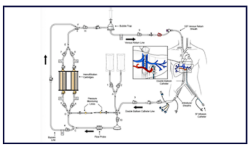
NARRATIVE REVIEW



Treatment of Liver Metastases from Uveal Melanoma with Percutaneous Hepatic Perfusion

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ABSTRACT

Uveal melanoma frequently metastasizes to the liver, with over 90% of metastatic cases involving hepatic spread. Despite systemic therapy advances, prognosis remains poor in hepatic-dominant disease. Percutaneous hepatic perfusion (PHP) with melphalan, now U.S. Food and Drug Administration (FDA)–approved via the Hepzato Kit, delivers high-dose chemotherapy directly to the liver while reducing systemic toxicity through extracorporeal filtration. This review outlines PHP's rationale, technique, patient selection, and institutional requirements. Ideal candidates have multifocal, bilobar liver metastases and limited extrahepatic disease. PHP requires coordinated care across interventional radiology, anesthesia, perfusion, and pharmacy. Clinical data show encouraging survival and disease control with manageable hematologic toxicity and rapid recovery. Research into improved filtration, optimized dosing, and immunotherapy integration may further improve outcomes.

ABBREVIATIONS

BCNU = 1,3-bis(2-chloroethyl)-1-nitrosourea, CBC = complete blood count, ECOG = Eastern Cooperative Oncology Group, FDA = U.S. Food and Drug Administration, G-CSF = granulocyte macrophage colony–stimulating factor, IE = immunoembolization, LRT = liver-directed therapy, MR = magnetic resonance, ORR = objective response rate, OS = overall survival, PFS = progression-free survival, PHP = percutaneous hepatic perfusion, QOL = quality of life, TACE = transarterial chemoembolization, UM = uveal melanoma

LIVER METASTASES FROM UVEAL MELANOMA

Uveal melanoma (UM) is the most common primary intraocular malignancy in adults, with an incidence of 4.3 to 10.9 cases per million per year (1–3). Fifty percent of patients with UM develop metastases, and most have hepatic metastases. Once UM metastasizes to the liver, prognosis worsens, with median survival less than a year without treatment. Given this unique metastatic pattern, management of hepatic metastases is critical in prolonging survival and preserving quality of life (QOL).

Recent Advances and Research on UM

Management of these patients focuses on both systemic therapies and liver-directed therapies (LRTs). Tebentafusp, a bispecific fusion protein immunotherapy agent, demonstrated an improvement in overall survival (OS) compared with standard therapies (21.7 vs 16.0 months; hazard ratio, 0.51; $P < .001$), despite a 9% objective response rate (ORR) (4). Effectiveness is limited to patients who are HLA-A*02:01-positive, which represents less than 50% of the population. Given the low response rate and suitability in a fraction of the population, regional LRTs have gained traction for managing liver metastases in UM.

Overview of LRTs for UM

LRTs, including immunoembolization (IE), transarterial chemoembolization (TACE), transarterial radioembolization, and percutaneous hepatic perfusion (PHP), aim to deliver high concentrations of therapeutic agents directly to hepatic metastases while minimizing systemic exposure. PHP with

Appendix A can be found by accessing the online version of this article on *www.jvir.org* and selecting the Supplemental Material tab.

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RESEARCH HIGHLIGHTS

- Uveal melanoma metastasizes to the liver in >90% of cases. Liver-directed therapies play a significant role in extending survival and sustaining quality of life.
- Percutaneous hepatic perfusion with melphalan enables whole-liver, high-dose chemotherapy delivery with extracorporeal filtration to reduce systemic toxicity, making it particularly suited for multifocal, bilobar uveal melanoma metastases.
- Prospective and retrospective studies consistently show meaningful objective response rates of 36%–60%, and median survival ranging 15–20 months, with manageable hematologic toxicity.
- Ideal candidates have liver-dominant disease (<50% hepatic involvement), good performance status, preserved hepatic function, and limited extrahepatic spread; careful cardiopulmonary assessment is essential.
- Research is ongoing into optimizing drug filtration and dosing, combining percutaneous hepatic perfusion with immunotherapy, and extending its use to other metastatic cancers such as breast and colorectal cancers.

melphalan delivers high-dose cytotoxic chemotherapy to the entire liver (5,6). This technique minimizes systemic toxicity through drug sequestration and filtration (7). The use of a nonembolic therapy minimizes the postembolization effect and risk of hepatic parenchymal injury that can be seen with other embolic liver-directed therapies. A commercially available PHP system (Hepzato Kit; Delcath Systems, Wilmington, Delaware) received U.S. Food and Drug Administration (FDA) approval in 2023 as liver-directed treatment for adult patients with UM with unresectable hepatic metastases affecting less than 50% of the liver and no extrahepatic disease or controlled/treatable extrahepatic disease limited to the bone, lymph nodes, subcutaneous tissues, or lung.

Although there are several recognized locoregional therapies used to treat liver metastases from UM, there are numerous important considerations including most notably the prioritization of liver preservation.

