Abstract

Purpose: Chemosaturation with percutaneous hepatic perfusion (PHP; Hepatic CHEMOSAT® Delivery System; Delcath Systems Inc, USA) is a minimally invasive, repeatable regional therapy for unresectable hepatic metastases. It uses a system of catheters and filters to isolate hepatic venous blood from the systemic circulation, allowing delivery of high-dose chemotherapy to the hepatic artery. Effluent hepatic venous blood is filtered before being returned to the systemic circulation, thereby reducing exposure to chemotherapy. We describe our experiences with chemosaturation-PHP at 2 European centers.

Materials and Methods: 14 patients presented unresectable hepatic metastases from solid tumors; 13 received 1–3 sessions of chemosaturation-PHP. Melphalan 2.0 (n = 1) or 3.0 (n = 12) mg/kg was given as a 30-minute infusion into the hepatic artery. One complete (cholangiocarcinoma, n = 1) and 6 partial responses (ocular, n = 3 or cutaneous melanoma, n = 3) were observed, 5 patients had stable disease (ocular melanoma, n = 3; breast cancer, n = 1; gastric cancer, n = 1). Mild to moderate filter-related toxicity (i.e. thrombocytopenia, anemia) was observed immediately post-procedure. Grade 3/4 melphalan-related pancytopenia developed after 1–2 weeks. All hematological events were managed effectively with transfusions and/or other supportive measures. The new high-efficiency filter showed milder toxicity and faster recovery. In one case, chemosaturation-PHP was abandoned prematurely due to heparin-induced vaginal bleeding, and one patient died due to retroperitoneal hemorrhage from heparin anti-coagulation.

Conclusion: Chemosaturation-PHP for non-resectable liver metastases is a feasible treatment option when performed by an experienced mul-

Zusammenfassung


Material und Methoden: 14 Patienten zeigten nicht resezierbare hepatische Metastasen solider Tumoren; 13 Patienten wurden in 1–3 Therapiesitzungen mittels Chemosaturation-PHP behandelt. Melphalan 2,0 (n = 1) und 3,0 (n = 12) mg/kg wurde 30 Minuten in die hepatischen Arterien infundiert. 14 Patienten zeigten nicht resezierbare hepatische Metastasen solider Tumoren; 13 Patienten wurden in 1–3 Therapiesitzungen mittels Chemosaturation-PHP behandelt. Melphalan 2,0 (n = 1) und 3,0 (n = 12) mg/kg wurde 30 Minuten in die hepatischen Arterien infundiert. Für das Tumoransprechen waren 12 Patienten auswertbar.

Ergebnisse: Komplette Remission wurde in einem Patienten beobachtet (Cholangiokarzinom, n = 1), partielle Remission in 6 Patienten (Aderhautmelanom, n = 3; malignes Melanom, n = 3), 5 Patienten zeigten stable disease (Aderhautmelanom, n = 3; Brustkrebs, n = 1; Magenkarzinom, n = 1). Milde bis mäßige filterassozierte Nebenwirkungen (z. B. Thrombozytopenie, Anämie) wurden unmittelbar nach der Behandlung beobachtet. Grad 3/4 Melphalan-assoziierte Pancytopenien entwickelten sich nach 1–2 Wochen. Alle hämatologischen Ereignisse wurden effektiv mit Transfusionen und/oder anderen unterstützenden Maßnahmen behandelt. Mit dem neuen, hocheffizienten Filtersystem gab es geringere Nebenwirkungen und eine beschleunigte Erholung. In einem Fall musste das Verfahren aufgrund von einer heparininduzierten
The liver has a unique dual blood supply which makes regional treatment possible. Whereas normal hepatocytes receive their blood primarily from the portal vein, liver tumors are supplied almost exclusively (up to 95 %) by the hepatic artery [1]. This allows isolation of the hepatic arterial inflow and venous outflow, and selective delivery of cytotoxic drugs to unresectable liver metastases while sparing healthy liver tissue. Regional chemotherapy procedures include hepatic arterial infusion, percutaneous hepatic perfusion, transarterial (chemo)embolization (TACE) and selective internal radiation therapy [2].

