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TECHNICAL NOTE

Chemosaturation with Percutaneous Hepatic Perfusion for Unresectable Isolated Hepatic Metastases from Sarcoma

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Abstract
Purpose Treatment of patients with unresectable liver metastases is challenging. Regional therapies to the liver have been developed that maximize treatment of the localized disease process without systemic toxic adverse effects. We discuss the procedural aspects of liver chemosaturation with percutaneous hepatic perfusion (CS-PHP).
Methods We present as an illustration of this technique a case report of the treatment of unresectable metastatic leiomyosarcoma of the liver.
Results A randomized phase III trial for unresectable liver metastases from melanoma was recently completed comparing CS-PHP with melphalan vs. best alternative care (BAC). When compared with BAC, CS-PHP was associated with a significant improvement in hepatic progression-free survival (8.0 months CS-PHP vs. 1.6 months BAC, $p < 0.0001$) and overall progression-free survival (6.7 months CS-PHP vs. 1.6 months BAC, $p < 0.0001$), respectively. On the basis of these results, and given our experience as one of the treating institutions for this phase III trial, we appealed for compassionate use of CS-PHP in a patient with isolated bilobar unresectable hepatic metastases from leiomyosarcoma. Four target lesions were identified and monitored to assess treatment response. A total of 4 CS-PHP procedures were performed, with a 25 % reduction in size of the largest lesion observed and 16 month hepatic progression-free survival. Toxicity was mild (neutropenia) and manageable on an outpatient basis.
Conclusion CS-PHP offers several advantages for unresectable hepatic sarcoma metastases. CS-PHP is minimally invasive and repeatable, and it has a predictable and manageable systemic toxicity profile. For appropriately selected patients, CS-PHP can delay tumor progression and could potentially improve survival.

Keywords Chemosaturation · Liver tumors · Metastasis · Percutaneous hepatic perfusion · Sarcoma

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Introduction

The liver is a frequent site of metastasis for patients with visceral or retroperitoneal soft tissue sarcoma (STS). The outcome for patients with hepatic metastases from STS is generally poor, with a median survival of 12 months from the time of diagnosis of metastatic disease [1]. The appropriate management of these hepatic metastases has been historically poorly defined, and they are furthermore generally considered resistant to systemic chemotherapy with doxorubicin and ifosfamide [2]. Several therapeutic treatment options such as hepatic artery embolization,

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ablative techniques, hepatectomy, and even liver transplantation have all been described.

In the absence of extrahepatic disease, liver resection remains the best way to treat isolated hepatic metastases from STS. Investigators from the Memorial Sloan-Kettering Cancer Center (MSKCC) reported one of the largest surgical series of hepatectomies for metastatic STS. One- and 3-year actuarial survival rates of 80 and 50 %, respectively, were observed in patients who were able to undergo complete resection of their metastatic disease [3]. Recurrences were high, however, even after complete resection, and the overall survival for those unable to undergo complete resection was poor (4 %). Unfortunately, most patients with visceral STS who develop liver metastases have unresectable disease at presentation. Only 56 (17 %) of 331 patients in the MSKCC series were able to undergo resection of all gross hepatic disease [3]. One potential reason for this finding is that hepatic metastases from visceral STS origin tend to be diffuse and bilobar in nature, rendering the disease of many patients unresectable.

Management of these patients remains challenging. Several therapeutic treatment options have been described, including surgical resection [1, 4], transcatheter arterial chemoembolization [5], selective internal radiotherapy/yttrium-90 microsphere radiotherapy [6, 7], radiofrequency ablation [8], and transplantation [9].

As a potential alternative and adjunct to these therapies, we present the technique of chemosaturation with percutaneous hepatic perfusion (CS-PHP) for the treatment of hepatic metastases from STS (Fig. 1). CS-PHP was recently demonstrated to offer an improved hepatic progression-free survival and overall progression-free survival for metastatic melanoma to the liver [10]. When compared with best alternative care (BAC), CS-PHP was associated with a significant improvement in hepatic progression-free survival (8.0 months CS-PHP vs. 1.6 months BAC, $p < 0.0001$) and overall progression-free survival (6.7 months CS-PHP vs. 1.6 months BAC, $p < 0.0001$), respectively.

