Isolated Hepatic Perfusion with Melphalan for Primary or Metastatic Unresectable Cancers of the Liver: Safety and Feasibility in A U.S. Academic Medical Center

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Abstract

Background: Although isolated hepatic perfusion (IHP) has been under clinical evaluation for over 50 years, it has not gained wide application due to both the complexity and the insufficient efficacy of the procedure. This study evaluated the feasibility and safety of this procedure at Massachusetts General Hospital.

Methods: Five patients with unresectable primary or metastatic cancer of the liver were included in this study. All patients received 60 minutes IHP with melphalan at 1.5 mg/kg based upon ideal body weight.

Results: The median operation time was 6 hours and 37 minutes, with the median blood loss of 2 liters. The median hospital stay was 9 days. Two patients experienced grade 4 liver toxicity. One postoperative death was due to multiple organ system failure. One patient experienced disease progression at one month after surgery, two patients had stable disease (5 months) and one patient achieved partial response (8 months).

Conclusion: IHP with melphalan for primary or metastatic unresectable cancers of the liver can be safely performed at an academic medical center outside of NCI surgical branch with comparable toxicity profile. Although the length of hospital stay and toxicity are acceptable, the absence of durable responses tempers enthusiasm for this invasive approach.

Background

Unresectable primary and metastatic cancers of the liver remain a frequent and challenging clinical scenario to both liver surgeons and medical oncologists. In many cancers, the finding of liver metastases is indicative of widespread disease present in several organs. But specific cancers, such as colorectal cancer, ocular melanoma, and neuroendocrine carcinoma commonly metastasize to the liver, without spread to other organs [1-5]. Systemic therapy remains the mainstay of treatment for patients with these conditions; however, because of systemic-toxicity related dosage limitations the efficacy is generally limited. For example, even with aggressive treatment, the median survival in patients with liver metastases from ocular melanoma is between 2 and 7 months [4,6]. While neuroendocrine carcinoma liver metastases sometimes have an indolent biology with a slow rate of growth, poorly differentiated neuroendocrine carcinomas are much more aggressive and are generally associated with a very poor prognosis. With an eye towards development of more effective treatments for malignancies confined to the liver, regional therapies have been an active area of investigation for these metastatic cancers, as well as for intrahepatic cholangiocarcinomas and hepatocellular carcinomas.

Liver directed regional therapies include infusion of therapeutic agents directly into the hepatic artery or portal vein using either percutaneously positioned catheters or an implantable pump; local ablative techniques such as cryotherapy, radiofrequency ablation, or alcohol injection; intratumoral injection of cytotoxic agents; external or internal radiation of tumors; and tumor hyperthermia [7-13]. Therapies administered into the hepatic artery have also been combined with intra-arterial administration of absorbable or non-absorbable particles (chemo-embolization) [14], delivered in lipid emulsions that are selectively retained in tumor [15], or delivered in combination with hemofiltration device to increase drug clearance [16]. None of these treatments have had sufficient established efficacy to the degree that they have been accepted as standard therapy.

Isolated hepatic perfusion has been under clinical evaluation for over 50 years [17]. This technique represents the ultimate refinement in regional treatment strategies by achieving complete isolation of the hepatic circulation from the systemic circulation, thereby exposing liver tumors to extremely high local concentrations of therapeutic agents for prolonged periods of time. This procedure also lowers the risk of systemic toxicity; by confining the major exposure of the therapeutic agent to the liver. Isolated hepatic perfusion also allows for creation of hyperthermic conditions in the liver. Hyperthermia...
enhances cytotoxicity of specific therapeutic agents [18]. Phase I and phase II clinical trials have been conducted in Europe since the 1990s with acceptable morbidity and toxicity [19-21]. Approximately 15 years ago the Surgery Branch at the National Cancer Institute initiated clinical trials of isolated hepatic perfusion with several refinements and modifications to improve the potential safety and efficacy of this treatment technique. The partial response observed in the NCI experience is reported to range from 62% to 75% [22-24]. At the time we initiated the clinical trial reported herein, isolated hepatic perfusion had not been performed in the United States outside of the Surgery Branch of the National Cancer Institute. This pilot study was conducted during October, 2003 – October, 2004, to determine whether the technical knowledge and skills for the procedure could be transferred to another center with acceptable operative morbidity and mortality, and to determine the magnitude of resources required to support this procedure.