Introduction

The liver has a unique dual blood supply which makes regional treatment possible. Whereas normal hepatocytes receive their blood primarily from the portal vein, liver tumors are supplied almost exclusively (up to 95 %) by the hepatic artery [1]. This allows isolation of the hepatic arterial inflow and venous outflow, and selective delivery of cytotoxic drugs to unresectable liver metastases while sparing healthy liver tissue. Regional chemotherapy procedures include hepatic arterial infusion, percutaneous hepatic perfusion, transarterial (chemo)embolization (TACE) and selective internal radiation therapy [2].

Patients and Methods

Patients

Between January 2012 and February 2013, 14 consecutive patients with unresectable hepatic metastases from various solid tumors underwent chemosaturation-PHP with melphalan at the Frankfurt University Hospital (n = 7) and the European Institute of Oncology in Milan (n = 7). Both centers adhered to the Hepatic CHEMOSAT® Delivery System product instructions with regard to contraindications and precautions. Data evaluation was performed retrospectively.

Pre-procedural assessments

Prior to treatment, a physical examination, laboratory tests, and comprehensive imaging including computed tomography (CT) of the thorax and abdomen, upper abdominal magnetic resonance imaging (MRI) and, if clinically indicated, a brain MRI, bone scintigraphy or positron emission tomography (PET) scan were performed. The day before (Frankfurt) or the same day (Milan) of treatment, a complete visceral angiogram was performed to identify potential variant vascular anatomy. Embolization of selected arterial branches supplying the gastrointestinal tract was performed as needed to avoid inadvertent administration of chemotherapy into gastrointestinal or visceral arterial branches.

Treatment

Patients received melphalan delivered using the Hepatic CHEMOSAT® Delivery System (Fig. 1). The procedure was performed under general anesthesia in an interventional radiology suite. Melphalan was given at a dose of 3.0 mg/kg ideal body weight (maximum 220 mg/treatment) as a 30-minute infusion into the hepatic artery. Venous effluent blood was filtered via the extracorporeal hemofiltration circuit during and for 30 minutes after each infusion. Percutaneous venous access was performed under ultrasound guidance in order to reduce the number of puncture attempts and any possible cause of bleeding. Heparin (400 IU/kg body weight) was administered during the procedure to ensure free extracorporeal flow and filtration.
Response and toxicity

CT, MRI and/or PET scans of the liver were performed at 4- to 8-week intervals. Tumor response of liver lesions was assessed using RECIST criteria [25]. Systemic and local adverse events were classified by the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. Only systemic events (which did not normalize within 24 hours) and elevations of hepatic transaminases (which did not normalize within 7 days) were reported.

Results

Patients

Patient demographics and tumor characteristics are shown in Table 1. Patients had ocular (n = 8) or cutaneous melanoma (n = 3), breast cancer (n = 1), gastric cancer (n = 1) and cholangiocarcinoma (n = 1). All patients, except for 1, had metastases confined to the liver. All patients had disease progression despite receiving a range of other treatments for hepatic metastases.

Chemosaturation-PHP

13 patients received treatment; melphalan was not administered in 1 patient because of vaginal bleeding. Patients treated in Frankfurt received a single chemosaturation-PHP treatment, and patients treated in Milan received 1 – 3 treatments. A total of 18 (Frankfurt, n = 6; Milan n = 12) chemosaturation-PHP procedures were performed. The interval between repeat treatments ranged from 57 – 177 days. The recommended melphalan dose of 3 mg/kg was given in all patients but one who received a 2 mg/kg dose because of aberrant hepatic vascularization.

The first-generation filter only was used in 3 patients (Frankfurt, n = 2; Milan n = 1), the second-generation filter only was used in 7 patients (Frankfurt, n = 4, Milan, n = 3), and 3 patients (Milan, n = 3) were treated using the first-generation filter for their first treatment and the second-generation filter for repeat treatment(s).

Table 1 Baseline characteristics.

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Fig. 1 Schematic diagram of the chemosaturation-PHP delivery system (Hepatic CHEMOSAT® Delivery System; Delcath Systems Inc., New York, NY) which consists of a closed circuit of catheters and filters designed to deliver chemotherapy to the hepatic artery and then filter effluent hepatic venous blood before it is returned to the systemic circulation.

