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Minimally invasive intra-arterial regional therapy for metastatic melanoma: isolated limb infusion and percutaneous hepatic perfusion

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Abstract

Introduction—In-transit melanoma or melanoma presenting as unresectable liver metastases are clinical situations with limited therapeutic options. Regional intra-arterial therapies provide efficacious treatment alternatives for these patients. Through surgical techniques of vascular isolation, regional therapies deliver high-dose chemotherapy to tumor cells while minimizing systemic exposure. However, percutaneous techniques such as isolated limb infusion (ILI) and percutaneous hepatic perfusion (PHP) have been developed, which provide a minimally invasive means of obtaining vascular isolation of target organs.

Areas covered—Areas covered in this review include the techniques of ILI and PHP, the chemotherapeutic agents utilized during these regional therapies and the clinical responses seen after ILI and PHP. The pharmacokinetics of regional chemotherapy utilized during ILI and PHP is also reviewed with an additional focus on novel ways to optimize drug delivery to improve response rates and attempts to define the potential systemic manifestations of regional therapeutics.

Expert opinion—Unresectable hepatic and limb in-transit metastases from melanoma are very difficult to treat. Systemic chemotherapy has largely been ineffective. Both the minimally invasive, percutaneous techniques of ILI and PHP are excellent methods used to deliver extremely high-dose chemotherapy regionally to patients harboring metastatic melanoma confined to an

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Declaration of interest

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extremity or liver, respectively. Studies, from prospectively maintained databases as well as Phase II and III trials, have shown the great efficacy of these techniques.

Keywords

doxorubicin; ILI; in-transit melanoma; melanoma; melphalan; ocular melanoma; pharmacokinetics; PHP

1. Introduction

Regional intra-arterial therapies deliver high-dose chemotherapy to tumor cells while minimizing systemic exposure through vascular isolation of the target organ [1-3]. Organs that have been amenable to regional intra-arterial therapy include the extremities and the liver. Regional therapies are especially attractive in clinical situations where therapeutic options, such as surgery, radiation or systemic chemotherapy, have shown marginal benefit. In particular, patients with either in-transit melanoma confined to an extremity or unresectable metastatic melanoma isolated to the liver represent optimal target patients for regional intra-arterial therapy.

Approximately 50% of new primary cutaneous melanomas occur in the extremity and 2 – 10% of these patients will recur in a locoregional manner called in-transit metastases whereby tumor spreads through lymphatic channels into dermal and subcutaneous tissues [4]. Although, in-transit melanoma represents advanced locoregional disease, a proportion of patients with in-transit lesions of the extremity, despite eventually developing bulky disease, do not develop hematogenous metastases [5]. With effective locoregional control, a certain subgroup of patients demonstrates long-term survival [5].

Melanoma may also clinically present as distant metastatic disease either widely disseminated or isolated to a single organ such as the liver. In particular, uveal melanoma has a predilection for metastasizing to the liver [6-12]. Uveal melanoma is the most common primary malignancy of the eye in adults and represents an aggressive subtype with ~ 50% of patients developing metastases [6,7]. Up to 95% of cases that develop metastatic disease have liver involvement and in 80% of these cases, metastatic disease is predominantly or only in the liver [8-12].

In general, the prognosis is poor for melanoma patients with either in-transit disease or distant metastases to the liver [6,8,13]. Five-year survival rates for cutaneous melanoma is in the range of 30 – 50% for stage IIIB and IIIC and 20% or less for stage IVB [13,14]. For patients with uveal melanoma metastatic to the liver (stage IV), median overall survival is < 9 months and the 1-year survival is ~ 10 – 15% [6,8-12]. Clinical treatments for melanoma are generally aimed at local and regional tumor control; however, systemic therapies for patients with metastatic melanoma generally have limited benefit and trials using chemotherapy have shown disappointing results with response rates at best ranging from 5 to 20% [15].

In the case of in-transit melanoma, local and regional control can be extremely difficult to obtain because there is a constant risk for recurrence and the development of additional

lesions in the entire affected extremity. Amputation of an extremity with bulky melanoma disease has been associated with long-term survival (15 years) in 25 – 30% of patients suggesting that local control of disease may be beneficial [5]. The regional delivery of chemotherapy (usually melphalan) to an isolated limb using the techniques of hyperthermic isolated limb perfusion (HILP) and more recently isolated limb infusion (ILI) have proven to be an effective limb sparing treatment for patients with in-transit melanoma with the goal of controlling extremity disease. These techniques have been found to achieve durable complete responses (CRs), in the range of 40 – 80% for HILP and 30 – 38% for ILI, which are much higher than can be obtained with any other form of therapy currently available [16-20].

