Primary and metastatic liver tumors account for one of the largest cancer-related mortalities in the world. Hepatocellular cancer causes over 1 million deaths per year, and this rate is progressively rising. A variety of gastrointestinal (GI), pancreatobiliary, and extra-abdominal tumors metastasize to the liver. Oftentimes, the liver remains the only or predominant site of treatment failure until the time of death. Surgical resection remains the only curative modality for liver tumors, but this approach is only applicable in a limited group of patients. Because of the lack of response of hepatic tumors to systemic therapy, regional chemotherapy is being attempted (1).

Hepatic metastases will develop in up to one fourth of the 140,000 annual new cases of colorectal cancer diagnosed yearly in the United States, and the majority of these patients will have unresectable disease (2). For these patients, systemic and hepatic arterial chemotherapy results in median survivals ranging from 12–24 months (3,4). For patients with metastatic ocular melanoma who recur, 70–90% will develop disease confined to the liver that is multifocal and not amenable to surgical resection (5). Median survival in this group of patients is less than 1 year.

**BACKGROUND**

The prevalence, morbidity, and lack of effective treatments for hepatic malignancies have spawned efforts to establish more organ-specific techniques to minimize systemic toxicity while maximizing targeted delivery. Such local or regional techniques take advantage of the steep dose-response curves of modern chemotherapies. Because
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 takes advantage of the fact that most hepatic tumors parasitize the majority of their blood flow from the hepatic artery. However, with hepatic arterial infusion, drugs such as doxorubicin that are not easily extracted by the liver still create systemic exposure and can thereby limit treatment (6).

In isolated hepatic perfusion (IHP), the vascular supply to the liver is isolated, 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 a chemotherapy agent. Using this technique, overall objective response rates as high as 76% with median response durations of 10.5 months have been observed. The major disadvantages of this approach are that only a single treatment can be applied and it requires open surgery with associated morbidity that includes: bleeding, infection, postsurgical adhesions, paralytic ileus, and shock. Moreover, further treatments are limited or prevented by a lack of a suitable cannulation site for arterial infusion by the formation of postoperative adhesions around the vena cava, hepatic artery, and portal structures (7).

Although several different chemotherapies have been used with IHP, the success of isolated limb perfusion using melphalan to treat melanoma, sarcoma, and other histologies has suggested its use in IHP as well. Studies examining the use of melphalan in IHP to treat hepatic metastases from colorectal cancer have shown promising results.

The National Cancer Institute at the National Institute of Health is conducting a phase III Trial of people with unresectable ocular or cutaneous melanoma. This trial involves 92 patients, who are equally randomized between best alternative care and percutaneous hepatic perfusion (PHP). The study’s primary objective is to determine the progression-free survival of these patients. Secondary, it aims to identify the objective response, and the duration of the objective response of these tumors, the incidence of the development of new, or progression of extra-hepatic disease. It also seeks to determine the overall response rate, duration of the overall response, and the survival. For patient randomizing to the best alternative care arm, they may be treated with any systemic or regional therapy, chemo-embolization, yttrium beads, or observation. However, they may cross-over to the PHP arm if progression of the disease is noted on imaging. Patients randomizing to the PHP arm may be treated with up to six procedures using the Nitrogen Mustard Alkylating agent, Melphalan Hydrochloride. The drug is administered at a dose of 3.0 mg (mg) per kilogram (kg) of ideal body weight with a maximum dose of 220 mg. The treatments are spaced between 4–8 weeks apart with computerized tomography or magnetic resonance imaging in addition to liver function and comprehensive metabolic panel testing to assess the status of the patient’s recovery and the disease state. Objectively, the targeted hepatic lesions will be assessed using the Response Evaluation Criteria in Solid Tumors guidelines.

**MATERIALS AND METHODS**

PHP is a procedure that permits high-dose hepatic chemotherapy using Delcath’s fenestrated multi-lumen double-balloon catheter and two biocompatible hemoperfusion activated charcoal filters. This study, which was approved by the Internal Review Board at the National Cancer Institute, evaluates the efficacy of this percutaneous isolated liver perfusion technique that could be administered repeatedly and would provide the benefits of IHP without the complications of a surgical procedure. The equipment used for this procedure includes: Medtronic Bio-Medicus 550 or 540 Bio-Console with the TX50P or TX40P Pediatric flow transducer (BioMedicus, Eden Prairie, MN), a Capiox BT05 pediatric bubble trap with ¼ inch connectors (Terumo Cardiovascular Systems Corp., Ann Arbor, MI). Delcath System (Delcath Inc., Stamford, CT) includes the following: Disposable Extracorporeal Circuit, two activated carbon biocompatible hemoperfusion cartridges, a 10 French (F) Introducer Set (“venous return sheath”), 6F Introducer Set, and 5F Infusion Catheter (“hepatic arterial catheter”). The venous catheter is a 16F, polyethylene double-balloon catheter that has one large lumen and three accessory lumina. Two lumina provide for individual inflation of each of the balloons while the accessory port to the large central lumen, near the proximal end, is designed for hepatic venous blood sampling and retrograde injection of iodinated contrast dye to check catheter position. An 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 a guide wire.

