Review

Percutaneous hepatic perfusion with melphalan for unresectable liver metastasis

Humair S. Quadri[1], Eden C. Payabyab[1], David J. Chen[1], William Figg[2], Marybeth S. Hughes[1]

[1]Thoracic and Gastrointestinal Oncology Branch, National Cancer Institute, Bethesda, MD 20892, USA.
[2]Genitourinary Malignancies Branch, National Cancer Institute, Bethesda, MD 20892, USA.

Humair S. Quadri, M.D., is a general surgery resident at Georgetown University Hospital in Washington, D.C. who completed a two year surgical oncology fellowship at the National Cancer Institute of the National Institutes of Health in Bethesda, Maryland. He received his M.D. from Georgetown University School of Medicine in Washington, D.C.

ABSTRACT

Percutaneous hepatic perfusion (PHP) is an investigative technique for treating patients with diffuse unresectable metastatic liver disease. The technique has been clinically evaluated and shows great treatment potential for regional therapy to the liver. The advantage of PHP lies in its minimally invasive approach and ability to be repeated when compared to isolated hepatic perfusion. In a literature search, 135 publications were screened and 16 of these publications, including clinical trials and reviews, contributed to this review of PHP with melphalan. Melphalan is an alkylating agent that, when used as the chemotherapeutic agent in PHP, has shown potential for significant control of tumor burden in the liver, especially in metastatic ocular melanoma. In the current landscape of liver directed therapy, PHP is a viable option for those with unresectable metastatic disease to the liver. This article will focus on the technical aspects of PHP and describe the current data available from clinical trials, including outcomes of patients treated with this minimally invasive approach.

Key words: Percutaneous hepatic perfusion; melphalan; unresectable liver metastasis; metastatic melanoma to the liver; ocular melanoma

Corresponding Author:
Dr. Marybeth S. Hughes, Thoracic and Gastrointestinal Oncology Branch, National Cancer Institute, Room 4-5940, Building 10 - Hatfield CRC, Bethesda, MD 20892, USA. E-mail: hughesm@mail.nih.gov

Received: *24-06-2016*; **Accepted:** *28-06-2016*

INTRODUCTION

What is percutaneous hepatic perfusion

The treatment of metastatic disease to the liver is an evolving paradigm that has been evaluated with increasing potential over the past few decades. Though there are treatment options for solitary or localized liver lesions, there is no treatment consensus when multiple metastatic lesions are found throughout the liver.[1] It is estimated that approximately 80% of people with liver metastasis are considered unresectable due to excessive tumor burden, tumor location, effect on inflow or outflow, an insufficient liver remnant, or a significant comorbidity.[2] Most patients with liver-only unresectable metastatic disease have options of directed treatment. Percutaneous hepatic perfusion (PHP) is one of these novel techniques for patients with diffuse liver-only metastatic disease.

PHP is a minimally invasive procedure which allows for regional therapy to the liver. Arterial cannulation of the

Access this article online	
Website: http://www.hrjournal.net/	Quick Response Code
DOI: 10.20517/2394-5079.2016.24	

How to cite this article: Quadri HS, Payabyab EC, Chen DJ, Figg W, Hughes MS. Percutaneous hepatic perfusion with melphalan for unresectable liver metastasis. Hepatoma Res 2016;2:197-202.

hepatic artery via a femoral artery puncture is used to selectively administer an anti-neoplastic agent directly to liver tumors. By endovascular venous cannulation, a unique double balloon catheter (Delcath catheter) is inserted into the inferior vena cava (IVC) to capture the hepatic venous outflow from the liver. Using veno-venous bypass, the chemotherapy laden blood can be captured at the hepatic vein confluence and filtered before returning to the systemic circulation by a central venous line. This novel treatment technique has evolved from original operative liver isolation techniques, which capitalized on the hepatic anatomy for inflow and surgical outflow control in liver directed perfusion.[3]

History and development

The first use of hepatic perfusion was reported by Dr. Robert Ausman in 1961 as a surgery resident at the Roswell Park Cancer Institute where he developed the technique. His initial studies were performed on animal models, and once the technique was standardized it was tested on 5 patients with different types of hepatic malignancies. Though there was no long term follow-up and significant toxicity noted with the procedure, there was a therapeutic effect described in 2 patients.[3] This initial study helped lay the foundation for isolated hepatic perfusion (IHP) which has been refined over 60 years. Multiple centers have evaluated IHP with various chemotherapy agents, various tumor histologies, hyperthermic perfusion, and improved techniques.[4]

With data from isolated limb perfusion by Lienard *et al*.[5] in 1992, melphalan was initially tested in combination with tumor necrosis factor alpha (TNFα). This regimen was used for IHP to treat liver disease. Early results at the National Cancer Institute showed a 75% radiographic response rate with this combination and no diminishment of antitumor activity with advanced disease burden in the liver.[3] However, due to the unavailability of TNFα for continued clinical testing in the United States, melphalan has been the most widely used chemotherapeutic agent in current trials. Through these early studies of the operative technique for IHP, key elements and principles were noted and carried over to the minimally invasive PHP technique in use today.