On the bases of these results and our institutional experience with the delivery of CS-PHP, we discuss the rationale for use and technical delivery of CS-PHP and provide an illustrative case report of the compassionate use of CS-PHP for the treatment of unresectable hepatic metastases from leiomyosarcoma (LMS).

Case Report

A 66 year-old woman presented with vague abdominal pain and a palpable pelvic mass in March 2007. She had no significant medical history except for a vaginal hysterectomy in 1976 for cervical dysplasia. A computed tomographic (CT) scan obtained by her primary care physician revealed a 12.6 cm pelvic mass. Exploratory laparotomy was performed in May 2007, revealing a solid tumor arising from the sigmoid mesentery in the pelvis. The mass was resected with final pathology consistent with a 16 cm high-grade LMS. The patient was followed postoperatively with close observation and surveillance imaging by her local oncologist.

The patient did well for approximately 23 months when, at surveillance imaging in April 2009, she was noted to have two small lesions within the right lobe of the liver.

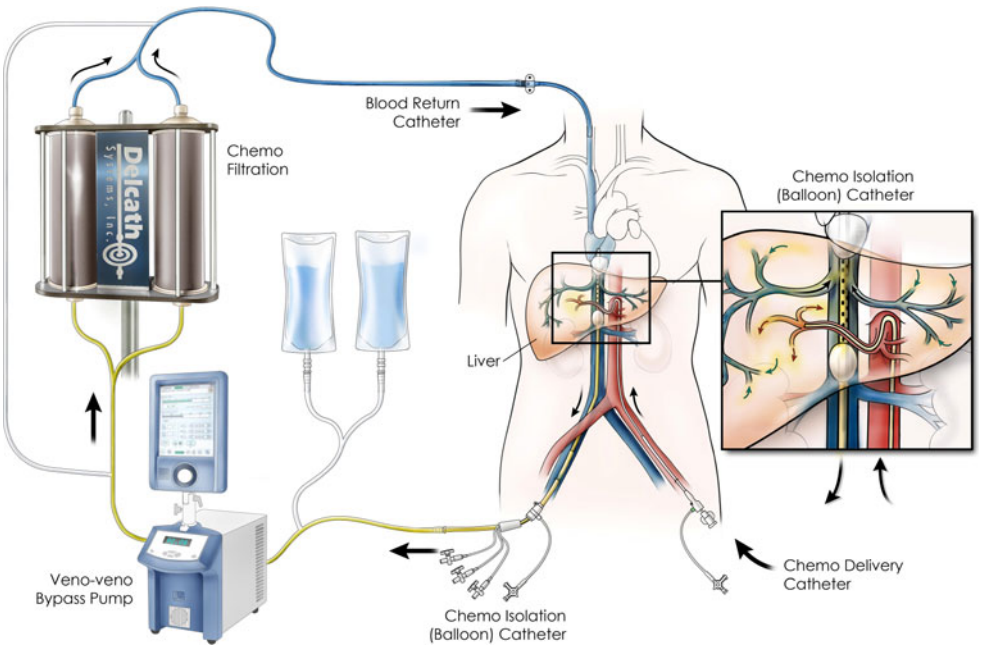

Fig. 1 Diagram of the Delcath Hepatic Chemosat Delivery System. The technique of chemosaturation with percutaneous hepatic perfusion is performed via a specialized double balloon catheter, which occludes the intrahepatic IVC adjacent to the hepatic venous outflow. This allows extracorporeal filtration of the chemotherapeutic agent in the effluent venous blood, with subsequent return to the systemic circulation via a veno–veno bypass into the internal jugular vein

She had no additional evidence of distant metastases. A percutaneous liver biopsy was attempted but was unsuccessful. A repeat CT scan in September 2009 revealed an interval increase in size of the suspicious metastatic lesions. She was referred to our institution for surgical resection of her presumably metastatic liver lesions. Percutaneous liver biopsy revealed metastatic disease. She received two cycles of doxorubicin and ifosfamide and was taken to the operating room in December 2009 for possible liver resection. Intraoperative ultrasound revealed several hepatic metastases that had not been evident on CT imaging, and thus hepatic resection was not performed.