Thermal ablation has limited utility given the multifocal nature of UM metastases to the liver. Nevertheless, in the oligometastatic clinical scenario, it is a reasonable approach with proper patient selection, such as size less than 3 cm with well-defined margins, technically feasible for ablation, and lack of adjacent critical structures (8).

IE of liver disease also has limited data supporting its use; however, as opposed to thermal ablation, this is related to the limited number of centers offering this therapy worldwide. Valsecchi et al (9) studied IE with granulocyte macrophage colony–stimulating factor (G-CSF) emulsified in ethiodized oil followed by gelatin sponge versus bland embolization in a 52-patient Phase 2 trial; ORRs were 21.2% and 16.7%, respectively. Median OS was only in favor of the IE in the 20%–50% tumor burden subgroup.

Chemoembolization with 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU, carmustine) has been used with limited effectiveness. In a series of 50 treatment-naïve patients, response rate following BCNU chemoembolization was 6%, and median survival was 7.1 months (range, 1.2–32.3 months) (10). At our institutions in contemporary clinical practice, this (BCNU TACE) is uncommonly utilized.

Transarterial yttrium-90 radioembolization for UM liver metastases has recently been the most commonly used transarterial therapy. With localized (eg, 1 lobe or less) or focal large tumors that can be targeted with an increased tumor-to-normal ratio, transarterial radioembolization may have considerable benefit with respect to tumor response. In patients where the whole liver needs to be treated (ie, multifocal bilobar metastases), dosing strategies limit the potential benefit as the risk of hepatic fibrosis must be taken into account. Gonsalves et al (11) in a Phase 2 study compared radioembolization in patients who were treatment-naïve or who had received previous IE. Radioembolization was performed with resin microspheres using body surface area dosimetry, with some patients receiving unilobar treatment and others receiving sequential bilobar treatment. ORRs were 39% for treatment-naïve and 33% for those who had received previous IE; median OS durations were 18.5 and 19.2 months, respectively.

Given the frequent need for repeat whole-liver treatments in this malignancy, PHP has gained favor in recent years. Kolb et al (12) retrospectively compared radioembolization and PHP in 62 patients and found a significant difference in OS in favor of PHP (300 vs 516 days, $P = .006$). Outcome data for PHP and their corresponding studies are listed in the **Table** (13–22).

Table. Clinical Outcomes from Percutaneous Hepatic Perfusion

Author	Year	Study type	No. of patients	OS (mo)	PFS (mo)	ORR (%)
Zager et al (13)	2024	Prospective	91	20.5	9	36.3
Meijer et al (14)	2021	Prospective	35	19.1	7.6	72
Tong et al (15)	2022	Retrospective	101	20	9	59.5
Modi et al (16)	2022	Retrospective	81	14.9	8.4	60.5
Dewald et al (17)	2021	Retrospective	30	12	6	42.3
Estler et al (18)	2021	Retrospective	29	12.9	7.1	NR
Brüning et al (19)	2020	Retrospective	19	16.7	14.1	NR
Artzner et al (20)	2019	Retrospective	16	27.4	11.1	NR
Karydis et al (21)	2018	Retrospective	51	15.3	8.1	47
Vogl et al (22)	2017	Retrospective	18	9.6	12.4	NR

NR = not reported; ORR = objective response rate; OS = overall survival; PFS = progression-free survival.

PATIENT SELECTION AND PREPARATION

Patient selection criteria are based on clinical trials and expert consensus, with specific emphasis on liver tumor involvement, overall health status, and absence of significant extrahepatic disease (13,18,23). Prospective trials combining immune checkpoint inhibitors and PHP are ongoing (24).

The primary use and advantage of PHP is to treat the entire liver. Therefore, patients with multifocal, bilobar (especially miliary) metastases are likely the best candidates. Conversely, these patients are not appropriate candidates for thermal ablation. Radioembolization is best suited for disease confined to 1 hepatic lobe or less or where tumor-to-normal ratio is high, resulting in higher-dosing strategies that will yield better response rates. Whole-liver (or sequential lobar) radioembolization can be performed safely; however, repeat treatments may results in eventual hepatic fibrosis. Patients who are not candidates for PHP due to underlying cardiovascular disease or those who have progressed after PHP may be suitable candidates for radioembolization. Similarly, those who have progressed after radioembolization may be candidates for PHP.

Key Criteria for Patient Selection

The following criteria are considered for ideal patient selection:.

- Liver only or liver-dominant metastases with controlled/minimal extrahepatic spread.
- Multifocal and bilobar or miliary tumors, with an overall tumor burden of less than 50% in the parenchyma of the liver.
- Eastern Cooperative Oncology Group (ECOG) performance status of 0–1. Normal functional capacity and have no or limited cardiopulmonary comorbidity.
- Normal hepatic function. Liver function enzymes should be within normal limits. Given minimal hepatotoxicity from PHP, it is currently unknown what the upper limit of liver function may be to consider treatment.
- Complete blood count (CBC) within normal limits: a platelet count of >100,000/μL, hemoglobin level of ≥10.0 gm/dL, white blood cell count of >2,000/uL, and absolute neutrophil count of $\geq 1.5 \times 10^9$/L.

