Percutaneous Hepatic Perfusion (PHP) with Melphalan for Patients with Metastatic Melanoma (MM) to the Liver


*Surgery Branch, NCI, and **Diagnostic Radiology Department, HMRI, BMRI, Bethesda, MD

ABSTRACT

Introduction: Patients with metastatic melanoma to the liver have a median survival between 6-9 months and different treatment strategies have not meaningfully altered the natural history of the disease. This study examined whether a minimally invasive hepatic perfusion therapy (PMP) with melphalan has efficacy in patients with isolated or predominant hepatic metastases from metastatic melanoma (MM).

Methods: Between August 2001 and July 2004, 17 MM patients (mean age: 50 y; M: 9, F: 8; ocular: 13, cutaneous: 4) were enrolled on an IRB approved PHP protocol for unresectable liver metastases using melphalan. Analysis included previous treatment, PHP toxicities, assessments, responses, progression-free and overall survival. PHP consisted of a 30 minute hepatic artery infusional perfusion of melphalan via a percutaneously placed catheter with hepatic venous hemofiltration using a double balloon catheter (Debakey 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 21-28 days with follow-up and imaging evaluation after treatment and every 3-4 months thereafter. Survival curves were estimated by the Kaplan-Meier method.

Results: 15 patients received 49 treatments (mean: 3.3/pt); 2 patients were not treated due to anatomic limitations or other technical reasons. Previous treatment included surgery (n=10), biochemotherapy (n=7), and isolated perfusion (n=6). Melphalan dose was 163.5 mg (range: 116-257). Five patients (28.6%) had isolated or predominant hepatic disease at presentation with 8 of 15 patients (53.3%) having metastatic MM confined to the liver. The disease duration from diagnosis to presentation with MM was 4 years. Intrahepatic progression was detected in 13 of 15 patients (86.7%) and 14 of 15 patients (93.3%) had died with primary MM at the time of last follow-up. Mean progression-free survival was 11 months (range: 5-15.5) and overall survival was 14 months (range: 6-33). Conclusions: This study shows that PHP with melphalan has efficacy in patients with MM of the liver with low morbidity and warrants further clinical investigation.

BACKGROUND

The liver is a common site of metastases in both cutaneous and ocular melanoma. Seventy to 90% of patients with metastatic ocular melanoma will develop disease confined to the liver and even with aggressive treatment, survival is less than a year. The lack of effective therapy for hepatic malignancies has focused efforts on establishing regional techniques to minimize systemic toxicity while maximizing targeted delivery. Such local or regional techniques take advantage of the high drug concentration delivered to selected organs or tissues. Since systemic toxicities are dose-limiting in traditional strategies, these techniques allow for higher dosing of chemotherapy to the affected organ while minimizing systemic exposure, providing a potential therapeutic advantage. Hepatic arterial infusion (HAI) takes advantage of the fact that liver metastases recruit their blood supply predominantly from the hepatic artery rather than the portal vein. However, with HAI drugs without first pass extraction by the liver still create systemic exposure and can thereby limit treatment.

In isolated hepatic perfusion (PHP), an operative strategy is used to isolate the vascular supply to the liver, and systemic blood is shunted using a veno-venous bypass circuit. The liver is then attached to a continuous perfusion circuit containing high dose chemotherapy. Using this technique, overall objective response rates as high as 42% have been observed in malignant melanomas, with median survival of 12 months. The major disadvantages of this approach are that only one single treatment can be applied and it requires open surgery with the associated morbidity. Further treatments are limited by postoperative adhesions around the vena cava and portal structures and lack of a suitable cannulation site for arterial infusion.

Although several different chemotherapies have been used with PHP, the success of isolated limb perfusion using melphalan to treat in-transit melanoma and extremity sarcoma led to its use in PHP. This ongoing study was performed to evaluate a prospective isolated liver perfusion technique using melphalan in patients with MM to the liver, that could be administered repeatedly and would allow the benefits of PHP without the complications of a surgical procedure.