Abb. 1 Schematische Darstellung des Chemosaturation-PHP Zuführsystems (Hepatic CHEMOSAT Hepatic CHEMOSAT® Delivery System; Delcath Systems Inc., New York, NY) bestehend aus einem geschlossenen Kreislauf aus Kathetern und Filtern, welches der Infusion der Chemotherapie in die Leberarterie dient sowie das hepatisch venöse Blut filtert, bevor es in den systemischen Kreislauf zurückgeführt wird.

Procedural care

Frankfurt experience

Preprocedural embolization was necessary in 6 patients because gastroduodenal artery (GDA) branches were close to the proper hepatic artery. In one patient with metastases in both liver lobes, chemotherapy was injected into the right hepatic artery rather than the proper hepatic artery to avoid unwanted infusion of...
the gastrointestinal vessels. One patient developed hepatic arterial spasm during the angiogram which was treated successfully with intra-arterial glyceryl trinitrate 0.6 mg. On inflation of the occlusion balloons and establishment of the hemofiltration circulation, transient hypotension was seen in all patients. The median total procedure time was 225 (range, 145–270) minutes. The average venovenous bypass time was 74 (range, 68–81) minutes which included positioning and inflation of the occlusion balloons, the melphalan infusion and washout period.

**Milan experience**

Preprocedural embolization was performed in 6 patients. GDA coiling was necessary in 2 patients because the proper hepatic artery was very short. Right gastric artery embolization was also necessary in 1 of these patients. 3 patients underwent embolization of the right phrenic arteries. In all patients but one, superselective drug injection was achieved by separately cannulating the left and right arteries. One of the patients in whom the hepatic infusion system had previously been implanted was treated separately through the left and right hepatic arteries because of the presence of new tiny vessels from a previously coiled GDA, feeding the duodenum and pancreas.

**Hospitalization**

**Frankfurt experience**

After chemosaturation-PHP, patients were kept in the intensive care unit (ICU) or recovery room and transferred to the ward within a maximum of 24 hours when no complications occurred. Patients remained in the hospital for 4–8 days.

**Milan experience**

After treatment, all patients were admitted to the ICU for an average of 12 hours, except for one patient who died in the ICU 30 hours post-treatment. There was no difference between the first- and second-generation filters in terms of hospital stay (average 5.5 days).

**Tumor response**

1 complete response (Milan, n = 1) and 6 partial responses (Frankfurt, n = 2; Milan, n = 4) according to RECIST criteria were observed. Stable disease was documented in a further 5 patients (Frankfurt, n = 4; Milan, n = 1). 2 patients were not evaluable for tumor response (procedure abandoned because of vaginal bleeding, Frankfurt, n = 1; patient died shortly after treatment, Milan, n = 1).

**Frankfurt experience**

One patient with cutaneous melanoma and multiple liver metastases (diameter ≤ 20 mm) had a tumor response (tumor volume decrease 95%) after one chemosaturation-PHP treatment (Fig. 2). The residual tumor was treated successfully with vemurafenib plus laser-induced thermotherapy (LITT). On the MRI scan 3 months after chemosaturation-PHP, no more perfused tumor was visible. The patient remained tumor-free for 10 months; disease recurrence (> 50 hepatic lesions) was documented 13 months after treatment. Another patient with multiple liver metastases from ocular melanoma had a partial response (Fig. 3). Stable disease (tumor volume decrease < 5%) was observed in a patient with hepatic and bone metastases from breast cancer. Two months after chemosaturation-PHP, the follow-up MRI scan

![Fig. 2](image_url)  
*Fig. 2* Magnetic resonance images (T2 haste) of a patient with diffuse liver metastases from malignant melanoma *a, b* and the corresponding images taken 4 weeks after chemosaturation-PHP *c, d* with significant reduction in the size of the metastases (partial response). After two treatments with laser-induced thermotherapy, full hepatic remission, which lasted for 10 months, occurred. Regional disease recurrence (> 50 single lesions) was documented 13 months after treatment *e, f.*