For patients with uveal melanoma and unresectable liver metastases, effective therapeutic options are even more limited. Techniques such as ablative treatments are limited by the number and size of lesions while other therapies such as selective internal radiation and chemoembolization generally do not significantly impact outcomes [21]. Liver tumors obtain the majority of their blood supply from the hepatic arteries [22]. Therefore, chemotherapy given through the hepatic arteries would expose liver lesions to higher doses of the drug. Several methods for regional therapy have been described for treating unresectable liver metastases including isolated hepatic perfusion (IHP) and more recently percutaneous hepatic perfusion (PHP) which is currently being evaluated for treatment of liver metastases [23-25]. IHP has been studied extensively and shown to be an efficacious treatment option for patients with unresectable liver metastases [3].

Although ILP and IHP have been shown to be effective in the treatment of extremity in-transit disease and of unresectable liver metastases, respectively, these procedures require surgery and in the case of IHP can only be performed once. Minimally invasive techniques such as ILI and PHP are appealing methods for intra-arterial therapy in that they avoid the potential morbidities associated with open surgical techniques and patients can potentially have repeated treatments. However, optimizing the therapeutic effects of administration of chemotherapy via regional techniques requires a precise understanding of how active drug is delivered to tumor tissue and ultimately delivered to the cellular target. Work dedicated to the pharmacokinetics (PK) of regional chemotherapy is reviewed here with an additional focus on novel ways to improve regional response rates and attempts to define the potential systemic manifestations of regional therapeutics.

2. Isolated limb infusion

2.1 Drug delivery in HILP vs ILI

Both HILP and ILI involve a method of vascular isolation and intra-arterial delivery of high-dose chemotherapy. Isolation of the limb from the body with the use of an extremity tourniquet allows delivery of high-dose chemotherapy while serious systemic side effects and myelosuppression are avoided for both techniques with patient monitored systemic leak rates of < 1% reported for both procedures [26-29]. Major similarities and differences between the procedures are listed in Table 1 [27,30]. The relatively low flow system of ILI compared with HILP may theoretically lead to lower levels of melphalan uptake by tumor cells. Whether the hypoxia and acidosis that develop in the limb during ILI (but not during

HILP) may be advantageous and confer some of the antitumor response by augmenting the effects of the alkylating agent, melphalan, is currently unknown [31,32]. For patients with in-transit melanoma of the extremity, HILP is associated with single institution CR rates of 40 – 80% [16-18,33] while ILI is associated with CR rates of 30 – 38% [19,20]. Although the spectrum of toxicities from the procedures is similar, the rate of catastrophic toxicities (requiring extremity amputation) was higher with HILP (2/77) than ILI (0/148) in a recent review [33]. While HILP is still considered the gold standard regional treatment for advanced extremity melanoma at many centers, ILI remains popular as a less invasive initial treatment reserving HILP for ILI failures or in those cases with clinically involved lymph nodes.

2.1.1 Melphalan as the current drug of choice for regional chemotherapy—

Although several different drugs have been tried in regional perfusion treatments [34,35], the alkylating agent L-phenylalanine mustard, also known as melphalan, has emerged as the drug of choice for HILP and ILI [34]. When given systemically, melphalan has limited activity against melanoma; however, when given regionally melphalan has shown effectiveness in part due to the ability to achieve a much higher dose [36]. Peak perfusate melphalan concentrations are 10- to 100-fold higher than peak levels with maximally tolerated systemic intravenous melphalan [17]. Melphalan is a bifunctional alkylating agent, active against both resting and rapidly dividing tumor cells. The level of cytotoxic melphalan-induced DNA interstrand crosslinks reaches a maximum within 4 h of a regional treatment and then declines slowly thereafter [37]. *In vitro* studies using melanoma cell lines have demonstrated that uptake of melphalan into melanoma cell lines is a rapid, active, sodium and temperature dependent process that achieves saturation of the uptake mechanism after ~ 10 min [37]. In both human and animal models, studies during HILP have shown similar PK, with rapid melphalan uptake in the first minutes of perfusion and a relatively linear dose–response relationship with respect to toxicity [17,38-39]. These properties have established melphalan as the current agent of choice for both HILP and ILI.

While melphalan has been the standard, current evidence in animal models suggests that temozolomide used as an intra-arterial agent in regional chemotherapy may improve response rates [40]. A Phase I dose escalation trial of temozolomide via ILI that will include a study of temozolomide PK is currently accruing patients.

2.1.2 Melphalan dosing—The optimal melphalan dose maximizes response while minimizing toxicity. Doses for both ILI and HILP are currently based on limb volume after Wieberdink *et al.* demonstrated that calculating drug on the basis of total body weight may actually double the amount of drug delivered to the same mass of tissue between two individuals [41]. This discrepancy is the result of the wide variation in body habitus among individuals or the varying content of muscle, fat and other tissue components in different individuals. The current most widely used dosing of melphalan for HILP is 10 mg/l for the lower extremity and 13 mg/l for the upper extremity [42,43]. For ILI, the dose of melphalan is 7.5 mg/l of tissue for the lower extremity and 10 mg/l for the upper extremity. Limb volume is calculated using a water displacement method or taking circumferential measurements of the extremity every 1.5 – 2 cm, encompassing the entire region to be

infused from distal to proximal. These measurements are then entered into the limb volume calculation program and the melphalan dosed accordingly [20]. Toxicity after ILP with melphalan has been shown to be related to peak concentration of melphalan in the perfusate [44]. Currently, melphalan is infused over 5 min during a 60 min perfusion to optimize tissue exposure to melphalan and minimize toxicity [33]. In ILI, melphalan is infused rapidly into the arterial line (2 – 5 min) and then circulated for 30 min.

