158

CONTINUOUS HEMOFILTRATION OF HEPATIC VENOUS EFFLUENT ALLOWS REGIONAL DELIVERY OF HIGH-DOSE MELPHALAN VIA A MINIMALLY INVASIVE APPROACH

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Introduction. Unresectable hepatic metastases represent a significant clinical challenge. Peripheral hepatic perfusion (PHP) is a minimally invasive regional therapy designed to deliver high-dose hepatic arterial chemotherapy while minimizing systemic exposure utilizing a double balloon catheter (Delcath Systems, Inc.) positioned in the retrohepatic inferior vena cava facilitating hepatic venous effluent hemofiltration. Described are the regional and systemic toxicities and pharmacokinetics associated with a 30 minute infusion of melphalan (MEL) via PHP.

Methods. Between August 2001 and August 2007, 81 pts underwent 220 PHPs with MEL on an IRB approved phase I, II, or III trial for treatment of metastatic melanoma (n!30), neuroendocrine tumors (n!19), colorectal carcinoma (n!11), HCC (n!8), and others (n!13). Laboratory tests were performed daily during hospitalization and at regular intervals thereafter. Toxicities were divided into acute (! 5 days post-PHP) and delayed (! 5 days post-PHP). A 2nd generation charcoal filter was utilized for the most recent 98 procedures. In 24 pts, MEL pharmacokinetics were measured from the pre- (PRE) and post-filter (POST) perfusion circuit as well as systemically (SYS).

Results. 160 treatments were performed at doses from 2.5#3.0 mg/kg. MEL dose was 2.5 mg/kg for 35/160 treatments and 3.0 mg/kg for 120/160 treatments. Acute grade 3/4 hematologic toxicities were anemia (46/160, 29%) and thrombocytopenia (75/160, 47%). Delayed grade 3/4 hematologic toxicities were anemia (48/160, 30%), thrombocytopenia (76/160, 48%), and neutropenia (118/160, 74%). Acute grade 3/4 hepatic toxicities included elevated bilirubin (18/160, 11%) and LFTs (26/160, 16%). Delayed hepatic toxicity occurred in 32/160 (20%). Average maximum PRE concentration of MEL was 10.4 ug/mL. POST MEL levels fell to 2.0 ug/mL with the SYS average maximum of 1.4 ug/mL. The area under the curve (AUC) in the concentration-time graph yielded a PRE mean of 258,000 ng/ml*min. POST AUC fell to 56,000 ng/ml*min, with SYS of 42,000 ng/ml*min. PRE AUC was significantly higher in the patients receiving 3.0 mg/kg compared to 2.5 mg/kg (mean of 286,000 vs. 195,000, p!.03). Using the PRE and POST AUC, mean filter efficiency was calculated to be 77%.

Conclusion. PHP achieves high regional concentration of MEL with predictable myelosuppression. PHP demonstrates a potential advantage for MEL administration versus other regimens, with deliverable doses above the MTD of systemic (.5 mg/kg) or other regional (1.5 mg/kg) MEL dosing strategies.