Contraindications include the following:

- Patients who are unable to undergo general anesthesia.
- Those with New York Heart Association active cardiac conditions. An evaluation of risk must occur for those with functional Classification II, III, or IV.
- Patients with a history of bleeding/clotting disorders or evidence of intracranial abnormalities, which would put them at risk for bleeding with anticoagulation (eg, heparin intolerance, history of spontaneous bleeding, strokes, and active intracranial metastases).
- Known varices at risk of bleeding.
- Patients with prior Whipple procedure or biliary stents can be considered a relative contraindication. Given the lack of acute necrosis of tumor related to PHP (unlike TACE and ablation), it is unknown whether this constitutes a risk of hepatic infection. Patients with prior biliary intervention have not been included in studies, and therefore, there is no information on which to base a recommendation.

Preprocedural Patient Preparation

The following should be included in the preprocedural assessment (20,25):

- Magnetic resonance (MR) imaging of the liver with Eovist allows for the greatest sensitivity in detection of hepatic metastases. Imaging is also used to define arterial anatomy and aberrant venous anatomy precluding double-balloon catheter use. Intraprocedural cone-beam computed tomography (CT) may also help with evaluation of vascular anatomy and allows for restaging tumor burden.
- Laboratory examinations: CBC, comprehensive metabolic panel including liver function enzymes, and lactate dehydrogenase.
- Cardiac function evaluation: given the wide periprocedural blood pressure fluctuation, resting and/or stress echocardiography or myocardial perfusion imaging should be obtained. This can be performed based on institutional preference.
- Brain MR imaging: although the incidence of brain metastases is very low, baseline brain MR imaging should be considered due to the use of high-dose anticoagulation during the procedure.

DESCRIPTION OF PHP DEVICE (HEPZATO KIT)

The components of the PHP device and guidance for use are described in **Appendix A** (available online on the article's Supplemental Material page at *www.jvir.org*.) and **Figures 1–4**.

POSTPROCEDURAL MANAGEMENT INCLUDING ADVERSE EVENTS

In most cases, postprocedural care consists of laboratory monitoring, electrolyte repletion, and transfusion of blood products when needed. Most patients are extubated upon procedure completion and normotensive without vasopressor support (13,15,26). If vascular access is removed with hemostasis, critical care monitoring is not mandatory. Intensive care unit–level care following the procedure may be needed if sheath removal is delayed or continued pressor support is needed (27).

