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# A dose-escalation 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. Systemic chemotherapy for unresectable primary hepatocellular carcinoma (HCC) and 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.) with return to the systemic circulation. Pharmacokinetic analysis included drug levels at regular intervals in the HA, the HVE before (PreHVE) and after (PostHVE) 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 (PreHVE-PostHVE)/PreHVE. Patients were assessed for hepatic and systemic toxicity. Twenty-five patients (mean age: 49, M: 12, F: 13) with primary and metastatic hepatic tumors received 62 treatments (mean; 2.5/pt) under an IRB approved protocol of melphalan dose escalation. A treatment course consisted of four treatments separated by 28 days, with an interval imaging evaluation before the third treatment. Four patients remain on active treatment. Three additional patients were not treated due to hepatic vascular anomalies precluding safe delivery and extraction of drug. Primary tumors were OM (n=10), CM (n=2), colorectal (n=1), biliary (n=3), NE (n=4), sarcoma (n=1), renal cell (n=1), adrenal (n=1), peri-ampullary (n=1), and breast (n=1). Mean melphalan dose increased from 128.1 mg (range, 90-150) at the initial dose level (2.0 mg/kg) to 223.7 mg (range, 175-257) at the maximum tolerated dose (MTD). Mean hepatic AUC was 4.24 mcg/ml (+/− 1.87) at the initial dose level and rose to 6.50 mcg/ml (+/− 1.84) at 3.5 mg/kg. FE was 77% and remained consistent across all doses. Reversible grade III/IV hepatic (10%) and systemic (hematologic) (70%) toxicity (NCI CTC) was experienced at the MTD. The grade III/IV

systemic toxicity was myelosuppression, including DLT in 1 of 6 patients treated at this level. Anti-tumor activity was observed in 13 of 22 (56.1%) patients evaluable for response (CR, n=1; PR, n=6; Minor Response, n=4; Disease Stabilization, n=2). Maximum tolerated dose was defined as 3.5 mg/kg. Of the 10 patients with OM, 9 are evaluable for response, with one CR (10 months), 3 PRs (7, 7+, 6+ months), and 2 MRs (8, 2+ months) and disease stabilization (7 months), for an overall response rate of 44.4%. Delivery of melphalan via this system is possible with limited, manageable toxicity and has efficacy against a variety of histologies, most notably OM. A phase II study is planned.