Percutaneous Liver Perfusin for Patients with Metastatic Neuroendocrine Tumors


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ABSTRACT

Introduction: Patients with metastatic neuroendocrine tumors (NET) to liver are faced with multiple treatment strategies including resection, ablation, and a variety of regional therapies which have been successfully utilized in this heterogeneous group of patients. This study selected a minimally invasive regional therapeutic percutaneous hepatic perfusion (PHP) with melphalan has efficacy in patients with isolated or predominant hepatic metastases from NET.

Methods: Between December 2001 and February 2007, 17 NET patients (mean age: 50 ± 10; 10 F; 7 pancreatic neuroendocrine; 12 carcinoid; 5) were enrolled on one of two IRB-approved PHP protocols using melphalan. Analyte included PHP parameters, complications, toxicity, response, progression-free and overall survival. PHP consisted of a 30 minute hepatic artery infusion of melphalan via a percutaneously placed catheter with subsequent return to the systemic circulation. Treatment course consisted of four PHPs every 38 to 35 days. Survival curves were estimated by the Kaplan-Meier method.

Results: Seventeen patients received 45 treatments (median: 2.5). Reversal grade IV toxicities observed were hematologic (82%) and hepatic (16%). An overall radiographic response was seen in 9 of 12 evaluable patients (75%; complete n=2, partial n=7). At a median follow-up of 18 months, progression of inpatient disease was observed in two patients (45 and 60 months, respectively) and all 17 patients have died secondary to progression of extrapancreatic disease. Median duration of ongoing hepatic response in eight patients is 15 months (mean: 15, range: 3-28).

Conclusions: This study shows that PHP with melphalan has efficacy in patients with diffuse NET of the liver when hepatic disease is too extensive for resection, ablation, or embolization strategies.

INTRODUCTION

Neuroendocrine tumors are rare malignancies, which are frequently associated with excessive hormone production and resultant paraneoplastic syndromes. This group of cancers has a variable rate of metastasis, but shows the liver to be a common site of tumor progression. In fact, NETs account for roughly 10% of all hepatic metastases. Surgery has been the mainstay of therapy for patients with resectable disease in the liver, and there is increasing data to suggest its effectiveness. Approximately 90% of patients, however, have hepatic metastases that are multifocal and bilateral – tumors not easily amenable to surgical resection. Systemic chemotherapy offers modest, short-lived responses and is often ineffective at managing symptoms in patients with hormonally active tumors. Therefore, a number of local approaches (including ablation, embolization, and infusion) have been employed to stabilize these patients and minimize morbidity/mortality from their hepatic disease.

Regional perfusion strategies have been utilized to treat hepatic malignancies in an attempt to minimize systemic toxicity while maximizing targeted delivery. These techniques take advantage of steep dose-response curves and allow for higher doses to the tumor without concomitant increases in systemic toxicity. Hepatic arterial infusion takes advantage of the fact that most hepatic tumors parasitize the majority of their blood flow from the hepatic artery. In isolated hepatic perfusion (IHP), the vascular supply to the liver is separated 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 high-dose melphalan, a non-specific alkylating agent. Using this approach, overall objective response rates as high as 55% with median response durations of 9 months have been observed. The major limitations of this approach are that only a single treatment can be applied and that it requires open surgery with associated morbidity.

Subsequent study has evaluated a percutaneously isolated liver perfusion technique using melphalan that may be administered repeatedly and allows the benefits of IHP without the complications of a surgical procedure. Our aim was to determine the response rate and duration of response to PHP in patients with NET and significant liver disease. Secondary objectives were to assess the patterns of recurrence, as well as disease-free and overall survival.

METHODS

Patient Selection: Adult patients (age ≥ 16 years, weight ≥ 35 kg) with a pathologic diagnosis of NET and unresectable cancer predominately in the liver parenchyma were eligible for study. All had moderate functional status (ECOG ≤ 3) and adequate hepatic function. Those with severe cardiomyopathy, renal, and hepatic dysfunction or with intracranial abnormalities at risk for bleeding or coagulopathy were excluded. The investigational nature and objectives of this trial, the procedures and the treatments involved, the attendant risks and discomforts, potential benefits and potential alternative therapies were explained to all patients before obtaining a signed informed consent.