2.2 Assessing optimal drug delivery to tumor

Current pharmacokinetic studies have focused on plasma concentrations of drug. Because drug concentrations vary in different tissues such as fat, skin, muscle and tumor [45], the measured plasma concentrations may not correlate with melphalan concentration in tumor and thus may not correlate with tumor response or extremity toxicity. Microdialysis allows monitoring of the concentration of drug in various tissues and allows the relationship between vascular and tissue concentrations to be more accurately described [44]. Using microdialysis, Thompson *et al.* found a significant association between tumor response and melphalan concentrations over time in subcutaneous microdialysate ($p < 0.01$) while there was no significant relationship between severity of toxic reactions in the limb and peak melphalan microdialysate or plasma concentrations in patients undergoing ILI with melphalan [46]. The use of microdialysate is still being explored as a method for correlating melphalan concentration with toxicity. Other methods more accurately monitoring drug concentrations in various tissue types could help maximize melphalan dosing for ILI and HILP with respect to tumor response and limb toxicity. The use of functional imaging technologies may be able to characterize the tumor microenvironment during or after drug delivery [47]. For example, with dynamic contrast enhanced MRI, tissue perfusion can be evaluated using the kinetics of intratumoral water soluble contrast medium concentration, that is, signal as a function of time after intravenous injection [47]. Functional imaging has been explored as a tool to predict response to chemotherapy and may be a valuable tool for assessing drug delivery in regional chemotherapy [48].

2.3 Pharmacokinetic modeling

The kinetics of drug distribution in the limb has been described using a two-compartment vascular model [49]. In this model, drug distribution is divided into central (first) compartment and peripheral (second) compartment. Exact anatomical assignment to these compartments is not always possible; however, the rapidly perfused tissues often belong in the central compartment. The plasma melphalan concentrations versus time for each patient can be fitted to a bi-exponential equation using the nonlinear least-square method (WinNonlin Version 2.1, Scientific Consulting, Inc.). Analysis of melphalan concentrations in the perfusate during both HILP and ILI show agreement between concentrations predicted by the model and actual measured values [29].

Utilizing the two-compartment vascular model, we analyzed perfusate from 14 patients with malignant melanoma undergoing a standard HILP. The initial observation was that there were marked (up to fivefold) differences in melphalan plasma concentrations among patients despite using similar dosing guidelines. The strongest predictor of toxicity was the ratio of estimated limb volume to steady state limb drug volume of distribution ($V_{est}:V_{ss}$) where a

higher ratio was correlated with increased toxicities [29]. We hypothesized giving a reduced melphalan dose would attempt to minimize the risk of overdosing the main compartment (muscle) in which the drug is primarily distributed. Patients with a high V_{ss} are generally those with actual body weights greater than ideal body weights (IBW). Thus, we began to modify the dose of melphalan for HILP and ILI by correcting the dose for IBW. This calculation is performed by multiplying the melphalan dose by the ratio of IBW:actual body weight. Our subsequent experience in ILIs ($n = 122$) demonstrated that those who had a melphalan dose corrected for IBW had a significantly lower rate of high grade toxicity (15%) compared with those not corrected (50%) ($p = 0.003$) while there was no difference in CR rates between the two groups [33]. Additionally, a multi-center study ($n = 171$) showed that correction of the melphalan dose for IBW was associated with a lower risk of severe toxicity after ILI [50].

While pharmacokinetic modeling has shown promise in predicting some toxicity, around 10 – 20% of patients develop serious toxicities that appear unexplained by current pharmacokinetic models or various other procedural variables [33]. Additionally, current pharmacokinetic studies have been unable to accurately and consistently predict tumor response to chemotherapy [28]. The ability to predict response and toxicity to regional chemotherapy would be a valuable tool in the personalization of therapy. There are some major limitations for pharmacokinetic modeling to achieve this goal. First, animal models have shown a plateau in response to increasing levels of chemotherapy above which no additional tumor response is seen [51]. This suggests that ultimately tumor response may depend on intrinsic tumor biologic chemosensitivity to drug that is somewhat independent of drug levels when a minimum concentration is achieved. Mechanisms of resistance to melphalan have been well studied and include decreased drug entry into cells through downregulation of transporters [52], intracellular drug inactivation [53], enhanced repair of crosslinking [54] and increased drug efflux [55]. Targeting pathways of chemoresistance is a novel strategy to improve levels of active drug reaching cellular targets but are not reviewed thoroughly in this article. Hyperthermia, utilized in HILP and to a lesser extent in ILI, may also increase tumor cell uptake of drug and increase drug delivery to the tumor site as suggested by *in vitro* models [56]. However, thermal enhancement of melphalan cytotoxicity seen in *in vivo* models has not been readily explained by increased total tumor uptake of drug [57]. One explanation for the discrepancy in findings between *in vitro* and *in vivo* studies is that in *in vitro* systems, tumor cell accumulation of drug is not dependent on blood flow whereas in *in vivo* systems blood flow is a major determinant of tissue drug delivery. Other mechanisms such as an increase in the rate of melphalan created inter-strand crosslinks in DNA may also account for the thermal enhancement of cytotoxicity. In addition to hyperthermia, cytotoxicity may be enhanced by manipulation of blood flow to tumor ultimately impacting PK.

