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Regional therapy in metastatic melanoma: an update on minimally invasive intraarterial isolated limb infusion and percutaneous hepatic perfusion

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Introduction: The management of locoregioanlly metastatic melanoma of the limb and metastatic melanoma to the liver poses a clinical challenge with limited therapeutic options. An effective therapeutic modality includes regional intraarterial perfusion-based therapy. Percutaneous vascular isolation as in isolated limb infusion (ILI) and percutaneous hepatic perfusion (PHP) provide the additional advantage of minimally invasive techniques to further limit morbidity.

Areas covered: This review includes the technical aspects of ILI, PHP, the chemotherapeutic agents used and clinical responses. Also reviewed are pharmacokinetics and novel methods to enhance delivery of chemotherapeutics for both ILI and PHP and the efforts to improve therapeutic response and limit toxicity.

Expert opinion: Metastatic melanoma, particularly unresectable disease in the liver and in-transit disease in the limb, poses a clinical challenge with few effective treatments available. Although systemic therapy with immunotherapy or targeted therapy is an option, these modalities are associated with some systemic toxicity. Modalities that target treatment regionally, particularly minimally invasive techniques such as ILI and PHP, provide promising options to focus therapy on treating the affected limb or liver. The effectiveness of these minimally invasive methods has been supported by retrospective studies as well as prospective trials.

1. Introduction

The goal of regional therapy is to deliver chemotherapy in high doses while simultaneously limiting systemic toxicity [1-3]. Historically, reports of regional therapy have included the extremity, liver, abdomen, pelvis, thorax, head and neck, and even the brain by surgically isolating the vessels to these sites to allow for intraarterial therapy [4-7]. The vascular anatomy of the extremities and the liver are particularly amenable to isolation and intraarterial regional perfusion-based therapy with much less morbidity than surgical isolation of the other mentioned anatomic sites [4-7].

Although nearly half of all cases of cutaneous melanoma arise in the extremity, 2 – 10% of these cases may develop in-transit metastasis initially without distant disease [8]. In-transit metastasis is defined as tumor present in lymphatic channels which are found in the subcutaneous and dermal tissues [8]. Control of in-transit

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Article highlights.

- Minimally invasive regional perfusion-based therapies for metastatic melanoma are reviewed.
- The role of the technical and key safety and efficacy aspects of isolated limb infusion (ILI) for metastatic melanoma confined to a limb is reviewed.
- The technical and key efficacy and safety aspects of percutaneous hepatic perfusion (PHP) for melanoma (uveal or cutaneous) metastatic to the liver are reviewed.
- The pharmacokinetics (PK) and pharmacodynamics of ILI and PHP are reviewed.
- This review looks into the key aspects of why ILI and PHP are excellent models to trial new regional therapeutic agents, providing real-time PK, pharmacodynamics assays as well as tumor availability for biopsy before, during and after the procedure.

This box summarizes key points contained in the article.

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disease does potentially offer a benefit for certain patients with metastatic melanoma because a subgroup will not develop distant metastasis despite a high burden of regional disease. The 5-year survival rates for patients with cutaneous in-transit and distant metastases range from 30 to 50% in patients with stage IIIb or IIIc disease, and < 20% in patients with stage IV disease [8-11]. Accomplishing control of in-transit disease (stage IIIb/c) has demonstrated improved survival in select cases (25 – 30% 15-year survival) [8].

Although melanoma can present with diffuse metastatic disease, there are situations where even in the metastatic setting it will be limited to a single organ, such as the liver as particularly seen in patients with uveal melanoma. Uveal melanoma is the most common primary malignant neoplasm of the eye with over half of these patients eventually developing distant metastasis. Interestingly, 80% of those patients who develop metastatic disease have the liver as the only site of metastatic spread [8,9]. Accordingly, it provides a scenario for liver-directed regional therapy in select cases. One-year survival for patients with uveal melanoma with and liver metastasis is 10 – 15%, with < 9-months median overall survival [8-11]. Further more, systemic therapy has demonstrated little efficacy, as trials utilizing chemotherapy produced only 5 – 20% response rates [8-11]. This review provides a comprehensive overview of all current data on isolated limb infusion (ILI) and percutaneous hepatic perfusion (PHP), including evidence on the pharmacokinetics (PK) of regional chemotherapy.