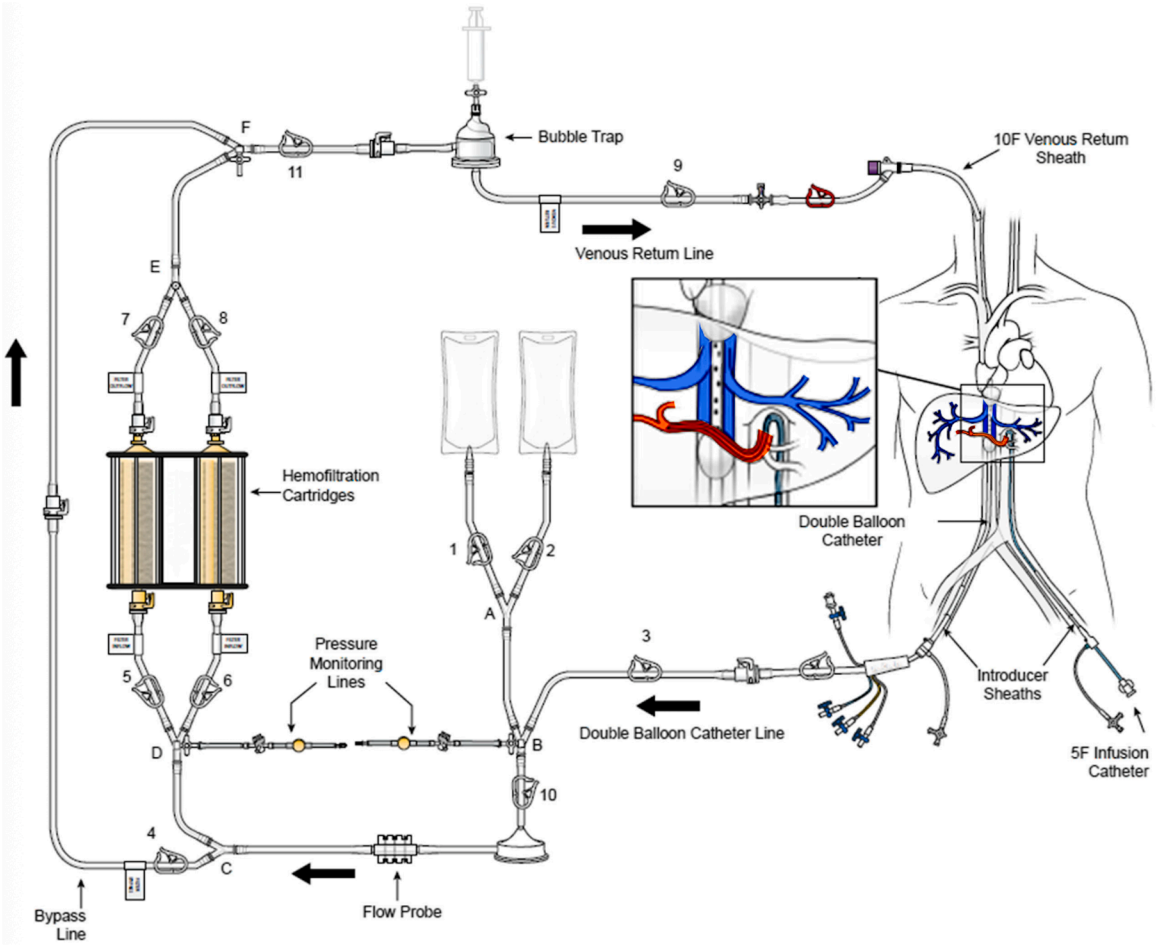

Figure 1. Schematic of the completed circuit (reproduced with permission from Delcath).

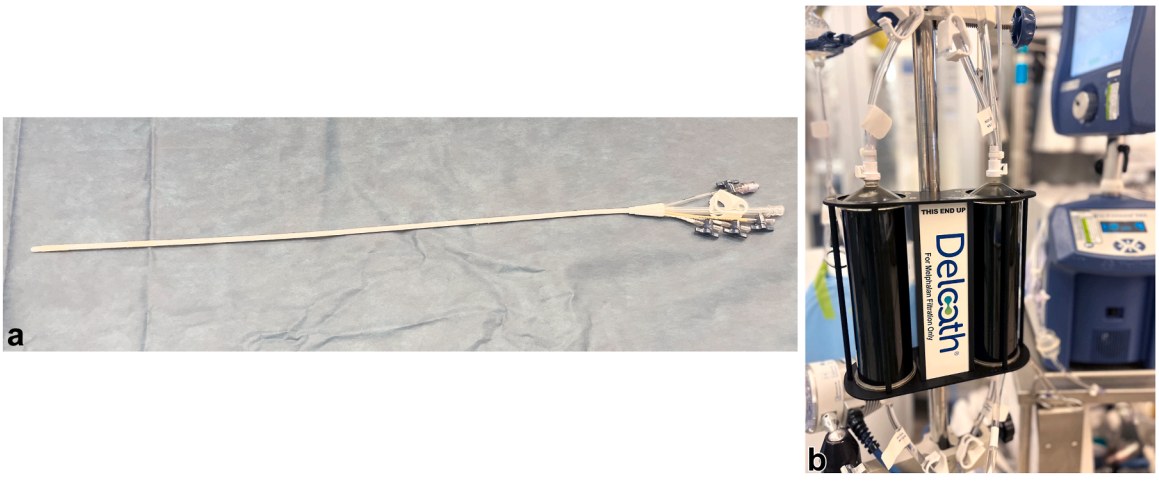

Figure 2. (a) A 16-F double-balloon catheter, a component of the Hepzato Kit. **(b)** Carbon-based melphalan filtration system, a component of the Hepzato Kit.

Postprocedural Care

- Cardiac and hemodynamic monitoring: once the extracorporeal filtration circuit is stopped and vasopressors are weaned off, hypotension is uncommon, and arterial blood pressure monitoring is not needed. If there is unexpected difficulty weaning from pressors, cardiology evaluation should be considered including electrocardiography and echocardiography with cardiology consultation as needed. Asymptomatic

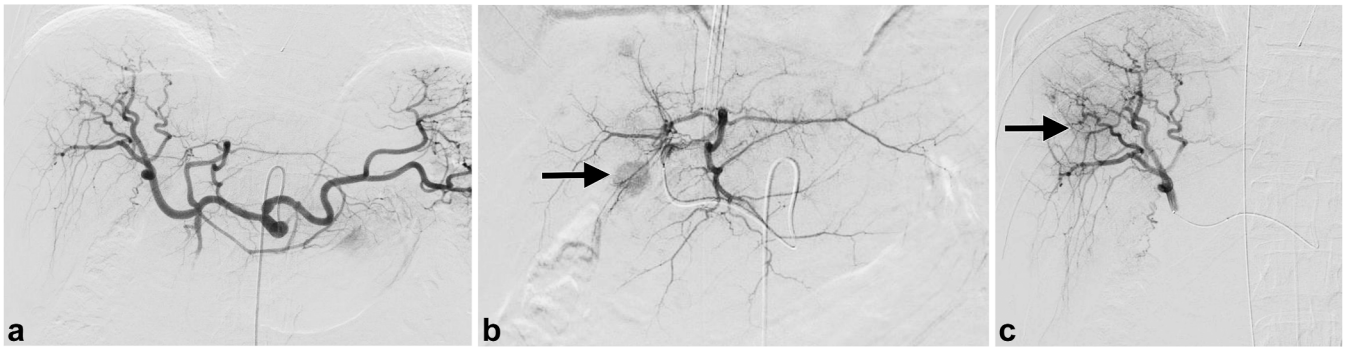

Figure 3. Hepatic angiogram during percutaneous hepatic perfusion. **(a)** A 5-F reverse catheter engaged in the celiac artery with digital subtraction angiography (DSA). **(b)** Microcatheter selection of the left hepatic artery with DSA demonstrated multiple hypervascular tumors (arrow). Melphalan was infused from this position. **(c)** Microcatheter selection of the right hepatic artery with DSA demonstrated multiple hypervascular tumors (arrow). Melphalan was infused from this position.