2.4 Vascular targeting to enhance drug delivery

Melanoma and other solid tumors induce angiogenesis that results in tumor vasculature which is anatomically and functionally distinct from that seen in normal tissue [58,59]. This altered pattern in tumor vasculature may be a barrier to optimal cytotoxic drug delivery. Potential exists to selectively target this aberrant vasculature with targeted agents. We have

studied the novel pentapeptide ADH-1 and demonstrated that ADH-1-induced disruption of N-cadherin adhesion complexes induces alterations in vascular permeability leading to increased melphalan drug delivery to tumors [60,61]. In pre-clinical studies that use a rat xenograft model of extremity melanoma, tumors treated with systemic ADH-1 in combination with melphalan via ILI (M-ILI) demonstrated decreased growth and increased apoptosis when compared with tumors treated with M-ILI alone [60]. In a recent multi-center Phase II trial, 42 patients received systemic ADH-1 before and after M-ILI [62]. The combination was found to be a well-tolerated treatment for patients with advanced extremity melanoma; response rates with the addition of ADH-1 compared with melphalan alone were additively larger by 16% although there was no difference in the overall time to progression in-field (below tourniquet) of regional disease [62]. Notably, we did not observe a correlation between tumor N-cadherin expression and response. However, recent studies suggest that vascular N-cadherin as opposed to tumor N-cadherin expression may be important in the mechanism of action of ADH-1 [61]. Future studies will explore the relationship between tumor and vascular N-cadherin and how disrupting this interaction can make tumors more sensitive to chemotherapy.

Another important mediator of tumor angiogenesis is VEGF, a multifunctional cytokine capable of stimulating endothelial cell proliferation, migration and survival in addition to being a potent stimulator of vessel permeability [63-65]. Bevacizumab is an FDA-approved mAb to VEGF that has been used in combination with standard chemotherapies in patients with metastatic colorectal, brain and lung cancers and is being investigated in combination with other chemotherapy agents for malignant melanoma [66,67]. Evidence demonstrates that vascular targeting agents such as bevacizumab can transiently 'normalize' tumor microvasculature to mirror that seen in normal tissues thereby creating an optimal window for delivery of regional chemotherapy treatment [68]. In a melanoma xenograft model, bevacizumab given 3 days prior to ILI with melphalan caused significant decreases in vasculature in concordance with spectroscopic imaging which showed significant vascular tumor normalization [69]. A clinical trial of bevacizumab given systemically 3 days prior to ILI-M in patients with in-transit melanoma has yet to be performed.

Sorafenib (Nexavar®) is a multi-kinase inhibitor which has been shown to antagonize both Raf serine/threonine kinases and receptor tyrosine kinases associated with tumor proliferation and survival in melanoma [70]. In addition, sorafenib effectively inhibits the activity of VEGFR tyrosine kinase [71] which may lead to reduced micro-vessel density thereby increasing melphalan delivery to tumors [72,73]. In an animal model of extremity melanoma, sorafenib in combination with regional melphalan was more effective than either treatment alone in slowing tumor growth [74]. In a recently completed Phase I dose escalation trial of sorafenib in combination with standard melphalan dosing corrected for IBW via ILI, the addition of sorafenib did lead to a few marked responses but appeared to increase the local toxicity of ILI (n = 22) [75]. Interestingly, we did not observe significant inhibition of the RAF-MEK-MAPK signaling pathway by sorafenib as measured in tumor tissue before and after treatment. However, patients treated with 600 mg of sorafenib achieved a greater reduction in VEGFR2 expression than patients treated with 400 mg/day (p = 0.04). While the low number of patients treated in the Phase I study precluded finding an association of VEGFR2 with response, a previous analysis in metastatic melanoma

patients treated with sorafenib, paclitaxel and carboplatin found pretreatment expression levels of VEGFR2 to be significantly correlated with clinical response [76]. Ultimately, a better understanding of the mechanism of sorafenib may help to determine the optimal timing and dosing schedule needed to improve tumor response when used in combination with cytotoxic therapy. Several other agents including TNF- α have already been tested in Phase III regional chemotherapy trials in combination with melphalan and may also work by improving drug uptake and delivery but are not thoroughly discussed here [77].