![Abb. 2](image_url)  
*Abb. 2* MRT-Bilder (T2 haste) eines Patienten mit diffusen Lebermetastasen eines malignen Melanoms *a, b* und die entsprechenden Bilder 4 Wochen nach der Chemosaturation-PHP *c, d* mit deutlicher Größenreduktion der Metastasen (partielle Remission). Nach zweimaliger Behandlung des Restbefundes mittels laserinduzierter Thermotherapie zeigte sich eine hepatische Vollremission, welche für 10 Monate anhielt. Dann entwickelte der Patient 13 Monate nach der Behandlung ein regionales Rezidiv mit mehr als 50 Einzelläsionen *e, f.*
showed disease progression in the liver. Ten months after treatment, the patient died from progression of liver metastases. The remaining 3 patients with stable disease had ocular melanoma. Two months after chemosaturation-PHP, stable disease was maintained in 1 patient. Without any further therapy, the follow-up 6 months post-treatment imaging showed a partial response which is still ongoing 2 months later (Fig. 4). In another patient with bilobar disease, melphalan was infused only into the right hepatic artery, and complete hepatic perfusion was not achieved. Tumor response was evaluated only in the perfused right hepatic lobe (Fig. 5). The first follow-up after treatment showed stable disease in the right liver lobe and disease progres-
sion in the untreated left lobe. The left lobe was subsequently treated with TACE. However, disease progression in both liver lobes was documented after 2 months and the patient died shortly afterwards. In the other patient with metastatic ocular melanoma, the left and right hepatic arteries were cannulated separately and the right liver lobe was perfused with 2/3 of the melphalan dose and the left one with the remaining 1/3. One month after chemosaturation-PHP, stable disease was seen in the right liver lobe, whereas disease progression occurred in the left lobe. A follow-up scan 2 months post-treatment showed progressive disease in the whole liver. The patient died 6 months after treatment from massive progression of liver metastases.

**Milan experience**

Of the 6 patients evaluable for response, 1 patient with biliary tract adenocarcinoma achieved complete remission 6 months after chemosaturation-PHP. 2 patients with ocular melanoma had partial responses (MRI and PET) after the first of 3 sessions of chemosaturation-PHP. One of these patients remained stable with minimal disease after 2 further sessions (MRI/PET-negative but some small nodules visible). The other patient showed disease progression in the liver and bones after the third procedure, 1 year after the first session. One patient with cutaneous melanoma showed a partial response (MRI and PET) after the first chemosaturation-PHP session. The patient then received 4 courses of ipilimumab and recently had a second chemosaturation-PHP session. One patient with gastric cancer had a mixed response due to parasitic hepatic arteries that were not included during chemoperfusion. He had 3 consecutive liver resections before chemoperfusion. A huge portion of liver parenchyma, close to the previous resections, was fed by several arteries from the intercostal and mammary arteries. Lesions located within the non-perfused hepatic parenchyma grew after treatment, while metastases within the chemoperfused parenchyma showed a partial response. Because it was not possible to manage this kind of hepatic vascular supply, a second chemosaturation-PHP session was not scheduled. One patient with cutaneous melanoma had a mixed response after the first perfusion, due to the growth of some lesions deep within segment 7, located under the dome. A phrenic artery feeding that area was occluded immediately before the second session and a partial response was documented in all target liver lesions (tumor volume reduction > 40%). Unfortunately, this patient subsequently developed multiple lung metastases.

**Toxicity**

**Frankfurt experience**

In the 2 patients treated with the first-generation filter, both developed grade 1/2 increases in liver transaminases in the first 2 days after chemosaturation-PHP; all values returned to baseline levels within 1 week. Grade 1/2 fatigue, nausea and fever within the first 5 days after treatment were also reported. In both patients, grade 1/2 bone marrow suppression was observed initially. However, nadir blood cell counts were reached after 11–12 days and both patients were hospitalized for 8–9 days because of grade 3/4 pancytopenia. Grade 3/4 leukocytopenia was treated with filgrastim for 8–9 days in both patients, and antibiotics were required in 1 patient. Platelet transfusions were required for grade 3/4 thrombocytopenia (n = 2), and 2 units of packed red blood cells (RBC) were required for grade 3 anemia (n = 1). Of the 4 patients treated with the new filter system, 1 patient developed grade 1/2 pancytopenia after treatment which worsened to grade 3/4 pancytopenia after 1 week necessitating hospitalization for 6 days. However, only the leukocytopenia required treatment (filgrastim for 3 days plus an antibiotic). The second patient received a lower dose of melphalan and, with the exception of grade 1 anemia, did not experience any systemic adverse events. The last 2 patients both developed grade 1 anemia, grade 3/4 leukocytopenia and grade 2 or 4 thrombocytopenia and were treated as outpatients with platelet concentrates. Granulocyte colony-stimulating factor (G-CSF) was given for 4 days. No significant increases in transaminases occurred. A premenopausal patient developed vaginal bleeding after systemic heparinization. Treatment was stopped before melphalan
administration. A gynecological examination showed that the event was most likely caused by heparin-induced bleeding of the endometrium. The patient recovered without sequelae.