After multidisciplinary tumor board discussion, it was recommended that she be considered for CS-PHP of her unresectable hepatic metastases from LMS. Compassionate-use institutional review board and US Food and Drug Administration approval were obtained for CS-PHP using the Delcath Hepatic Chemosat Delivery System. Pre-CS-PHP cross-sectional imaging revealed four target lesions that were measured and monitored to follow response to treatment (Fig. 2). She was taken to the interventional radiology suite in February 2010, where pre-CS-PHP visceral angiography revealed an aberrant segment IV branch and a left hepatic artery arising from the left gastric artery (Fig. 3A). Her right hepatic artery was noted to be replaced and arising from the superior mesenteric artery (SMA) (Fig. 3C). Coil embolization (Fig. 3B) was performed of the segment IV branch and the aberrant left hepatic artery to avoid inadvertent chemotherapy exposure to nontarget organs (stomach and spleen) and with the intention of performing the CS-PHP via selective cannulation of the right hepatic artery. Repeat visceral angiography 2 weeks after embolization demonstrated redistribution of blood flow to the left liver from the right hepatic artery (Fig. 3D). Initial CS-PHP with melphalan (3 mg/kg based on ideal body weight) was performed in February 2010. She tolerated the initial procedure well and was discharged after 3 days. She had initial mild bone marrow suppression including thrombocytopenia and neutropenia, which were managed with filgrastim and human leukocyte antigen–matched platelet transfusion. Repeat interval surveillance imaging revealed no evidence of distant disease and revealed stable disease within the liver. She therefore underwent a second CS-PHP in April 2010. She tolerated the second CS-PHP with minimal toxicity and had a quicker recovery. A 25 % reduction in size of the largest target lesion was observed, with the other lesions also decreasing in size or remaining stable. CS-PHPs were performed on a 6–8 week basis, and she ultimately underwent two additional CS-PHPs in May and July 2010 (Fig. 2).

She remained with an Eastern Cooperative Oncology Group performance status of 0 and stable liver disease until positron-emission tomography imaging in June 2011 (16 months after the initial CS-PHP) revealed new left supraclavicular lymphadenopathy. Core needle biopsy was performed; results revealed metastatic LMS, and a completion left neck dissection was performed. As of January 2012, she remains alive, with some mild to moderate progression in her dominant liver lesions.

Discussion

CS-PHP has been used for treatment of metastatic disease arising from colorectal, ocular melanoma, adrenal, renal cell, neuroendocrine, and hepatobiliary origins, among others [11–13]. This case report represents what is to our knowledge one of the first descriptions of CS-PHP for isolated metastatic retroperitoneal sarcoma to the liver. Although we did not perform a direct comparison of CS-PHP to alternative therapies, we do believe the potential benefit demonstrated in this case to be clinically important, demonstrating that CS-PHP may serve as an additional treatment alternative for a select group of STS patients who present with isolated metastatic disease to the liver.

Rationale for CS-PHP

Hepatic metastases from a variety of tumors derive most of their blood supply from the hepatic artery. The hepatic vascular anatomy, therefore, by isolation of its arterial inflow and venous outflow, is potentially a target for liver specific regional therapy. Surgical isolation of the hepatic vascular anatomy for treatment was first described over 50 years ago [14]. Refinements in isolated hepatic perfusion have been further developed that allow administration of high-dose regional chemotherapy via the hepatic artery [15–17]. Early experience, however, was limited by significant morbidity and treatment-related mortality in the range of 10–25 % [16]. Recently, the technique of isolated hepatic perfusion has been further developed so that it may be performed percutaneously without the associated morbidities of an extensive surgical procedure [11, 18].

CS-PHP allows the regional delivery of chemotherapy while isolating hepatic venous outflow. The Delcath Hepatic Chemosat Delivery System includes a percutaneously placed double balloon catheter that occludes the intrahepatic inferior vena cava (IVC), thereby isolating the hepatic venous outflow. This vascular isolation allows extracorporeal filtration of the chemotherapeutic agent (often melphalan) administered via a separate catheter placed within the hepatic artery, and subsequent return of the effluent venous blood into systemic circulation via a veno–veno bypass circuit. CS-PHP has been demonstrated in early phase I studies to be safe and beneficial for