Study Design: The PHP procedure utilizes a percutaneously placed double balloon, inferior vena cava (IVC) catheter system (Delcath System, Delcath Inc., Stamford, CT) to isolate hepatic venous outflow and to allow high dose hepatic arterial infusion of melphalan to the liver. The main component of the system is a Teflon polyethylene double balloon catheter with one large lumen and three accessory lumina (Figure 1A). The two low-pressure occlusion balloons are inflated independently through sapheous lumen. The cephalic balloon blocks the IVC prior 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 fossilized segment that feeds into the large, central lumen which exits the catheter from the proximal end.

Treatments were administered under general anesthesia. Under ultrasound guidance, bilateral internal jugular veins and one common femoral vein were accessed, as well as bilateral common iliac veins. The extracorporeal circuit, which consisted of a centrifugal pump (BioMedicus, Eden Prairie, MN) and two activated carbon fiber filtration cartridges (Hemosorba, Aasth Medical Co, Tokyo, Japan) in parallel, was assembled and primed while the hepatic arterial catheter was positioned in the proper hepatic artery (Figure 1B). A virual angigram was performed to completely identify the arterial supply to the IHP. In some cases, arteries were embolized to ensure that the infused chemotherapy was administered solely to the liver. Gastrointestinal arterial embolization has been used to treat duodenal bleeding and has been well tolerated. The double balloon catheter was then positioned in the IVC and attached to the extracorporeal circuit tubing; the outflow line of the filtration circuit was connected to the venous return sheath. Intrahepatic vasculature was administrated prior to infusing the cephalic balloon under fluoroscopic guidance and released as needed to maintain the activated clotting time (ACT) at therapeutic levels. Once the shape of the balloon inflated to the IVC was maximized and inflated floating in the right atrium, gentle traction was applied until induration of the hepatic arterial catheter was visible at the inferior margin. The caudal balloon was then inflated and utilized to perform the distal contour of the wall (Figure 1C). Contrast medium was injected through the catheter's fenestrated portion to ensure proper placement and isolation of hepatic venous outflow (Figure 1D). This maneuver was repeated until the filters were brought on line. Venous return may have been compromised with the infation of the IVC balloons and systemic catecholamine levels decreased at the time of filter inflation such that pressures were usually required to maintain hemodynamic stability. Coordination with anesthesiologists experienced in the effects of catecholamines on the heart rate and the ability of all systems were functioning properly, melphalan was infused over 30 minutes via a separate catheter in the hepatic catheter. Once completed, the extracorporeal circuit was continued for an additional 30 minutes to ensure removal of any residual melphalan. The pumps were then shut down and the balloons were deflated. The catheters were removed and patient was kept on telemetry during a 12-hour period of intensive monitoring. Proteinase sodium and/or fresh frozen plasma were often given following the procedure to facilitate coagulation.

Data Collection and Evaluation: Target lesions were identified, measured, and recorded at baseline imaging studies. Progressive disease was defined for the purposes of reporting were assessed approximately four weeks after the second PHP procedure. Duration of response was calculated using the Kaplan-Meier method. The NCI Common Toxicity Criteria was used to determine toxicity.

This trial was conducted using a Simon optimal phase II design with the objective of identifying a reasonably high 45% response rate with a type I error probability (α) of 0.10 and a type II error probability (β) of 0.20. With α = 0.10 and β = 0.20, initially 14 patients were enrolled. In a response to 4 in 14 patients, the accrual was continued with an aim of 25 total evaluable patients.

RESULTS

Seventeen patients have been enrolled in this study, as outlined in the schema above. Patient demographics are provided in Table 1. One patient was unable to undergo PHP due to aberrant vascular anatomy and one patient was lost to follow-up prior to 16 weeks. All patients have completed at least one treatment but have not reached the end point by the interim analysis. Ten patients have completed two or more treatments, these others have completed at least one treatment but have not reached the intermediate analysis. All patients have received a total of 45 treatments (median: 2.5). All patients have been evaluated for safety and efficacy. Treatment response data are summarized in Table 2. The radiographic response of a patient with poorly-differentiated NET to the liver after PHP with melphalan is provided in Figure 3. A dose of melphalan administered during PHP and PHP was comparable (Figure 3). Kaplan-Meier curves of overall and hepatic progression-free survival are depicted in Figure 4 and 5, respectively.

CONCLUSIONS

For many patients with NET, the liver is the sole or life-limiting component of disease. This study shows that PHP with melphalan has efficacy in patients with extensive, unresectable hepatic disease. Given the response rates of this initial cohort, we have continued to accrue patients to enroll 25 evaluable patients and feel this treatment is worthy of further evaluation in subsequent studies.