In addition to targeted agents that alter tumor vasculature and thereby improve drug delivery, emerging technologies such as electrochemotherapy may ultimately improve drug delivery to tumor [78]. Electrochemotherapy uses the local application of pulses of electric current to tumor tissue which renders cell membranes permeable to anticancer drugs (bleomycin, cisplatin). In addition to effects on cell membranes, electrochemotherapy appears to have effects on tumor vasculature whereby the electric pulses cause local vasoconstriction [79]. This effect appears to be even more pronounced in tumor vasculature compared with normal tissue [80]. As such, chemotherapy delivered before the application of electrochemotherapy may 'trap' the drug within the electroporabilized area, creating a 'vascular lock' [78]. Early clinical applications include work the European Standard Operating Procedures of Electrochemotherapy trial which demonstrated objective response rates of 85% in 41 patients with cutaneous and subcutaneous malignancies including 98 melanoma lesions treated in the study [81]. The technique of electrochemotherapy may ultimately provide effective drug delivery for treatment of intransit disease although further development of the technology is needed.

3. Percutaneous hepatic perfusion

3.1 Technique of PHP

PHP is a minimally invasive technique of vascular isolation of the liver and regional intra-arterial therapy with veno-venous bypass and hemofiltration. In contrast to IHP in which an exploratory laparotomy is required to expose and isolate the inferior vena cava (IVC), porta hepatis, gastroduodenal artery and perihepatic collaterals, PHP utilizes catheters and balloon occlusion of the IVC to obtain the same type of vascular isolation seen in IHP (Figure 1) [23]. Furthermore, although IHP may be performed once, PHP treatments may be repeated. Table 2 illustrates some of the differences between IHP and PHP [3,82-84]. There has already been extensive work evaluating the efficacy of IHP in the treatment of liver metastases from ocular melanoma. Overall response rates for IHP treatment of metastatic ocular melanoma are reported to be 62% (10% CR and 52% partial response, PR) with a mean duration of response being 10 months [85]. The median overall survival was 12 months which is higher than the median survival of < 9 months seen in patients diagnosed with liver metastases from uveal melanoma [6,8-12,85].

At the heart of PHP is a special double balloon catheter system created by Delcath System (Delcath, Inc., New York, NY, USA). This catheter permits occlusion of the IVC and allows for vascular isolation of the liver. High-dose chemotherapeutic agents are then infused into the liver via a catheter in the hepatic artery. The principle component of the system involves use of a 16 Fr polyethylene catheter with a distal balloon, a proximal balloon and a

fenestrated segment between the balloons. The distal and proximal balloons are positioned superior and inferior to the hepatic veins, respectively, thereby providing for complete isolation of the hepatic venous outflow from the systemic circulation. The low pressure balloons are inflated in the IVC under fluoroscopic guidance and occlusion of the IVC is demonstrated with an IVC venogram. The outflow of the hepatic veins enters the fenestrated segment of the catheter and enters the extracorporeal circuit.

The procedure has been performed under both general anesthesia and local anesthesia with sedation [24,82-84]. After determining that the inflow catheter is properly positioned in the hepatic artery and any accessory arteries are embolized to prevent infusion of organs outside of the liver, contrast is injected into the main lumen to ensure proper positioning of the IVC catheter and balloons and to ensure appropriate isolation of the hepatic circulation with no leakage past the IVC balloons. The IVC catheter is attached to the extracorporeal circuit consisting of a centrifugal pump and drug filtration cartridges. The hepatic venous outflow is circulated into the pump and subsequently into two activated carbon filtration cartridges that are connected in parallel. The filtered blood is then returned to the systemic circulation through an introducer catheter in either the internal jugular or subclavian veins (Figure 1).

3.2 Clinical results of PHP for melanoma

A Phase I trial by Ravikumar *et al.* was conducted that assessed treatment of various liver tumors with IHP using either 5-fluorouracil or doxorubicin [82]. This study was not primarily designed to assess tumor response or survival; however, a significant response was reported in one patient with a scalp melanoma and symptomatic liver metastases. After two PHP treatments with doxorubicin at 90 mg/m², a 50% reduction was noted in the liver metastases. After two additional PHP treatments, there was a 96% reduction of the liver lesions and resolution of symptoms. For the second patient with metastatic melanoma treated with PHP, the type of response and the chemotherapy used were not reported.