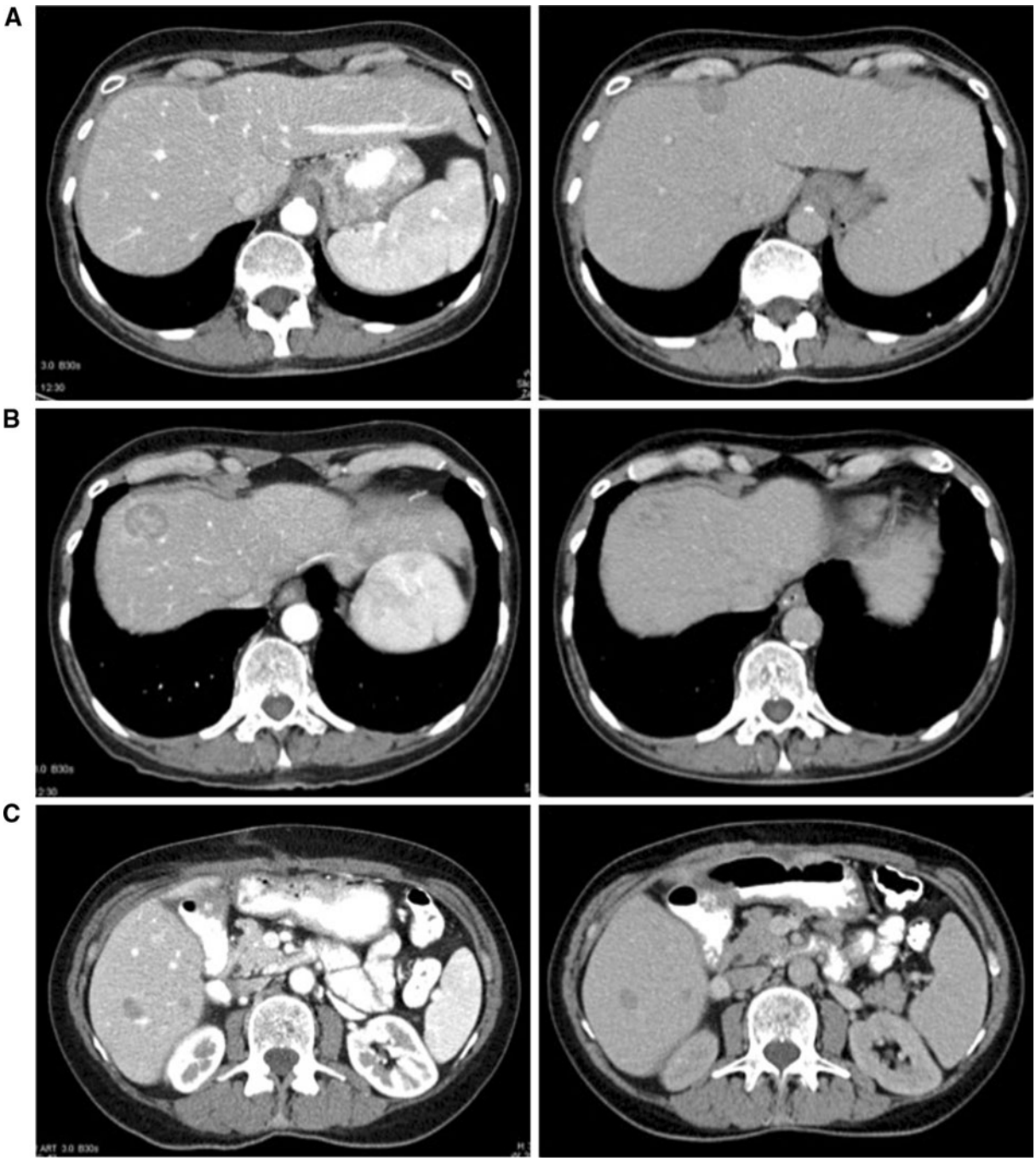

Fig. 2 CT scans reveal target lesions followed for treatment-related response to chemosaturation with percutaneous hepatic perfusion (CS-PHP) in the case patient with metastatic sarcoma isolated to the liver. The CT scans on the *left* were taken on January 25, 2010, before the initial CS-PHP, while the CT scans on the *right* were taken on June 28, 2010, after third CS-PHP. **A** Target lesion 1. **B** Target lesion 2. **c** Target lesions 3 and 4

unresectable hepatic metastases from a variety of histologies [11, 18]. A randomized phase III trial using CS-PHP with melphalan for metastatic melanoma to the liver was recently completed [10]. When compared with BAC, CS-PHP was associated with a significant improvement in hepatic progression-free survival (8.0 months CS-PHP vs. 1.6 months BAC, $p < 0.0001$) and overall progression-free survival (6.7 months CS-PHP vs. 1.6 months BAC, $p < 0.0001$), respectively. It was on the bases of these results and our institutional experience that we appealed for compassionate use of CS-PHP for our patient with unresectable metastatic STS of the liver.