Patients and Methods

Patients

A pilot study of isolated hepatic perfusion (IHP) with melphalan for primary or metastatic unresectable cancers of the liver was approved by the board of human research ethics committee of the Dana-Farber/ Harvard Cancer Center. The protocol was designed to recruit 5 patients and written consent form was obtained from all patients. Patients with unresectable metastatic ocular melanoma, metastatic colon or rectal carcinoma, metastatic islet cell tumors, hepatocellular carcinoma, or cholangiocarcinoma were eligible to participate. Patients with colon or rectal carcinoma, metastatic islet cell tumors, hepatocellular carcinoma, or unresectable metastatic ocular melanoma, metastatic colon or rectal carcinoma, metastatic islet cell tumors, hepatocellular carcinoma, or cholangiocarcinoma were excluded. Patients who did not have received chemotherapy, radiotherapy, or biologic therapy for their malignancy in the month prior to the liver perfusion and must have recovered from all side effects of previous treatments. Patients were required to have an ECOG performance status of 0, 1 or 2 on the day of treatment. Adequate hepatic function as evidenced by bilirubin < 2.0 mg/dL and a PT within 2 seconds of the upper normal limit was required. Elevations in serum transaminases not due to hepatitis were required. Patients with cirrhosis or evidence of significant portal hypertension were excluded. Patients with a history of congestive heart failure with an LVEF < 40%, with COPD or other chronic pulmonary disease with PFT’s < 50% predicted for age, hepatitis C or chronic active hepatitis surface antigen B were excluded.

IHP methods

Extracorporeal bypass circuit

Patients initially underwent a limited right subcostal laparotomy incision for exploration of the peritoneal cavity to assess the suitability for proceeding with an isolated hepatic perfusion. The subcostal incision was then extended and the liver fully mobilized in a standard fashion. Anterior and posterior phrenic, right adrenal and retroperitoneal veins were ligated to minimize leak of perfusate into the systemic circulation. The portalhepatic structures were fully isolated. The suprahepatic inferior vena cava and infrahepatic inferior vena cava just beneath the diaphragm and across the common hepatic artery. Rummel tourniquets were secured around the infrahepatic IVC and proximal portal vein. The veno-veno bypass flow rate was kept at approximately 1200 ml/minute. Fluorescein and a Wood’s lamp were used for leak monitoring.

Following the isolated hepatic perfusion with melphalan under hyperthermic conditions as described below, the vascular clamps across the common hepatic artery and supra hepatic inferior vena cava were removed to restore arterial flow to the liver with normal venous outflow into the right atrium. The arterial cannula was then removed and the gastroduodenal artery was ligated. The veno-veno bypass cannulas were removed. The hepatic venous return cannula was removed from the infrahepatic inferior vena cava and the venotomy was repaired. The portal vein cannula was removed and the portal venotomy was repaired. The veno-veno bypass cannulas were removed after autotransfusion of blood from the Biomedicus bypass circuit back into the patient.

Liver perfusion circuit

The extracorporeal hepatic perfusion circuit consisted of a roller pump, membrane oxygenator and heat exchanger comparable to the extracorporeal circuit used in cardiac surgery procedures. The initial perfusate was a balanced salt solution (700 ml) primed with 300 ml packed red blood cells. Sodium bicarbonate was added to the perfusion circuit during the procedure as needed to maintain an arterial pH in the range of 7.2 to 7.4. Flow rates were adjusted according to acceptable perfusion line pressures and were typically in the range of 600 - 1000 ml/min. Perfusion temperatures were maintained in the range of 39.5 - 40C and parenchymal liver temperatures were approximately the same. The perfusion proceeded for 60 minutes. At the completion of the perfusion, the liver was flushed via the perfusion circuit with 1,500 cc of saline and 1,500 cc of hepsan. The portal vein was flushed with 1 liter of normal saline through a separate cannula and flush system.

Melphalan

The dose of melphalan administered via isolated hepatic perfusion in this study was selected based upon the maximum safe tolerated dose as defined in a previous Phase I hepatic perfusion trial (NCI 97-C-0200). The dose was 1.5 mg/kg administered based upon ideal body weight males: 50kg plus 2.3kg for every inch over 5 feet; females: 45.5kg plus 2.3 kg for every inch over 5 feet. The minimum and maximum total dose of melphalan was 90 and 120 mg, respectively. The dose of melphalan was delivered into a liter circuit volume and was further diluted by the blood volume in the liver.

Toxicity and complication

Toxicity data were collected and graded using the National Cancer Institute common toxicity criteria version 2.0. Hepatic toxicities were considered treatment related if the abnormality continued beyond 7 days after IHP [22]. Any post-operative complication were prospectively collected and reported.

Tumor response

Tumor response was evaluated with imaging studies (CT or MRI) by using Response Evaluation Criteria In Solid Tumors (RECIST).
Complete Response (CR) is defined as the disappearance of all target lesions. Partial Response (PR) is defined as at least a 30% decrease in the sum of the largest dimension (LD) of target lesions, taking as reference the baseline sum LD. Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum LD since the treatment started. Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.

Statistical Analysis

All patients’ demographic and clinical characteristics and toxicity were reported with descriptive statistics. The treatment parameters were reported with median and range. The treatment effects were listed by each individual patient. The median survival was estimated using Kaplan-Meier method. All the statistical analysis was conducted with SAS 9.2.