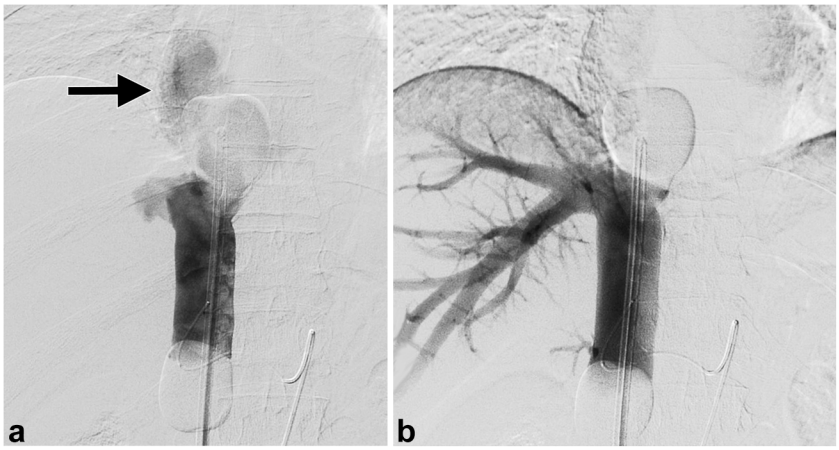

Figure 4. Double-balloon catheter in the inferior vena cava (IVC), with the superior balloon in the right atrium at the IVC junction and the inferior balloon in the intrahepatic IVC. **(a)** Initial digital subtraction angiography (DSA) demonstrated opacification of the IVC and hepatic veins with transit of contrast into the right atrium (arrow), consistent with an incomplete seal. **(b)** After readjustment of the balloons, angiogram showed containment within the IVC and hepatic veins.

increase in troponin level with a peak in less than 24 hours is not uncommon and does not require any further action unless accompanied by concerning signs, symptoms, and electrocardiography changes (27,28).

- Neurologic checks: due to intraprocedural hemodynamic shifts and use of anticoagulation, neurologic checks after the procedure are recommended to monitor for any early signs of cerebrovascular compromise or hemorrhage (29).
- Access site monitoring: due to the multiple vascular access sites and anticoagulation during the procedure, frequent examination of the access sites to monitor for hematoma or vascular injury should be performed per institutional protocol (26).
- Blood transfusions: the procedure is associated with transient cytopenia. Platelets, red blood cells, fresh frozen plasma, and/or cryoprecipitate may be administered depending on blood counts and coagulation status (27). It is common to check laboratory values in the procedural suite immediately after anticoagulation reversal and then every 6 hours until reaching safe levels for discharge (21,26,27).
- Electrolyte repletion: laboratory examinations including complete metabolic panel, magnesium, phosphorus, and ionized calcium should be checked immediately after procedure. Electrolyte abnormalities should be repleted per institutional guidelines (27).
- Patients can typically be discharged within 24 hours after the procedure (16,26).

POSTPROCEDURAL MANAGEMENT INCLUDING OUTPATIENT ADVERSE EVENTS

Follow-Up Schedule for Laboratories and Clinic Visits

- Laboratory monitoring: serial monitoring (ie, weekly) with at least CBCs is advised after treatment with PHP, until normalization of blood counts.
- Clinic visits: clinic reassessment is advised prior to retreatment to assess tolerability, laboratory evaluation, and response to prior treatment to determine appropriateness of a repeat procedure (21).

Management of Hematologic Toxicity: Use of G-CSF

G-CSF is often prescribed immediately after discharge (within 24–72 hours of procedure) to prevent neutropenia (21,30). Long-acting growth factor such as pegfilgrastim is advised (16). Occasionally, patients will develop cytopenia (s) 10–14 days after the procedure, so weekly laboratory results should be obtained. If this occurs, additional growth factor should be given. Additionally, use of antibiotics and an infectious workup are recommended in the setting of neutropenic fevers (17). G-CSF is commonly administered as an outpatient, based on hematologic response and risk assessment for neutropenic complications (16).

EFFECTIVENESS MEASUREMENTS, INCLUDING FUTURE TREATMENTS

Evaluating the effectiveness of PHP requires repeated interval imaging and clinical assessments to measure response, guide future treatments, and adjust therapy based on individual outcomes.

Imaging and Tumor Response Assessment

- Follow-up imaging: follow-up imaging is usually conducted 1–2 months after the second, fourth, and sixth cycles.
- Response criteria: tumor response is evaluated using Response Evaluation Criteria in Solid Tumors 1.1 criteria, with special consideration for changes in tumor vascularity and size reduction in hepatic lesions.