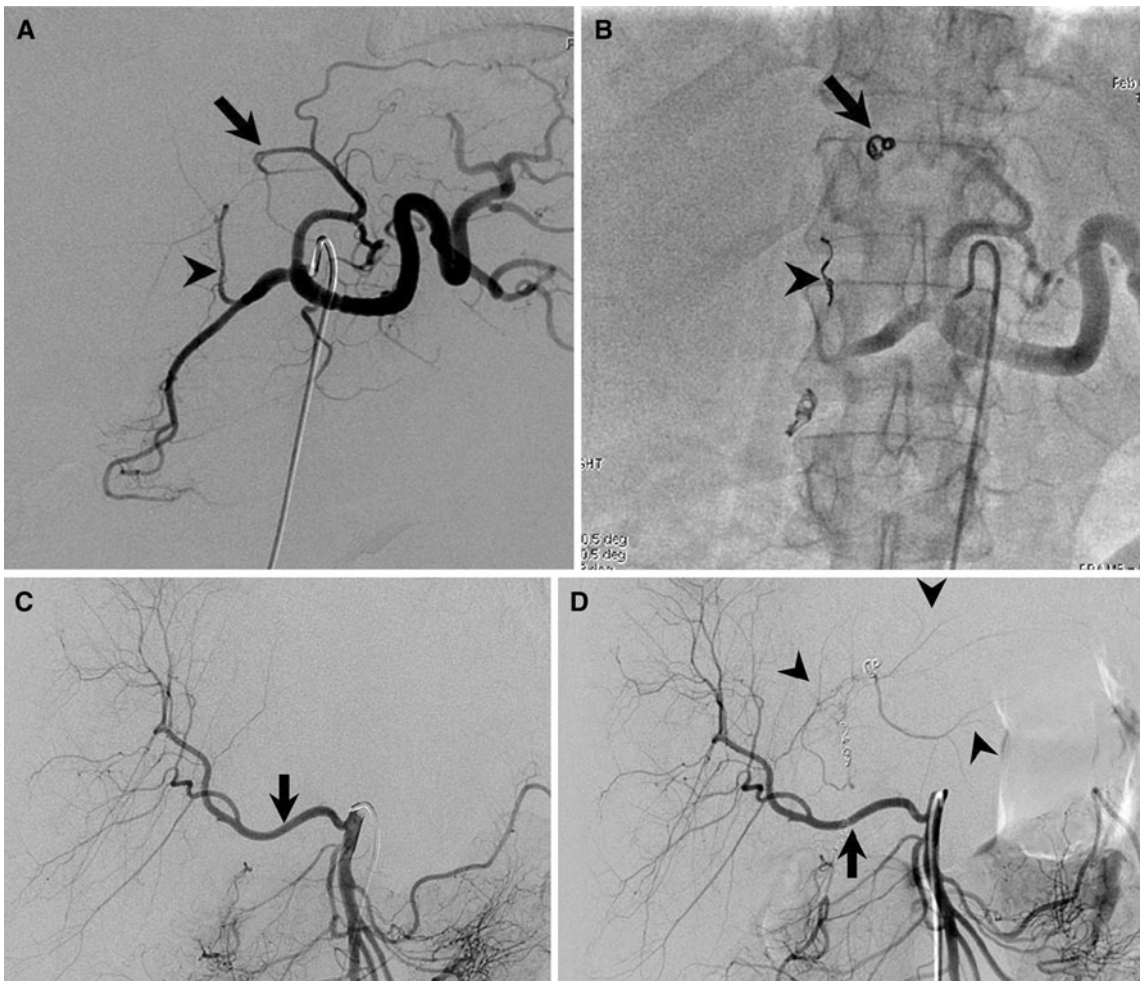

Fig. 3 Celiac axis angiography revealed a segment IV hepatic branch (*arrowhead*) arising from the hepatic artery and an aberrant left hepatic artery arising from the left gastric artery (*arrow*). **A** Coil embolization was selectively performed with postembolization angiogram revealing absence of flow. **B** SMA angiography revealed the right hepatic artery (*arrow*) arising from the SMA. **C** Selective SMA angiography 2 weeks after embolization demonstrates redistribution of left hepatic blood flow (*arrowhead*) from the right hepatic artery (*arrow*). **D** CS-PHP was selectively performed via the right hepatic artery

