastases were noted in different locations. The patient subsequently underwent a second series of 4 treatments, with similar response, and no additional toxicity.

Conclusion

Treatment strategies against primary and metastatic liver tumors are limited by low resectability rates and significant toxicity from systemic chemotherapy. We have previously demonstrated the efficacy of isolated hepatic perfusion (IHP) with hyperthermia and melphalan for the treatment of unresectable hepatic metastases from colorectal cancer, ocular melanoma, and neuroendocrine tumors, as well as for primary hepatic malignancies. In an effort to minimize the side-effects of melphalan delivered via IHP, we initiated a trial of intra-arterial melphalan with subsequent hepatic venous hemofriltration. Our initial experience demonstrates that delivery of high-dose intra-arterial melphalan via this system is possible with limited, manageable systemic toxicity. Hepatic toxicity was minimal and self limited.

On this initial cohort of 15 patients, 12 were successfully treated and evaluable for toxicity. Aberrant anatomy prevented the safe treatment of 3 patients. No dose limiting toxicities were observed in the 30 treatments received by the 12 patients. Anti-tumor activity was observed in 5 of 12 patients treated. At present, dose escalation studies are proceeding.