Result

Patients demographic and tumor characteristics

Five patients including 1 female and 4 male were included in this study. Two patients had ocular melanoma liver metastases. The other three patients had liver metastases from rectal cancer, pancreatic cancer and cholangiocarcinoma. The median age was 61 years with the range of 53 - 77 years (Table 1).

Treatment parameters and complications

All patients received the full 60 minutes of IHP with melphalan as per protocol. The median dose was 110 mg with the range of 92-120mg. The median operation time was 6 hours and 37 minutes, with the median blood loss of 2 liters (the majority of which consisted of effluent from the hepatic veins during the wash phase, which was discarded). The median hospital stay was 9 days. Three patients developed pleural effusions, and two of them required chest tube drainage. Reintubation for respiratory failure was observed in two patients. Renal insufficiency, mental status change, ascites, sepsis and clostridium difficile infection, each occurred once (Table 2). Liver toxicity as assessed biochemically is presented in Figure 1 and Table 3. Alkaline phosphatase levels dropped quickly below the pre-operative levels. Total bilirubin level dropped below 2 within 7 days post operation except for one patient, who developed rapid onset liver failure and septic shock within 2 weeks post operatively and died at post-operative day 17. The AST and ALT took longer to return to pre-operative levels with the median value of 146 units and 120 units at the end of post-operative day 7 respectively. Two patients experienced transient grade 4 liver toxicity. None of the patients had renal function impairment from the IHP (Table 4).

Discussion

Our observations in this pilot study demonstrated that isolated hepatic perfusion with melphalan for primary or metastatic unresectable cancers of the liver can be safely performed at an academic center outside of NCI surgical branch with comparable toxicity profile. Although this study was designed to evaluate primarily the toxicity and feasibility of this treatment modality as well as the magnitude of resources required, observations were that three of the five patients...
experienced partial response and one had stable disease. The range of
time to death or last follow-up was 3.7 to 15.6 months (excluding the
perioperative death case). Admitting there is no randomized clinical trial
to compare the efficacy of IHP and various regional treatment strategies
including direct intra-arterial chemotherapy, chemoembolization and
cryo therapy, IHP does have several theoretical advantages. Compares
with intra-arterial chemotherapy and chemoembolization, IHP
establishes a near complete vascular isolation of the liver, allowing
delivery of higher doses of chemotherapeutic agents, which will create
intolerable toxicity and produce significant morbidity and mortality if
given via the systemic circulation. Furthermore, unlike cryotherapy,
IHP is not as limited by the number and the size of metastatic loci and
has the potential to treat subclinical/microscopic disease. The high
response rate (62%-83%) of IHP makes it a very attractive procedure to
patients with limited choices of alternative therapy.

However, there are several issues that hamper the wider
implementation of this procedure. First, it is a time consuming,
resources intensive and expensive procedure that requires multiple
surgeons familiar with liver surgery, veno-veno bypass, hyperthermia
and regional therapy. Our experience indicated that a team approach
is needed to carry out the procedure and the median operation time is
over 6 hours. It typically requires two attending HBP surgeons rather
than an attending and a resident; perfusionists; an anesthesia team who
is comfortable with veno-veno bypass; and an ICU team familiar with
the post-operative hemodynamics and liver function changes. Second,
it is a complex procedure with higher risks of complications, morbidity
and mortality. The common morbidity and toxicity including bleeding
(3%), pleural effusion (7%-15%), atrial fibrilation/arrythymia (5%-8%),
asites (2.5%-8%), renal failure (8%), wound infection (2.5%-8%) and
liver function derangements (56%-62%) [25-27]. The post-operative
mortality ranges from 3.3% to 22.2% [26,28]. In our series, 3 patients
(60%) developed pleural effusion and two patients required chest tube
placements. All the patients experienced grade 3 or 4 liver toxicity
derangement of alkaline phosphase, AST or ALS), although, this
disturbance resolved reasonably well within 2 weeks after surgery. One
of the patients experienced renal failure after other stressful events. He
experienced respiratory distress after extubation at post-operative day
one and required re-intubation at post-operative day four. The same
patient died 17 days after surgery with multiple organ system failure.
This patient was the first subject in our series and had much more of
his liver replaced by tumor than was recognized on scans, which were
performed 6 weeks prior to the operation. This outcome lead to changes
in the protocol, the most notable of which were restriction of the liver
tumor burden to less than half of the liver volume, and requirement of
eligibility scans to be within 4 weeks of the procedure. The subsequent
patient expressed signs of fluid overload, pleural effusion required
chest tube placement, renal failure, clostridium difficile infection and
septic shock. Third, although IHP offered relative high response rate,
the efficacy profile is still unsatisfactory. For colorectal cancer liver
metastasis patients, the response rate can reach to 77% [29], however
the median survival remains in the ranges of 10.3 months to 27 months
dependant on the patient population selected for study, regimens used,

*The results of liver function tests (LFT) within 7 days post operation were used for the comparison.

Figure 1. Liver function change between preoperative and within 7 days post-operative*
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