Dosing and Scheduling for Future Treatments

- **Subsequent PHP procedures**: a pair of PHP sessions is spaced 6–8 weeks apart to allow for hepatic and bone marrow recovery. Two initial treatments are recommended prior to the first imaging assessment. Dosing reductions, delays to the time interval between treatment cycles, or discontinuation of treatment may be considered for future treatments based on toxicity profiles and delayed bone marrow recovery observed in the initial or subsequent PHP sessions. If a patient demonstrates disease control after 2 treatments with an acceptable toxicity profile, an additional 2 sessions is recommended. In some cases, response rates are dramatic with a greater than 90% reduction in tumor burden. Then, further treatments could be deferred until progression. If a patient shows progression after the initial 2 treatments, then further treatments are discouraged as the benefit is likely minimal.
- Subsequent therapies: both locoregional and systemic therapies can safely be used after PHP. Safety of concurrent combination therapy with immune checkpoint inhibitors is currently being studied (24).

DATA REVIEW INCLUDING QOL DATA

The clinical effectiveness and tolerability of PHP with melphalan in UM liver metastases have been investigated in several studies, focusing on OS, progression-free survival (PFS), and QOL (**Table**).

The FOCUS trial was initially a randomized controlled trial (13). Due to crossover from the best alternative care arm to the PHP arm, the trial was converted to a single-arm study. OS was 20.5 months, and PFS was 9 months with duration of response of 14 months. ORR was 36.3%, and disease control rate was 73.6%. Of all the patients, 37.4% completed 6 cycles of treatment. Objective response was typically observed after 2 treatments; however, over 40% of patients showed objective response after 3 or more treatments. Serious treatment-related adverse events were hematologic in nature, and 31.6% of patients had dose reduction or treatment discontinuation. A large retrospective cohort from Europe evaluated 250 PHPs in 81 patients. The study (16) demonstrated a disease control rate of 89% and an ORR of 60.5%, whereas PFS and OS were 8.4 and 14.9 months, respectively. Only 10% of patients discontinued treatment secondary to toxicity, whereas 6% of patients required dose reduction. Finally, patients who received 3 or more treatments had significantly improved median OS compared with historical controls.

QOL Considerations

Two recent studies (31,32) have evaluated QOL after PHP. In a prospective trial of 24 patients receiving PHP, global health status did not change from baseline to postprocedural Day 21 (31). However, physical functioning, role functioning, and fatigue scores remained worse at 21 days. A second retrospective study (32) in 20 patients undergoing PHP demonstrated that by Day 28, QOL scores

did not differ from baseline scores. Additionally, emotional well-being scores improved at 28 days.

AREAS OF FUTURE NEED/RESEARCH AND GAPS IN CURRENT UNDERSTANDING OF TREATMENT WORKFLOW

Although PHP has demonstrated substantial impact in managing UM liver metastases, ongoing research is necessary to optimize drug delivery, enhance effectiveness, and further minimize systemic toxicity.

Key Areas for Improvement and Research

- Optimizing drug extraction and minimizing systemic dose: advances in filtration technology may enhance drug extraction, reduce systemic exposure, and minimize hematologic toxicity. Additionally, monitoring of the pharmacokinetics might aid in optimizing or minimizing the duration of filtration and bypass.
- Dose optimization for liver and tumor targets: the current melphalan dosing regimen is based on a formula using the patient's gender and height. Research into dose escalation and the pharmacokinetics of melphalan within liver tissue could optimize therapeutic outcomes and reduce off-target effects. Additionally, targeting dose to disease volume in the liver may help optimize tumor response. This is analogous to personalized dosimetry for radioembolization and would allow for a more nuanced and precise individualized dosing, customized for the tumor distribution and volumes in the liver.
- Combination with systemic therapies: PHP could potentially be combined with systemic immunotherapies or targeted agents, which may enhance tumor control and systemic immunity against UM metastases (24). PHP can potentially serve as tool that enhances immunotherapy because it leads to a release of antigen from the tumor resulting in priming of the immune system. At the same time, melphalan is known to be a lymphotoxic drug, and therefore, it may potentially lead to depletion of the immune cells from the tumor environment and decrease the benefit from immunotherapy. Caution must be observed secondary to the possibility of additive bone marrow or hepatic toxicity from combination therapy, thus potentially interrupting or delaying treatment as has been seen with other liver-directed therapies combined with immune checkpoint blockade.
- Applicability to other cancer subtypes: several other metastatic malignancies to the liver could be considered in the future if survival benefit from trials is seen. Prospective randomized trials are in early development for metastatic breast and colorectal cancer are underway (NCT06875128 and NCT06607458).