2. Isolated limb infusion

2.1 Method of drug delivery
The treatment of in-transit melanoma has focused on controlling disease at high risk of recurrence throughout the affected limb while preserving function. Intraarterial regional therapy with chemotherapy (most commonly melphalan) treats all areas with disease and/or at high risk of disease in the affected

limb without the morbidity of amputation. To date, no other therapeutic modality has produced similar high rates of response for in-transit metastatic melanoma. Hyperthermic isolated limb perfusion (HILP) and ILI are proven therapeutic modalities shown to provide locoregional control of in-transit melanoma while preserving limb function [8,12,13]. In fact, reported durable complete response (CR) rates have ranged from 40 to 80% for HILP and from 30 to 38% for ILI [8,12,13].

Regional therapies were first reported in the 1950s where open cannulation and surgical control of the vessels were achieved to provide intraarterial regional chemotherapy [4-7]. Although HILP has demonstrated efficacy for in-transit metastatic melanoma, it is associated with morbidity of the open and complex surgery. With the evolution of percutaneous techniques and advancements in endovascular technology, minimally invasive techniques such as ILI have been introduced to accomplish regional intraarterial chemotherapy without the morbidity of open and complex surgery and can be performed multiple times in the same patient [8]. The challenge to improve outcomes in these patients is not due to the technical aspects *per se*, rather it requires an optimization of delivering active agents delivered to cellular targets in the affected limb. Therefore, it is important to consider the PK efforts to improve response rates and limit systemic toxicity, as reviewed here (**Table 1**).

Intraarterial administration of chemotherapy into the affected limb and vascular isolation are the hallmarks of HILP and ILI. The combination of an extremity tourniquet to prevent venous outflow and systemic toxicity with intraarterial chemotherapy has demonstrated systemic leak rates of < 1%, with the most serious systemic side effect being myelosuppression [8,14,15]. HILP requires open surgical control of the vessels with 12 French catheters, a 60-min circulation time, high flow rates (average of 400 – 600 cc/min), aerobic and oxygenated with a pump oxygenator and hyperthermia (41 – 41.5°C) [8,14,15]. ILI requires endovascular control with 6 – 8 French catheters in combination with a pneumatic tourniquet, 30-min circulation time, flow rates of 80 – 120 ml/min, hypoxia and acidosis and hyperthermia (37 – 39°C) [8,14,15]. Both techniques utilize washout at the end of the procedure [8,14,15]. Theoretically, the lower perfusion pressure in ILI may lead to less melphalan uptake by tumor cells than HILP, whereas the hypoxia and more profound acidosis in ILI may magnify the antitumor effects of melphalan compared to HILP [8,14,15]. Although the range of toxicities is similar between techniques, HILP has been reported to have a higher incidence of catastrophic toxicity requiring amputation (2.6 vs 0%) [14].

Upper extremity ILI appears to be less morbid and potentially associated with a better response rates after repeat therapy than lower extremity ILI. In a retrospective study comparing 51 patients undergoing upper extremity ILI with 192 patients undergoing lower extremity ILI, there was a lower rate of toxicity in the upper extremity group, without

Table 1. ILI studies.