PHP was initially reported approximately 20 years ago by 2 centers. The largest study described by Ravikumar *et al*.[6] involved 28 patients who were treated with escalating doses of doxorubicin or 5-fluorouracil. Through the catheter based approach, the chemotherapy was administered via a hepatic artery catheter and collected and filtered using veno-venous bypass from the venous outflow of the liver. Concurrently, a phase I study by Curley *et al*.[7] was being performed in patients with hepatocellular carcinoma. Similar to the early use of IHP, no long term follow-up data was published and these studies were not continued at these centers. However, these studies described the potential use of this procedure and contributed to the refinement of its technical feasibility.

In 2005, the comprehensive evaluation of PHP was conducted as a phase I trial at the National Cancer Institute where 28 patients were treated with melphalan PHP, for 74 treatments in a dose escalation format. The overall radiographic response rate was observed to be 30% (RECIST criteria), with rates as high as 50% in 10 patients with metastatic ocular melanoma. Though transient hepatic toxicity and some hematologic toxicity were observed, this study helped determine the maximum tolerated dose of melphalan (3.0 mg/kg) and established the groundwork for a multicenter trial.[8] After

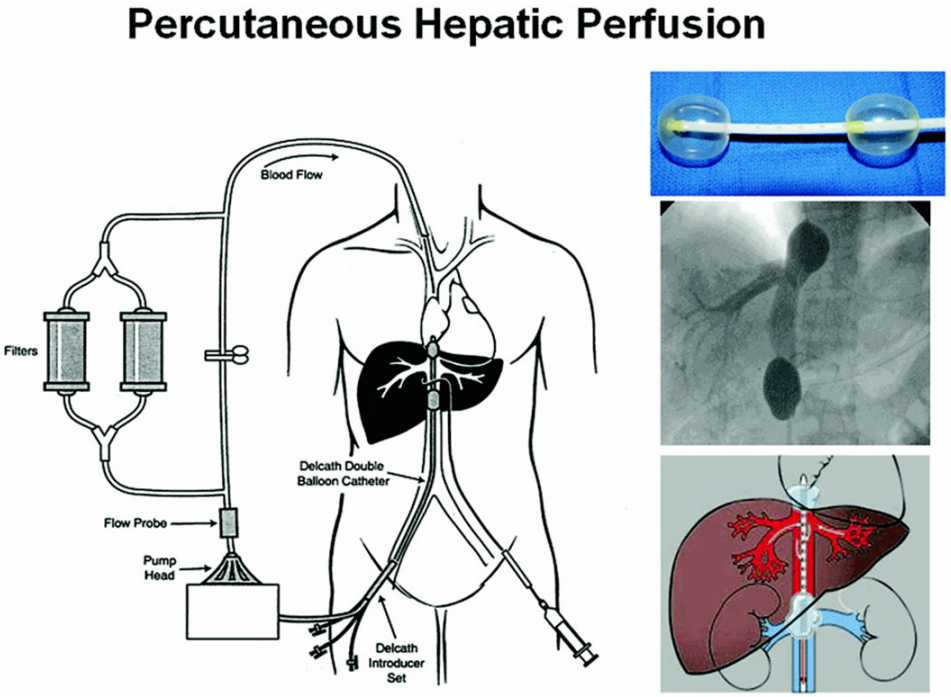

Figure 1: Diagram of the percutaneous hepatic perfusion system. This Delcath® Catheter System is used to infuse melphalan into the hepatic artery percutaneously (syringe) via the femoral artery. A double balloon catheter (shown in the upper right) is placed in the retro-hepatic inferior vena cava under fluoroscopic guidance (middle right image) to isolate the hepatic venous outflow. The multiple fenestrations along the balloon catheter then draw out the isolated blood which then is directed into the extracorporeal system. The blood is then pumped thorough a pair of activated charcoal filters, which extract the melphalan, before being returned to the systemic circulation. (This image has been reproduced with permission and purchase from *The Cancer Journal*)

publication of this phase I data, a multi-institutional phase III random assignment control trial was started in 2005, where PHP with melphalan was compared with the current best available care (systemic chemotherapy, embolization, supportive care) in patients with metastatic melanoma with the majority of tumor contained in the liver.[3] This trial was completed in 2010 and the results have recently been published, with analysis showing an increase in hepatic progression-free survival in the melphalan PHP arm compared to the best available care.[9] Currently, there are numerous centers throughout the world evaluating PHP and improving the technical aspects and treatment outcomes.