In a Phase I trial by Pingpank *et al.*, 74 PHP treatments with melphalan were performed on 28 patients of whom 10 had ocular melanoma [84]. As a Phase I trial, this study was also not established to primarily assess clinical response; however, in 27 of 28 patients, responses were able to be evaluated. Of the 10 patients with ocular melanoma, an objective tumor response was seen in 50% and consisted of 3 patients with a PR and 2 patients with a CR. The duration of responses for the two patients with a CR was 10 and 12 months. Based on these results, a Phase III randomized multi-center trial was initiated to assess PHP in patients with either ocular or cutaneous melanoma metastatic to the liver (NCT00324727). The trial involved randomization to either best alternative therapy (BAC) or PHP. Up to six PHPs at 4 – 8 week intervals were allowed to be given provided that the patients showed no disease progression based on RECIST and that the patients did not have systemic or regional toxicities that precluded another PHP. Each PHP consisted of 30 min perfusions with melphalan followed by a passive wash-out of the liver for up to 30 min. The primary end point assessment in this study was progression-free survival (PFS). The preliminary results of this Phase III trial were recently reported at the American Society of Clinical Oncology in 2010. A total of 93 patients were accrued in this study with 44 patients in the PHP arm and 49 patients in the BAC arm. Significant improvements in both PFS and overall response

rates were seen in patients treated with PHP compared with patients treated in the BAC arm. Median PFS in the PHP arm was significantly higher ($p < 0.001$) at 245 days compared with 49 days in the BAC arm while the overall response rate in the PHP arm was also significantly higher ($p < 0.001$) at 34.1% compared with 2% in the BAC arm [86]. Despite the improvements seen in PFS, there was no significant difference in overall survival between the PHP and BAC arms, but the crossover design of this trial may be a confounding factor in assessing overall survival.

3.3 PK of PHP

The drug concentration in the hepatic venous blood is assumed to be indicative of the drug concentration within the liver parenchyma. In addition, the use of an extracorporeal circuit that filters venous hepatic blood prior to returning it into the systemic circulation requires additional analysis of the filtration efficiency of the carbon filters. Higher filter extraction efficiency for a particular drug minimizes the introduction of chemotherapy into the systemic circulation. The studies that have evaluated PK during PHP often involved treatment of several different tumor types; however, the pharmacokinetic analysis was not subdivided by treated cancer type. The studies of PHP that included treatment of patients with metastatic melanoma have reported using two different agents, namely, doxorubicin and melphalan. Therefore, the PK of these two agents are discussed below.

3.3.1 Doxorubicin—Studies of PHP using doxorubicin utilized treatments for 15, 20 or 30 min. In the study by Ravikumar *et al.*, only 2 of 23 patients enrolled in this study had melanoma metastatic to the liver and at least 1 of these 2 patients was treated with doxorubicin [82]. In a second study of PHP using doxorubicin, 10 patients with hepatocellular carcinoma were treated [83]. Between a treatment range of 50 and 120 mg/m² of doxorubicin, there appeared to be a linear relationship between dosage and peak concentration of doxorubicin in the hepatic venous outflow [82]. Curley *et al.* showed that the peak prefilter doxorubicin concentrations increased from > 1600 ng/ml at 60 mg/m² to > 9000 ng/ml at 120 mg/m² [83]. Based on the calculated prefilter and postfilter AUC time curve at each respective treatment dosage, the extraction efficiency of the carbon filters for doxorubicin ranged from 65.6 to 85.6% [82,83]. Calculated systemic AUC ranged from 8.43 to 42.88 mg min/ml at a dosage range of 50 – 120 mg/m² [82]. In the study by Ravikumar *et al.*, the two patients treated with the highest dose of doxorubicin (120 mg/m²) developed dose-limiting toxicities [82]. Curley *et al.* showed that patients treated with 60 and 90 mg/m² of doxorubicin experienced no liver or hematologic toxicities, but patients treated at dosages of 120 mg/m² began to develop toxicities including neutropenia, reversible hepatotoxicity and alopecia [83]. Based on the toxicity data and the calculated AUC of the dose escalation, 90 mg/m² of doxorubicin appears to be the optimal maximal dose during PHP.

3.3.2 Melphalan—The PK of melphalan during PHP was studied by Pingpank *et al.* [84]. In this trial, 28 patients with various liver tumors were treated with 30 min PHP treatments with melphalan. Ten patients had metastatic ocular melanoma and three patients had metastatic cutaneous melanoma. Twelve patients were treated with the initial dose of melphalan at 2 mg/kg and an additional sixteen patients were treated with dose escalations

up to 3.5 mg/kg. The mean prefilter peak concentrations of melphalan in the hepatic venous outflow ranged from 7.197 to 11.9 µg/ml between a dose range of 2 and 3.5 mg/kg of melphalan. The extraction efficiency of the filters for melphalan ranged from 64 to 82% which was determined from the calculated mean prefilter and postfilter AUC at each respective treatment dose. Based on the calculated mean AUC and the toxicity profile in which dose-limiting toxicity was achieved at 3.5 mg/kg, the optimal maximal dose for melphalan during PHP is 3 mg/kg.