METHODS AND MATERIALS

Percutaneous hepatic perfusion (PHP) uses a percutaneous, double balloon, inferior vena cava (IVC) catheter system (Debakey Systems, Debakey Inc., Stamford, CT) to isolate hepatic venous outflow, allowing high dose infusion of chemotherapy to the liver. The main component of the system is a Teflon polyethylene double balloon catheter with one large lumen and three accessory lumina. The two low-pressure occlusion balloons are inflated independently using fluoroscopy. The catheter balloon blocks the IVC inferior to the hepatic veins, while the caudal balloon obstructs the IVC inferior to the hepatic veins, allowing complete isolation of hepatic venous outflow. The space between the two occlusion balloons consists of a fenestrated segment that feeds into the large, central lumen which exits the catheter at the proximal end. The additional lumen enters the catheter at a point inferior to the caudal balloon and exits at the distal tip. This lumen serves as a channel for delivery of the chemotherapy solution. A 6 French venous catheter bypasses the IVC blockage, enabling some flow from the lower IVC to the right atrium. In the procedure, melphalan is infused into the hepatic artery through a separate catheter. The melphalan is perfused into the liver and exits the organ through the hepatic veins. Hepatic venous flow is isolated using the occlusion balloon catheter and melphalan-dosed blood from the central lumen is pumped through an extracorporeal circuit consisting of a centrifugal pump (Biomedics, Eden Prairie, MN) and hemoperfusion drug filtration cartridges (Hemosorba, Asahi Medical Co, Tokyo, Japan). Melphalan flowing through the circuit is removed from the blood by binding to the two activated-carbon filter cartridges arranged in parallel. The filtered blood is added back to systemic circulation via an internal jugular vein sheath.

Treatments are administered with patients under general anesthesia. The extracorporeal circuit is assembled and primed with 0.9% Sodium Chloride Injection. The hepatic arterial catheter is positioned percutaneously in the proper hepatic artery using fluoroscopy. A complete visceral angiogram is performed and the arterial supply to the liver is completely identified. In some cases, arteries are embolized to ensure that the infused chemotherapy is administered solely to the liver. If an isolated abdomen is impossible or unsafe, the patient is taken off study.

The double balloon catheter is then inserted into the IVC using the Seldinger technique and is positioned under fluoroscopic guidance. The catheter is attached to the extracorporeal circuit and the inflow line of the filtration circuit is connected to the venous return catheter. Under fluoroscopy, the cephalad balloon is inflated with dilute contrast medium until the shape of the balloon is no longer round indicating that it is maximally inflated and free floating in the right atrium. The balloon is then manipulated with gentle traction until indentation of the diaphragmatic hiatus is visible at the inferior end. Under fluoroscopy the caudal balloon is inflated with dilute contrast medium until the lateral edges of the balloon conform to the walls of the IVC. Contrast medium is injected through the fenestrated portion of the catheter to ensure that the balloon catheter is properly placed and the hepatic venous outflow is isolated without leakage into the right atrium. The main lumen is flushed and the filters are brought on-line.

Once all systems are functioning properly, melphalan is administered as a 30-minute infusion via the hepatic artery. Following infusion, the extracorporeal circuit is continued for an additional 30 minutes to ensure the complete removal of residual melphalan that may be released into the blood from the liver parenchyma. Once completed, the pump is stopped and the melphalan in the catheters are removed. The patient is kept at bedrest and monitored in the intensive care unit overnight.

Heparin is administered during the procedure to maintain the activated clotting time (ACT) at therapeutic levels. Heparin and/or fresh frozen plasma may be given to facilitate early catheter and sheath removal. When the balloons are inflated, pressures are usually required to maintain hemodynamic stability, as venous return is compromised.

CONCLUSION

Treatment strategies for primary and metastatic liver tumors are limited by low resectability rates and significant toxicity from systemic chemotherapy with minimal improvement in overall survival. We have previously demonstrated the efficacy of isolated hepatic perfusion (PHP) with hyperthermic melphalan for the treatment of unresectable metastatic hepatic tumors from colorectal cancer, ocular melanoma, and neuroendocrine tumors, as well as for primary hepatic malignancies.

In this review we look at a subset of patients with metastatic melanoma to the liver treated on a Phase I protocol of PHP with melphalan. Fifteen patients were treated for a total of 49 treatments. Toxicities most commonly encountered included grade IV melphalan neuritis and thrombose, both of which were reversible. The overall radiographic response was seen in 6 patients (40%; complete n=2; partial n=4). Hepatic disease remained stable in 5 other patients. Median hepatic progression-free survival was 11 months (range: 5-18.5) and overall survival was 14 months (range: 3-32). While PHP has the benefit of providing multiple perfusion treatments with minimal toxicity, PHP with melphalan demonstrates potential toxicity in metastatic melanoma warranting further investigation and study.