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APPENDIX A. DESCRIPTION OF PHP DEVICE (HEPZATO KIT)

The PHP system consists of several key components (Fig 1):

- Infusion catheter (standard and off-the-shelf): a microcatheter placed in the target hepatic artery or branches to infuse melphalan directly into the liver's arterial supply.
- Double-balloon catheter: a specialized 16-F occlusion balloon catheter with an intervening fenestrated segment that is comprised a cephalad and caudal balloons (Fig 2a). When inflated, it occludes the inferior vena cava (IVC) superior and inferior to the hepatic veins (including the accessory hepatic vein but above the highest renal vein), isolating hepatic venous outflow from the systemic circulation. This catheter also includes lumens for contrast injection and a guide wire placement. The catheter is introduced through an 18-F venous sheath. There are 2 spacing options available between the cephalad and caudal balloons: (*a*) 62 mm (the most commonly used length) and (*b*) 50 mm. Length is based on presence of accessory hepatic veins and the spacing between the hepatic venous confluence and the superior most renal vein.
- Filtration system: an extracorporeal circuit that includes a pump and carbon-based filtration system to collect and filter blood from the hepatic veins (Fig 2b). The "GEN2" hemofiltration system that is clinically approved is comprised 2 hemofiltration cartridges in a single housing containing novel, proprietary, free-floating spherical filtration media. A preclinical swine study (1) showed a mean filter efficiency of 99.0% (SD ± 0.4). A clinical study (2) in 10 patients demonstrated an overall filter efficiency of 86% (range, 71%–95%).

Additional Off-the-Shelf Components

Some components of the PHP procedure, such as standard angiographic catheters, wires, microwires, and introducer sheaths, may be sourced as off-the-shelf products, compatible with the Hepzato Kit. The integration of these standardized tools facilitates the adoption of PHP in clinical centers with existing interventional radiology (IR) and perfusion capabilities.

INFRASTRUCTURE AND SUPPORT

Executing PHP with melphalan requires a dedicated multidisciplinary team and specialized infrastructure, including anesthesia, perfusion, IR specifically trained in PHP, and pharmacy support. A coordinated effort and cohesive approach (including situational awareness, decision-making, and teamwork) are required to safely and efficiently perform the procedure.

Anesthesia and Hemodynamic Support

Cardiovascular monitoring is essential, given the risk of hypotension, decreased central venous return and impaired cardiac output associated with balloon occlusion of the IVC, venovenous bypass, and use of carbon filtration of the venous return. High infusion rates of vasopressors are generally required during the perfusion period as a substantial amount of the sympathomimetics are cleared from the blood by the filters. It is recommended to balance increasing vasopressor dosage and large volumes of crystalloid fluid infusion. Body warmers such as "bair huggers" are used to minimize decrease in patient's body temperature, which occurs due to blood flowing through the nonheated extracorporeal circuit. Critical attention and timing of infusing vasoactive agents are essential during the procedure, especially during the high-risk moments (initiation of balloon occlusion, extracorporeal circulation, and closing the bypass circuit).

Perfusion Team

The extracorporeal filtration circuit requires a perfusion team to manage flow within the bypass system and ensure effective filtration of melphalan before returning blood to the systemic circulation.

Heparinization and activated clotting time (ACT) monitoring are always required. Goal ACT is above 450 seconds over the duration of venovenous bypass.

IR and Operator Requirements

The PHP procedure is performed by interventional radiologists skilled in catheter-based therapies, ideally in hepatic arterial therapy. Two operators—an interventional radiologist and a second assistant or cointerventionalist—are recommended to manage the access sites, confirm flow adequacy, inject vasodilators as necessary in between infusions, and handle any intraoperative adjustments to the intra-arterial catheters and the balloon catheter.

Pharmacy

Pharmacy support is essential for preparing melphalan, ensuring dosing accuracy, and facilitating timely drug delivery in adequate conduits for infusion to the IR suite. Melphalan must be reconstituted and administered within 60 minutes, requiring efficient coordination with the IR team.

TECHNIQUE DESCRIPTION

PHP with melphalan involves a sequential process to isolate, perfuse, and filter hepatic blood flow, ensuring concentrated drug delivery to the liver while limiting systemic exposure (Fig 1).

Prior to procedure, in patients with a high tumor burden approaching 50% replacement of the liver, starting allopurinol (300 mg/d) 3 days prior to the procedure is recommended to reduce potential risk of tumor lysis. A preoperative antinausea regimen should be prescribed, and patients also receive intravenous steroids (Solu-Medrol 125 mg).

After the induction of general anesthesia, a Foley catheter is needed due to the potential for high amount of intravascular fluid infusion and monitoring of urine output. An arterial line is needed for continuous arterial pressure monitoring.

Access Sites

- Triple-lumen catheter (7 F) is placed via the left internal jugular vein. This is needed for vasoactive agents, fluids, and sedation. Additionally, blood can be withdrawn during the procedure for laboratory testing, most often ACT. Blood can also be drawn via an arterial line.
- Arterial access is obtained via left (preferred) or right common femoral arteries with placement of a 5–6-F sheath. Radial artery access for intervention is not recommended. This access is used for hepatic arteriography and melphalan infusion. Sampling of blood from the sheath can be performed for intermittent laboratory testing and simultaneous hemodynamic monitoring.
- An 18-F sheath is placed via the right (preferred) or left common femoral vein. Once the patient is fully anticoagulated, the double-balloon catheter is inserted into the central IVC.
- A 10-F sheath is placed via the right internal jugular vein. This is used for the return from the venovenous bypass filtration circuit.