3.4 Toxicity after PHP

In general, the studies that have evaluated PHP have shown a low rate of technical complications and include balloon failure, hepatic artery dissection, pneumothorax and hematomas [82-84]. In addition, the development of deep vein thrombosis, heparin-induced thrombocytopenia and anaphylactic reactions to protamine have also been reported [84]. Only one mortality during PHP treatment has been reported and consisted of a patient who became severely hypotensive, bradycardic and eventually asystolic after balloon inflation [83].

One problem encountered in all studies of PHP was transient hypotension after inflation of the IVC catheter balloons secondary to decreased venous return to the heart [82-84]. Hypotension was noted to occur in 78.5% of treatments in the study by Ravikumar *et al.* and was partially dampened by treatment with fluids and by the hepatic venous return via the internal jugular or subclavian veins [82]. However, a second period of hypotension occurred after flow was diverted through the filters. This second episode of hypotension is attributed to potential depletion of circulating catecholamines and usually required treatment with vasopressors. Significant decreases in pH were also seen during perfusion, and in one protocol, sodium bicarbonate was given to treat metabolic acidosis if the pH dropped below 7.3 [87].

Dose-limiting toxicities related to the chemotherapeutic agent utilized during PHP were primarily hematologic. In patients treated with doxorubicin, no cardiotoxicity was reported. However, grade 3 – 4 neutropenia developed in 7 (36%) of 25 cases in the study by Ravikumar *et al.* and all patients treated with 120 mg/m² of doxorubicin in the study by Curley *et al.* developed transient grade 2 or 3 neutropenia [82,83]. Although minimal hepatotoxicity was reported by Ravikumar *et al.*, Curley *et al.* reported that three (30%) patients who were treated with 120 mg/m² of doxorubicin developed reversible grade 3 liver toxicity [82,83].

For patients treated with melphalan, grade 3 or 4 neutropenia was seen in 17 (56.7%) of 30 treatments at the lowest dose of melphalan (2 mg/kg), while at the same dosage, grade 3 or 4 thrombocytopenia and grade 3 or 4 anemia were seen 11 (36.7%) of 30 treatments and 3 (10%) of 30 treatments, respectively [84]. At the highest dose of melphalan (3.5 mg/kg), grade 3 or 4 neutropenia was seen in 10 (66.7%) of 15 treatments. At the currently used dose (in the Phase III trial) of 3 mg/kg of melphalan, rates of grade 3 or 4 neutropenia, thrombocytopenia and anemia were 73.7, 36.8 and 21.1%, respectively [84]. The patients who develop these transient bone marrow toxicities are largely managed as out-patients with either observation and spontaneous normalization of peripheral blood counts or with colony

stimulating agents. Furthermore, no renal, cardiac or pulmonary complications were reported after PHP treatments with melphalan.

Of note, in contrast to ILI in which a tourniquet is used to limit systemic exposure of chemotherapy agents, PHP relies on filters in the extracorporeal circuit to limit systemic toxicity. Despite high drug extraction and filtration efficiency during PHP for both doxorubicin and melphalan, there is ~ 10 – 20% leakage of either agent into the systemic circulation based on AUC calculations [82-84]. As mentioned previously, a certain proportion of patients still experience dose-limiting hematologic toxicities presumably due to this 10 – 20% systemic leakage. In the vast majority of cases, these hematologic toxicities were transient, but in a certain subset of patients, hematologic toxicities were prolonged thereby delaying further treatments [84]. In most of these cases, patients were able to eventually resume treatments after a dose reduction [84]. However, patients who experience these prolonged hematologic toxicities may not tolerate as many PHP treatments or may require dose reductions and, therefore, these patients may not garner as much benefit from this type of therapy.

4. Conclusion

ILI and PHP are minimally invasive methods of delivering high-dose chemotherapy regionally to a limb or the liver affected by unresectable melanoma. Pharmacokinetic studies have shown that extremely high doses of chemotherapy can be achieved regionally with very little leakage into the systemic circulation. In addition, both procedures have been shown to produce response rates much higher than that of systemic chemotherapy.

5. Expert opinion

Melanoma that presents as either in-transit disease confined to a limb or as isolated distant metastases to the liver represents difficult clinical problems for treatment. In both of these clinical situations, where therapeutic options are limited and have shown to provide minimal benefit, regional intra-arterial therapies provide effective treatment alternatives. Minimally invasive techniques such as ILI and PHP bring two very important concepts to the table when one is looking at options to treat patients with regionally metastatic melanoma to the liver or limb. First, both techniques are performed percutaneously and allow the patient to avoid the morbidity of open and complex surgical procedures. Second, these techniques provide a means for repeated treatments in case of progression and for use in trials with agents that require multiple doses at various time points akin to the Phase III PHP trial.

ILI and PHP have been shown to be extremely efficacious in obtaining regional control of a disease that presents as a therapeutic challenge. ILI and PHP are minimally invasive techniques that do not require open surgical access to regional blood vessels and instead utilize percutaneous methods. This further increases the attractive nature of performing ILI and PHP in the right clinical scenarios.