Once access is gained through the groin, the Interventional Radiologist uses real-time fluoroscopy and the modified Seldinger technique to accurately position the catheters in the targeted area (Figures 1 and 2). The arterial and venous catheters are placed in the left femoral artery and right femoral vein respectively. Angiography road mapping is performed for visualization of the vascular anatomy. This mapping allows the radiologist to identify aberrant arterial anatomy and if required, to selectively embolize vessels in a manner that direct the path of the Melphalan exclusively to the liver. A 5 French infusion catheter is then placed in the proper hepatic artery proximal to the takeoff of the gastroduodenal artery to minimize reflux and to limit potential preferential streaming to either branch of the hepatic artery. Completion of the embolization process readies the patient for
At the perfusionist’s direction, the patient is given between 150–200 units per kilogram of heparin to achieve an activated clotting time (ACT) above 300 seconds. The inlet end of the heparinized, .9% normal saline primed extracorporeal circuit is connected to the proximal end of the ballooned catheter while a 10F catheter, placed in the right internal jugular, is connected to the outlet for the filtered venous return to the patient.

Veno-veno bypass is initiated at a flow rate between 500–600 mL per minute and a negative inlet pressure at a range between 100–120 mm of mercury (mmHg). Blood is drawn into the circuit through the fenestrated portion of the double-balloon catheter which is positioned just below the right atrium in the retro-hepatic portion of the inferior vena cava. First the catheter’s proximal, and then distal balloon is inflated, properly positioned, and securely seated. Bypass is momentarily interrupted as a radiopaque contrast solution is infused through the accessory lumina and exits out the fenestrations into the occluded span of the vena cava. This pivotal maneuver fluoroscopically identifies leaks by the extravasations of contrast outside the inflated balloons or confirms that total occlusion of the vena cava above and below the level of hepatic veins was achieved. This is a critical task in the PHP procedure because it accomplishes two very important objectives. First, by occluding the cava at this location, venous blood returning to the heart is redirected to the azygos vein and thereby isolates the liver’s venous return from the systemic circulation. But most importantly, it ensures the carefully positioned arterial infusion catheter can now have its potent chemo-rich effluence extracted in isolation from any systemic blood.

After occlusion is confirmed, bypass is reinitiated with the blood being routed through the two parallel in-line carbon filters. Melphalan is infused for approximately 30 minutes after which there is an additional 30-minute period of post-infusion filtration. The procedure’s median time is 71 minutes, which includes balloon inflation and positioning, Melphalan infusion, and the post-infusion filtration (8). Once completed, the patient is separated from the bypass circuit and taken to the surgical intensive care unit where protamine sulfate is administered in the appropriate amount to neutralize the heparin and return the activated clotting time to the patient’s baseline level.

Before each subsequent treatment, patients were required to be recovered from all toxicity associated with prior treatments. After receiving the second treatment, assessment of tumor response using a magnetic resonance imaging and/or computerized tomography scan was performed. Patients with evidence of disease progression on interval evaluation were not offered additional treatments.

RESULTS

A phase I study reported that a total of 74 treatments were administered to 28 patients. A transient neutropenia, thrombocytopenia, and anemia were among the morbidities observed. The toxicity was predictable and manageable. The study did not demonstrate that a statically significant accumulation occurred after multiple treatments. Twelve patients with primary and metastatic hepatic tumors received 30 treatments (mean, 2.5 per patient) at an initial melphalan dose of 2.0 mg/kg. At 3.5 mg/kg, a dose-limiting toxicity (neutropenia and/or thrombocytopenia) was observed in two of six patients. Transient grade 3/4 hepatic and systemic toxicity was seen after 19% and 66% of treatments, respectively. An overall radiographic response rate of 30% was observed in treated patients. In the 10 patients...
with ocular melanoma, a 50% overall response rate was observed, including two complete responses (8) (Figure 3).

**DISCUSSION**

In addition to the National Cancer Institute at NIH, Phase III trials for this treatment modality is currently being conducted at University of Maryland Medical Center, Albany Medical Center, St. Luke’s Cancer Center of Bethlehem, Morristown Memorial Hospital, University of Texas Medical Branch, Moffitt Cancer Center, John Wayne Cancer Center, Providence Health Systems and Swedish medical Center.

Percutaneous hepatic perfusion offers patients and surgical oncologists several significant benefits. The technique is targeted, minimally invasive, and offers the option of being able to be performed multiple times, which is in sharp contrast to isolated hepatic perfusion. Furthermore, this targeted delivery method mitigates many of the risks such as small bowel obstruction, infection, and prolonged hospitalization associated with systemic chemotherapy or open abdominal surgery. This procedure can be performed safely by a well trained multi-disciplinary team.

**REFERENCES**