Procedural Details of CS-PHP

CS-PHP utilizes a specialized double balloon catheter system consisting of a 16F fenestrated polyurethane catheter with proximal and distal balloons that permit occlusion of the IVC. This results in vascular isolation of the liver and allows regional delivery of chemotherapy to the liver. We perform CS-PHPs at the Moffitt Cancer Center with the patient under monitored general anesthesia in the interventional radiology suite.

Patient Selection

Careful selection of appropriate candidates for CS-PHP is critical for successful outcome. Generally, patients should have metastases limited to the liver alone. The procedure is contraindicated in patients with liver failure or in those who have previously undergone major liver resection. Similarly, individuals weighing less than 35 kg, because of anatomical (distance between the IVC/right atrium and renal vein) and physical limitations inherent to the double balloon catheter size, should not undergo treatment with CS-PHP. Future catheter modifications (intraballoon distances) are being developed that will accommodate these potential anatomical constraints. A screening CT and/or magnetic resonance imaging to assess hepatic vascular anatomy and tumor burden is recommended. Diagnostic laparoscopy with biopsy to exclude miliary metastatic disease may be necessary in situations where tumor burden exceeds 50 % of liver volume based on cross-sectional imaging. A core needle biopsy of normal hepatic parenchyma is suggested to exclude other evidence of hepatic cellular dysfunction (e.g., steatosis, fibrosis, triaditis) and potential poor response to CS-PHP.

Preprocedure Preparation

Patients are admitted the day before the procedure for intravenous hydration. This is necessary to mitigate any intraprocedural hypotension and potential acute tubular necrosis that may occur as a result of the large amount of contrast medium required during CS-PHP. A week or two before definitive CS-PHP, a complete visceral angiogram (celiac axis and SMA) is performed to examine the arterial and portal venous anatomy of the liver. This is important to identify any potential variant hepatic vascular anatomy (as was the case for our patient) and allows treatment (embolization) before initial CS-PHP. Furthermore, the anatomic relationship of the hepatic artery with respect to the gastroduodenal artery (GDA) may be better defined as well. Coil embolization of the GDA may be required if there is less than 1 cm of the proper hepatic artery distal to the GDA branch or if there is a possibility of retrograde flow into the GDA after placement of the catheters. Prophylactic embolization in these situations avoids potential inadvertent chemoperfusion to nontarget gastrointestinal or visceral branches during CS-PHP.

Administration of CS-PHP

Vascular access consists of a 5F femoral arterial sheath, an 18F femoral venous sheath, and a 10F internal jugular central venous catheter. Systemic anticoagulation is achieved with heparin (200 U/kg) for a targeted activating clotting time of more than 400 seconds.

The three main principles of CS-PHP are isolation, chemosaturation, and filtration.

The first stage, isolation, consists of placement of the three catheters (Fig. 1). Before the catheters are introduced, the introducer sheaths are flushed with heparinized saline. First, the infusion catheter (5F Delcath Chemofuse Chemo Delivery Catheter) is introduced through an introducer sheath in the femoral artery. It is positioned into the hepatic artery well beyond the origin of the GDA and allows hepatic angiography to be performed as well as the delivery of the chemotherapeutic agent. A 16F double balloon isolation–aspiration catheter (Delcath Isofuse Isolation Aspiration Catheter) is introduced through an 18F venous sheath inserted in the femoral vein. Under fluoroscopic guidance, it is advanced into the IVC. The inflated cephalad balloon usually rests at the level of the diaphragmatic hiatus and fluoroscopically resembles an acorn. It is caudally retracted from the right atrium under fluoroscopic guidance, forming a seal at the cavo–atrial junction. With the cephalad balloon positioned in the right atrium/IVC junction, the caudal balloon rests at the intrahepatic IVC above the level of the renal veins. The effluent port of the isolation–aspiration catheter is then connected to the hemofiltration unit and the venous return sheath is connected to the perfusion adapter (Fig. 1). The third and remaining catheter, the veno–veno return catheter, is inserted through a 10F venous return sheath placed in the internal jugular vein.