Diagnostic Arteriography

A complete diagnostic angiography is performed via the superior mesenteric and celiac arteries. This includes microcatheter selection of all lobar branches with dedicated angiography (Fig 3). Arterial cone-beam CT delineates arterial anatomy, identifies potential extrahepatic flow or extrahepatic tumoral supply, assesses tumor burden, and calculates liver volumes. Because melphalan infusion is a nonembolic low-viscosity solution, arterial reflux into extrahepatic branches (eg, gastroduodenal artery) will be unusual. However, extrahepatic arteries in the lobar treatment field should be considered for prophylactic embolization to minimize risk of gastrointestinal ulceration. This most commonly involves an accessory left gastric artery, a right gastric artery, a supraduodenal artery, or a sizable hepatic falciform artery. Because patients are heavily anticoagulated during the procedure, coils alone can be insufficient for complete occlusion, particularly if embolization is performed at the time of initial treatment. Liquid embolic agents or vascular plugs may be more effective.

Flow redirection via proximal embolization (eg, embolization of a replaced left hepatic artery for complete treatment from right hepatic artery) is not recommended unless risk of extrahepatic perfusion cannot be controlled. This relates to the lack of full reperfusion of the distal territory.

Balloon Catheter Placement and Initiation of Extracorporeal Circuit

- Balloon catheter positioning: the double-balloon catheter is positioned in the IVC, with the cranial balloon at the inferior vena cava–right atrium junction and the caudal balloon located inferior to the hepatic veins (including the accessory hepatic vein if present) (Fig 4).
- Initiating extracorporeal circulation: once the patient is effectively anticoagulated with the ACT of >450 seconds, venovenous bypass is initiated with the connection of both the femoral double-balloon catheter and internal jugular venous return sheaths. Once appropriate flow rates are confirmed and with direct communication with the anesthesia team, the balloons are then inflated with dilute contrast to isolate hepatic venous outflow starting with inflation of the cranial balloon. After pausing the bypass circuit, venography is performed with 20–40 mL of dilute contrast via the balloon catheter to ensure a proper seal at both locations and to confirm flow into at least 1 hepatic vein. Once isolation of the IVC is confirmed, continuous and stable traction should be maintained through the end of the washout period. Filtration starts once the reconstituted melphalan arrives from pharmacy, which prevents prolonged filtration time and decreased filter efficiency.
- Filtration: 2 filters are opened sequentially in the bypass circuit. Open and continuous closed-loop communication is mandatory between IR, anesthesia, and perfusion teams during this time as this represents the most critical period for hemodynamic lability. Once both filters are fully open and hemodynamic stability is restored, the bypass line is clamped to ensure all blood flow is directed through the filters.

Drug Infusion and Management

Melphalan Infusion. Melphalan is infused through the microcatheter placed in the hepatic artery, delivering the chemotherapeutic agent directly to the liver. It takes 15–30 minutes to prepare by the pharmacy, and the drug "expires" (degrades) 60 minutes after preparation. Therefore, timing should be coordinated to minimize delay of drug delivery and subsequent infusion but also to minimize the duration of anesthesia as well as the venous blood filtration.

The total melphalan dose is based on the patient's ideal body weight, 3 mg/kg for a maximum dose of 220 mg. The calculation of weight per the package insert is calculated based on the patient's height, with adjustments for male versus female. The total volume of drug can then be given in a lobar fashion based on relative liver volumes. Adjustments are made based on variant hepatic vascular anatomy or hepatic angiosomes as well as tumor burden. Tumor burden, however, is currently not factored into dose distribution by instructions for use (IFU). Dose reduction to 2 mg/kg in subsequent treatments can be considered if cytopenia was a significant issue.

Infusion of the most difficult arterial selection should be performed first. This minimizes the time spent switching catheter locations after each infusion. Hepatic angiography is performed before each infusion to ensure adequate antegrade flow and absence of vasospasm. Intra-arterial nitroglycerin will improve vasospasm to prevent reflux of melphalan.

Washout and Closure of Access

Washout Phase. After the melphalan infusion, the extracorporeal circuit continues to filter hepatic venous blood for 30 minutes to reduce systemic drug levels.

Closure. After the completion of blood filtration, the caudal balloon followed by the cephalad balloon is deflated. Then, the circuit is clamped, and the bypass pump is stopped. The catheters are removed, and access sites can be closed. Intravenous protamine (total heparin dose divided by 200) and platelet transfusion will reverse the effects of heparin and filtration to allow for access site management in the IR suite. An arterial closure device can be used for the femoral arterial access. The femoral venous sheath can be removed with either manual hemostasis or 2 suture-mediated closure devices (Perclose; Abbott, Abbott Park, Illinois). These are placed at the time of initial access and can eliminate the need for manual compression of an 18-F venotomy. The jugular venous catheters can be removed with manual hemostasis. A purse string suture can be applied at the time of removal, which should be removed prior to the patient's discharge. Meticulous management of access site closure will minimize hemorrhagic complications and can potentially allow triage of patients to a step-down unit, for example, instead of an intensive care unit.

Struck et al (3) demonstrated that excessive use of perioperative fluids and lack of use of protamine correlated to bleeding complications perioperatively. Importantly, there were also no thromboembolic complications from protamine use. As a result, use of protamine for heparin reversal is recommended.

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