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 4 of 12 patients. Dose escalation studies are warranted.