To establish the hemofiltration circulation, the isolation–aspiration catheter and veno–veno return line are connected to the perfusion bypass machine, the clamps are released, and the pump is cycled at 1,000 rpm. To provide maximum flow through the isolation aspiration catheter, the pump speed is gradually increased to about 2,500 rpm, or until the hepatic venous pressure is slightly negative. In-line pressure transducers monitor pressure within the circuit. At this stage, melphalan is requested from the pharmacy.

To achieve complete isolation of the liver, the cephalad balloon must first be inflated with dilute contrast medium under fluoroscopic guidance. It is vital that this balloon is wedged into the right atrial–IVC border and secured to prevent migration or potential leakage of chemotherapy during the CS-PHP. The exact placement of this catheter is monitored repeatedly during the procedures as an additional safety measure. We found it useful to mark the catheter where it exits the sheath with a sterile marker pen as an indication of balloon migration during the procedure. If the tension on the cephalad balloon slackens, the marker line will disappear from view. After positioning the cephalad balloon correctly, the caudal balloon is inflated under fluoroscopic guidance. To confirm that the catheter properly isolates hepatic venous flow between the balloons, a limited hand-injected inferior vena cavagram is performed through the fenestrations located between the occlusion balloons. Once complete occlusion is confirmed, the catheter is flushed with heparinized saline and flow through the hemofiltration unit is reestablished.

Hemodynamic monitoring and blood pressure management are performed throughout the procedure but are crucial at two stages: inflation of the double balloon catheter and activation of the extracorporeal filtration circuit. Mean arterial pressure often precipitously drops with inflation of the double balloon catheter (occlusion of the IVC) and as a result of the removal of endogenous catecholamines by the filtration system. Aggressive hydration and administration of a vasopressor agent, such as phenylephrine or norepinephrine, may be necessary to maintain adequate blood pressure. It usually takes about 5 min to stabilize the mean arterial pressure after the double balloon catheter is inflated and the hemofiltration cartridges are brought online.

Before administration of the chemotherapeutic, an angiogram is performed to assess the patency of the hepatic artery. For patients who have undergone prior embolization, this demonstrates redistribution of blood flow to both lobes of the liver (Fig. 3D). If hepatic arterial spasm is noted, nitroglycerine is administered through the

chemodelivery catheter to alleviate the spasm; one dose of nitroglycerin (100 μg) usually relieves the spasm. It is essential to periodically repeat the hepatic artery angiogram to ensure that the spasm has been relieved and patency is maintained during the procedure. The catheter balloon position is also confirmed fluoroscopically every 4–5 min during chemotherapeutic administration to ensure continued hepatic venous isolation. The chemodelivery catheter is flushed with heparinized saline after administration of contrast or nitroglycerin and before delivery of the chemotherapeutic agent.

Once vascular isolation of the liver is confirmed and hepatic arteriogram reveals no vasospasm or reflux of contrast into the celiac axis, chemosaturation, the second step of CS-PHP is initiated by administering melphalan (at a total dose of 3 mg/kg corrected for ideal body weight, maximum 220 mg) at 25 ml/min for 30 min. Melphalan, a nonspecific alkylating agent, was demonstrated to have antitumor activity in a dose-dependent relationship when delivered via isolated hepatic perfusion [15]. It also has a high first-pass metabolism and a high hepatic clearance allowing delivery in higher doses to the liver [19]. Melphalan is prepared in the pharmacy and delivered to the procedural suite at the time of anticipated chemoperfusion. No specific handling is necessary intraoperatively; only standard chemotherapy precautions are required.

Typical flow rates during the CS-PHP range 0.4–0.75 L/min. It is usual to split the chemotherapy dose, administering 60 % to the right hepatic artery (300 ml) and 40 % to the left hepatic artery (200 ml) as a result of the differences in blood flow and volume of distribution between the right and left lobes of the liver. We found the left hepatic artery harder to access than the right, and therefore we preferentially started chemoperfusion on the left side first. Chemoperfusion was held or discontinued in situations of arterial spasm that were unable to be relieved with administration of nitroglycerin, or if extrahepatic perfusion of chemotherapeutic occurred or was suspected.