Evaluation

We evaluated data using previous publications on methods of liver perfusion, ranging from reviews to clinical trials. An initial PubMed search with the keyword "percutaneous hepatic perfusion" was performed yielding 135 publications. Publications were excluded if they were not in English, had no mention of liver metastasis or liver tumors, or were not available online or through an easily accessible source. We then screened 25 publications relating to PHP using the addition of the keyword "melphalan". This search yielded 17 publications, only those that linked or contained primary data relating to PHP or IHP were selected, and ultimately 16 publications contributed to this review.

TECHNICAL ASPECTS

Procedure

As mentioned previously, PHP is a technique where a chemotherapeutic or biologic agent is delivered via catheterization of the hepatic artery. The hepatic venous circulation is isolated via a special patented double balloon catheter directed via venous cannulation and fluoroscopically guided placement in the IVC (Delcath Catheter Systems, Delcath Inc., New York, NY). This allows for capture of the chemotherapy-laden effluent from the liver, which is filtered via veno-venous bypass prior to returning to the systemic circulation.[3,8] PHP takes advantage of the tumor blood supply in which 90% of the tumor is supplied by hepatic artery inflow. In contrast, normal hepatocytes receive over 50% of their blood flow from the portal venous inflow. By isolating the hepatic arteries, infusion of chemotherapeutic agents are able to take the most direct circulatory pathway to liver tumors while somewhat sparing normal hepatocytes. It is critical to ensure that flow is isolated to the liver to avoid inadvertent chemoperfusion of non-target organs. Once the agent has completed its hepatic circulation, it is collected via fenestrations situated between patented double balloons of the catheter, from the hepatic veins as it enters the IVC. This catheter is initially placed and tested under fluoroscopy in the retrohepatic IVC so that the balloons are carefully seated cephalad and caudad to the hepatic veins. The blood is then directed through an extracorporeal filtration system (containing activated charcoal filter cartridges) which removes the agent prior to return to the systemic circulation via an internal jugular venous catheter [Figure 1].

The procedure is usually performed using general anesthesia with arterial line access placed for blood pressure monitoring, as well as internal jugular venous access for infusion from the veno-venous bypass circuit. The extracorporeal pump is primed with normal saline, and during the procedure, heparin is administered to maintain an activated clotting time at therapeutic levels. Percutaneous access of the right common

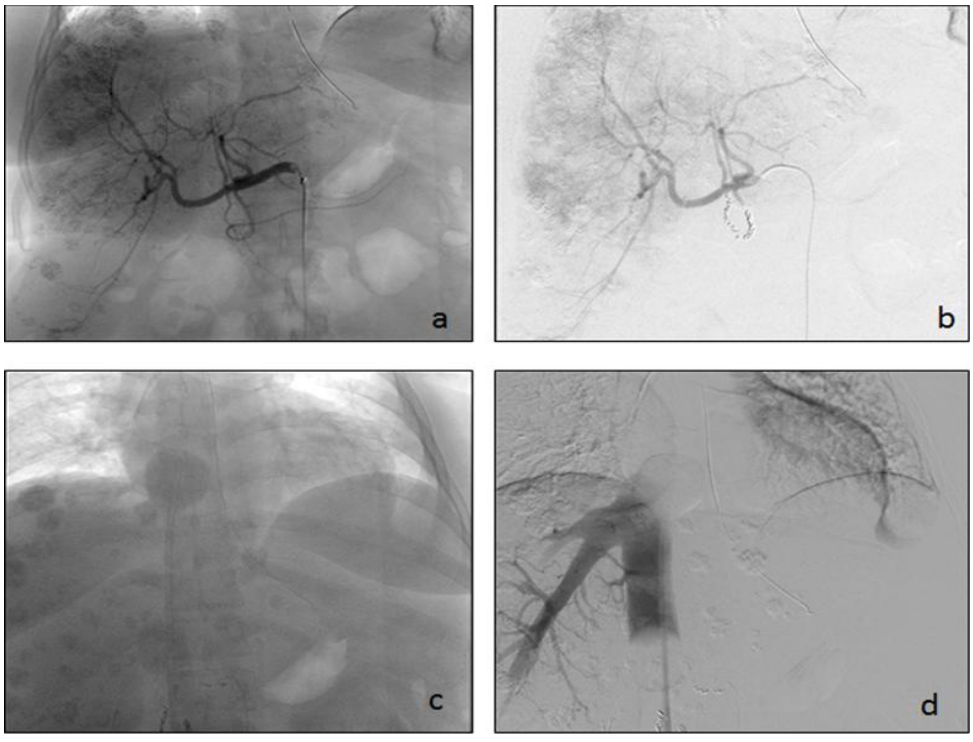

Figure 2: A 51-year-old female with a history of pancreatic neuroendocrine tumor and metastatic disease to the liver. (a) Common hepatic artery cannulated and filled with contrast defining the vascular anatomy of the liver. Visible are the numerous metastatic lesions which are contrast enhancing; (b) gastroduodenal artery coiled after contrast evaluation; (c and d) intra-procedural images of hepatic venous system isolation