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Analysis of Clinical Toxicity in Patients Undergoing Percutaneous Intra-Arterial Hepatic Perfusion (PHP) with Melphalan for Unresectable Hepatic Malignancies

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Background: Hepatic metastases (HM) represent a significant therapeutic challenge for patients with a variety of tumor histologic subtypes. For the majority of patients, the extent of hepatic tumor limits the application of surgical resection or ablative technologies. For patients with isolated HM, regional delivery of high dose chemotherapy is a potential alternative to systemic chemotherapy, and offers the potential an increased therapeutic index for cytotoxic agents such as melphalan.

Methods: Between December 2001 and January 2007, 74 patients with unresectable primary (n=9) or metastatic (n=65) hepatic neoplasms received a total of 190 PHP treatments with melphalan on 1 of 3 NCI IRB approved protocols. Analysis includes procedure related toxicities, pharmacokinetic analysis of melphalan delivery, and toxicity associated with systemic melphalan exposure. PHP consisted of a 30 minute hepatic artery infusion of melphalan via a percutaneously placed catheter with hepatic venous hemofiltration using a double balloon catheter (Delcath Systems, Inc.) positioned in the retrohepatic inferior vena cava and an activated charcoal filter with subsequent return to the systemic circulation. Treatment course consisted of four PHPs every 28 to 35 days.

Results: Successful treatment was accomplished in 182 of 190 (96%) planned treatments. Reasons for unsuccessful treatment included hepatic venous anomalies (n=3), hepatic artery dissection (n=2), and a sclerotic hepatic artery from previous, non-PHP regional therapy (n=3). Procedure associated complications included intrahepatic hemorrhage (n=1), catheter associated hematoma (n=2), pneumothorax (n=1), and melphalan anaphylaxis (n=1). Bone marrow suppression associated with systemic exposure was transient and observed in the majority of 172 patients treated for whom toxicity assessment has been completed, and included grade III/IV neutropenia (98 of 172 treatments, 57%), grade III/IV thrombocytopenia (68 of 172 treatments, 40%), grade III/IV anemia (32 of 182 treatments, 19%), and grade III/IV hepatic dysfunction (26 of 172 treatments, 15%).

Conclusions: This study shows that PHP with melphalan has efficacy in patients with diffuse HM when hepatic disease is too extensive for resection, ablation, or embolization strategies. This strategy appears to be a viable investigative approach for a variety of cytotoxic and biologic agents.