The third and final phase of CS-PHP consist of filtration. The hepatic venous effluent flows through the fenestrated portion of the double balloon catheter where it is filtered by the extracorporeal circuit. Melphalan admixed within the hepatic effluent is removed from circulation by two extracorporeal filters, a term defined as chemofiltration. These filters reduce the concentration of chemotherapeutic drug in the blood that is reinfused to the systemic circulation via the internal jugular vein return line.

At the completion of 30 min of chemoperfusion with melphalan, the bypass circuit continues to circulate for an additional 30 min to filter any residual drug within the circuit. The tension on the balloon catheter is maintained during the washout period to avoid potential drug leakage into the systemic circulation. At the end of the extracorporeal filtration washout cycle, the caudal balloon is deflated, followed by the cephalad balloon. The pump speed is reduced to 1,000 rpm and the bypass line opened. The cartridges and then the double balloon catheter line are clamped off. The isolation–aspiration catheter is removed. The introducers and remaining catheters are sutured in placed to prevent accidental removal. Protamine sulfate, fresh frozen plasma, and blood products are provided as needed, and the introducer catheters are removed when the activating clotting time, prothrombin time, and partial thromboplastin time return to baseline levels. Patients are monitored in an intensive care unit setting for 12–24 h after the procedure and then discharged home within 2–3 days.

Safety Monitoring

Perfusion-related events are continually monitored throughout the procedure. Transient hypotension during the CS-PHP procedure is commonly encountered corresponding to decreased venous return at the initial balloon inflation (IVC occlusion) and at the initiation of hemofiltration (filtration of circulating catecholamines) [12, 15]. These transient hemodynamic effects are easily managed with administration of intravenous fluids and low-dose vasopressor support. Blood loss is generally only mild to moderate and corresponds to the volume contained within the extracorporeal circuit.

The common adverse effects of melphalan result from bone marrow suppression leading to neutropenia, thrombocytopenia, and anemia. These can occur within 10–14 days of CS-PHP. Dose-limiting toxicities, when they occur, are the result of leakage of melphalan within the systemic circulation [17, 20]. The patient should be seen weekly or more frequently after discharge from the hospital until melphalan-related neutropenia resolves, after which the patient should be seen every 1–2 weeks. Hematopoietic support is provided with filgrastim, platelets (if $<20{,}000/mm^3$), and packed red blood cells for symptomatic anemia. Neutropenia should resolve within 2–4 weeks. Some patients, such as those previously treated with chemotherapy, may be sensitive to hematological toxicity and should be monitored more closely. Additional monitoring may also be required if a patient experienced a greater systemic exposure to melphalan than planned. We image patients at monthly intervals to assess treatment response and disease progression, as was the standard protocol for patients enrolled onto the phase III trial.

Repeated CS-PHP

One additional advantage of CS-PHP is that it is may be repeated multiple times without increased cumulative toxicity [21]. We found this to be the case for our patient in

particular. The average number of CS-PHP procedures performed per patient in the early phase I clinical trial for unresectable hepatic metastases was 2.5 [11]. Our patient underwent a total of 4 CS-PHPs with an average length of hospital stay of 2–3 days for each procedure. Although our patient experienced transient toxicity with her initial CS-PHP, this was self-limiting and was not experienced after additional treatments.

The initial institutional review board approval for compassionate-use CS-PHP in our patient was for four treatments. There are no known absolute limitations to the number of CS-PHP procedures that may be performed. Treatment decisions at our institution are made on the bases of close surveillance with monitoring for hematologic toxicity, patient tolerance to therapy, and routine CT imaging to assess treatment response and disease progression.

Conclusion

Results from this single-patient experience demonstrate that CS-PHP may represent an additional treatment option for isolated hepatic STS metastases. CS-PHP avoids an extensive surgical procedure, is repeatable, and has a low toxicity profile. CS-PHP maximizes treatment to the entire liver and may result in a sustainable favorable outcome in selected patients. Further study is required to determine whether the observed effects are long-lasting or whether it may be used in potential combination multimodal therapy.

Conflict of interest S. Stewart and J. Choi are paid consultants for Delcath Systems Inc. J. S. Zager is a consultant for and member of the medical advisory board for Delcath Systems Inc. The other authors declare that they have no conflict of interest.

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