**Milan experience**

Four patients were treated with the first-generation filter and all of them required multiple platelet and/or RBC transfusions after the procedure. One patient had grade 4 leukocytopenia, grade 3 anemia and grade 4 thrombocytopenia; the patient developed febrile neutropenia was admitted to the hospital to receive intravenous antibiotics and other support therapies. Three patients developed grade 4 leukocytopenia, grade 2/3 anemia and grade 1 or 4 thrombocytopenia which required transfusions without hospitalization. All of these patients had grade 2/3 fatigue and received filgrastim for at least 10 days. 3 of these 4 patients underwent 1–2 more sessions of chemoperfusion with the second-generation filter. These procedures were associated with markedly reduced hematological toxicity (grade 1 anemia) without any need for blood or platelet transfusions; G-CSF was required for 4 days only. All 3 patients experienced milder fatigue (grade 1). Of the 3 patients treated with the second-generation filter only, a similar toxicity profile was evident in 1 patient, while another patient developed febrile pancytopenia requiring transfusions because of a hepatic vascular shunt that avoided drug filtering. No patient had significant liver dysfunction, and grade 1–2 liver toxicity related to drug exposure was not influenced by the type of filter used. The remaining patient, who had a large fast-growing liver metastasis from ocular melanoma, died of a retroperitoneal giant hematoma 30 hours after chemosaturation-PHP. A *post-mortem* necropsy revealed multisite vascular bleeding with no damage to the inner surface of the abdominal veins and arteries. This unusual complication was most likely related to heparin which was needed for extracorporeal circulation.

**Discussion**

Chemosaturation-PHP is a minimally invasive, repeatable technique which delivers high doses of chemotherapy directly to tumors in the liver while limiting systemic toxicity through hemofiltration of the hepatic venous blood. Recently completed clinical trials performed in the US confirm the efficacy of chemosaturation-PHP delivery of melphalan in the treatment of patients with hepatic metastases from melanoma [10, 11] and neuroendocrine tumors [12, 13].

Our experience with chemosaturation-PHP at the University Hospital Frankfurt and the European Institute of Oncology is supportive of the findings of the clinical trial program, although it is too early to make definitive statements about tumor response rates and patient survival. Still, the data offer a number of insights. A complete response was documented in 1 patient, who had a large fast-growing liver metastasis from ocular melanoma, died of a retroperitoneal giant hematoma 30 hours after chemosaturation-PHP. A *post-mortem* necropsy revealed multisite vascular bleeding with no damage to the inner surface of the abdominal veins and arteries. This unusual complication was most likely related to heparin which was needed for extracorporeal circulation.

In April 2012, a second-generation high-efficiency filter (98 % bench-testing efficiency; Delcath Systems Inc., data on file) for use with the chemosaturation-PHP delivery system became commercially available in Europe. In Milan, three patients were treated initially with the first-generation filter and then switched to the new filter for repeated treatments, providing a unique opportunity to compare toxicities with the two systems. In these patients, toxicity with the new filter system was less severe and patients required fewer supportive measures (i.e., no transfusions, shorter courses of colony-stimulating factors, reduced fatigue). Further studies are required to confirm this positive trend. A phase III study to evaluate chemosaturation-PHP in the treatment of hepatocellular carcinoma is planned in Frankfurt, and the new filter system will also be investigated further. In summary, chemosaturation-PHP for the treatment of non-resectable liver metastases is a feasible treatment option when performed by an experienced multi-disciplinary team. Hematological events, which are the predominant toxicities associated with chemosaturation-PHP, are predictable and manageable with appropriate supportive care. Based on our findings, we believe that chemosaturation-PHP is a promising technique for patients for whom there are no effective treatments.
Affiliations
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