Furthermore, both ILI and PHP are excellent methods that can be used to evaluate novel therapeutic agents. The ability to obtain real time pharmacokinetic analysis through the circuit and systemic circulation is unparalleled. In addition, the availability of tumor during

ILI allows investigators to not only obtain pharmacokinetic values at various times points drawn off the closed loop system, but also to biopsy tumor in the field of regional perfusion, before, during and after the infusion.

We feel that both the ILI and PHP techniques can be used as models to test therapeutic agents with real time *in vivo* tumor and serum pharmacokinetic data that can theoretically serve as the cornerstone of systemic delivery of the same agents alone or in combination with other agents. As these novel strategies are developed, continued study of PK and drug delivery will be necessary to optimize the potential therapeutic effects of therapy for either in-transit melanoma of the extremity or unresectable metastatic melanoma isolated to the liver.

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Article highlights

- Isolated limb infusion and percutaneous hepatic perfusion (PHP) are minimally invasive regional therapies that are efficacious for the treatment of extremity in-transit melanoma and unresectable melanoma liver metastases, respectively.
- The study of melphalan pharmacokinetics in regional chemotherapy has led to important findings such as a method to modify melphalan dosing to reduce toxicity while not altering complete response rates.
- Traditional pharmacokinetic models of regional chemotherapy may not fully correlate with tumor response and toxicity due to factors such as varying degrees of inherent tumor biologic chemosensitivity, hyperthermia and alterations in tumor vasculature.
- A Phase III trial that has recently closed to accrual assessed the efficacy of PHP using melphalan for the treatment of unresectable metastatic melanoma of the liver.
- PHP for melanoma has been performed using melphalan at a maximal optimal dose of 3 mg/kg with toxicity being primarily hematologic.
- Future directions include application of novel techniques to assess drug delivery, new methods to deliver chemotherapeutic agents in a minimally invasive fashion, and application of novel chemotherapeutics and targeted agents in regional chemotherapy.

This box summarizes key points contained in the article.

Figure 1. Percutaneous hepatic perfusion circuit

The Delcath catheter is a 16 Fr polyethylene multi-lumen catheter that permits occlusion of the IVC proximal and distal to the hepatic veins and allows for vascular isolation of the liver. The Delcath catheter is percutaneously introduced into the IVC and fluoroscopically positioned. The catheter is attached to the extracorporeal circuit consisting of a centrifugal pump and drug filtration cartridges. The proximal and distal balloons are inflated and high-dose chemotherapy is then infused into the liver via a catheter in the hepatic artery. The hepatic venous outflow is circulated into the pump and subsequently into two activated carbon filtration cartridges that are connected in parallel. The filtered blood is then returned to the systemic circulation through a catheter in either the internal jugular or subclavian veins. This is an original image with copyright belonging to Delcath Systems, Inc.

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IVC: Inferior vena cava.

Table 1

Comparison between hyperthermic isolated limb perfusion and isolated limb infusion.

Hyperthermic isolated limb perfusion	Isolated limb infusion
Open surgical exposure of vessels for large bore catheter (12 Fr) insertion	Percutaneous vascular catheter insertion in a radiology department, usually 6 – 8 Fr catheters
Intra-arterial infusion	Intra-arterial infusion
60 min circulation time	30 min circulation time
Circulation rate 150 – 1000 ml/min	Circulation rate 60 – 120 ml/min
Higher perfusion pressures may predispose to systemic leakage	Low pressure system, ensuring effective vascular isolation with pneumatic tourniquet
Pump oxygenator maintains physiologic pH	Progressive hypoxia and acidosis
Hyperthermia (41 – 41.5°C can be achieved)	Hyperthermia at 37 – 39°C
Wash-out performed at the end of the procedure	Wash-out performed at the end of the procedure

Table 2

Comparison between isolated hepatic perfusion and percutaneous hepatic perfusion.

Isolated hepatic perfusion	Percutaneous hepatic perfusion
Open surgical exposure of vessels for large bore catheter (20 – 24 Fr) insertion into IVC and for establishing veno-venous bypass	Percutaneous vascular catheter insertion of 16 Fr Delcath catheter into IVC
Intra-arterial infusion with veno-venous bypass (liver entirely isolated and excluded)	Intra-arterial infusion with recirculation of filtered hepatic venous blood via veno-venous bypass
60 min circulation time	30 min circulation time
Flow rate 600 – 1200 ml/min	Flow rate 300 – 600 ml/min
Leak monitoring system generally no longer used due to consistent complete vascular isolation	Leak monitoring system not utilized. Delcath catheter inflated under fluoroscopic guidance to ensure complete hepatic venous isolation
Hyperthermia (38.5 – 40°C)	Hyperthermia not utilized
Wash-out performed at the end of the procedure	Hepatic venous outflow filtered during treatment. Additional wash-out performed at the end of the procedure

IVC: Inferior vena cava.