Authors	n	Design	Findings
Beasley *et al.* [12]	58 ILI versus 54 HILP	Retrospective	ILI: 30% CR, 14% PR, 56% NR, 12 months CR, 18% toxicity; HILP: 57% CR, 31% PR, 12% NR, CR duration not reported, 32% toxicity
Kroon *et al.* [13]	185 ILI	Retrospective	38% CR, 46% PR, 13 months duration of response, 22 months duration of CR, 53 months of survival; CR, stage of disease, primary melanoma, CO_2 level and toxicity score correlated with outcome
Raymond *et al.* [14]	62 HILP versus 126 ILI	Retrospective	ILI: 43% CR + PR, 30% CR with 24 months duration, 28% CR after repeat treatment, 0% limb loss toxicity; HILP: 81% CR + PR, 55% CR with 32 months duration, 50% CR after repeat treatment, 3.2% limb loss toxicity
Chai *et al.* [15]	44 repeat HILP or ILI, 70 ILI versus 28 HILP	Retrospective	There was no statistical difference in survival or toxicity after the repeat procedures
Vohra *et al.* [16]	22 STS ILI	Retrospective	42% overall response rate (24% CR, 18% PR, 18% SD, 41% PD), unknown duration of response
Wong *et al.* [17]	77 LE ILI versus 27 UE ILI	Retrospective	Improved ORR in repeat UE ILI than LE ILI, longer length of stay and toxicity in LE ILI
Beasley *et al.* [21]	19 TMZ ILI at MTD	Phase I dose escalation	10.5% CR, 5.3% PR, 15.8% SD, 68.4% PD without dose-limiting toxicities at the MTD
Turaga *et al.* [22]	22 non-melanoma ILI	Retrospective	79% ORR, 21% CR, 58% PR, 4% grade 4 toxicity, unknown duration of response
McMahon *et al.* [29]	13 ILI versus 29 ILI corrected for IBW	Observational study	No statistical difference in response rate, but lower toxicity in the corrected group including compartment syndrome
Beasley *et al.* [39]	51 UE ILI versus 192 LE ILI	Retrospective	UE ILI had lower limb volumes, melphalan doses, lower ischemic times, toxicity, but no difference in CR compared to LE ILI

CR: Complete response; HILP: Hyperthermic isolated limb perfusion; IBW: Ideal body weight; ILI: Isolated limb infusion; LE: Lower extremity; MTD: Maximum tolerated dose; NR: No response; ORR: Overall response rate; PD: Progression of disease; PR: Partial response; SD: Stable disease; STS: Soft tissue sarcoma; TMZ: Temozolomide; UE: Upper extremity.

any difference in the response rate [16]. In addition, in another study where patients underwent repeat ILI, those patients who had upper extremity ILI had better overall response rates than those with lower extremity ILI [17].

Reported CR rates have been 40 – 80% and 30 – 38% for HILP and ILI, respectively [8,12,13]. Although HILP has been considered the standard treatment, ILI provides a less morbid alternative, with HILP reserved for cases that fail initial ILI therapy or cases with positive lymph node disease [8].

2.2 Regional therapy with melphalan

Melphalan is an alkylating agent known as L-phenylalanine mustard that has been in use for regional therapy since the earliest reports in the 1950s [4-7]. The mechanism of action focuses on both resting and dividing cancer cells [8]. Although melphalan has not been demonstrated to have efficacy against metastatic melanoma when administered systemically, regional intraarterial high dose administration has demonstrated efficacy [8,18]. The difference has been thought to be secondary to the 10- to 100-fold higher maximally tolerated doses that are achieved in regional versus systemic administration [8,18].

Although melphalan is widely accepted as the standard agent for regional perfusion therapy, there are some interesting data in animal models that temozolomide may improve response rates [19]. Temozolomide is an imidazotetrazine derivative of dacarbazine, an alkylating agent, and it rapidly converts to an active 3-methyl-(triazen-1-yl)imidazole-4-carboxamide compound which interferes with DNA replication [19]. Although the efficacy of this agent systemically has not been demonstrated to be any better than dacarbazine [20], there is an interest in its role in high-dose ILI circuits [19]. A Phase I dose–escalation trial of temozolomide-ILI PK study in 28 patients demonstrated minimal toxicity [21].

Although melphalan has been used for regional perfusions performed for metastatic melanoma, there are some interesting data to consider it for the treatment of other cutaneous and soft tissue malignancies that present with locoregional metastatic disease in the limb. Response rates for non-melanoma cutaneous malignancies and soft tissue sarcoma in small series of patients have ranged anywhere from 42 to 79% [16,22]. However, the duration of response is unknown, as the retrospective studies did not have data on long-term follow up [16,22].

In regional administration, the peak level of melphalan-induced DNA interstrand crosslinks is achieved 4 h after infusion, followed by a gradual decline. Cellular uptake of melphalan achieved saturation after 10 min as demonstrated by *in vitro* studies [8]. PK studies using animal HILP models demonstrated rapid uptake of melphalan with a linear dose–response relationship to toxicity, similar to HILP studies

in humans. Because of these features, melphalan is considered the drug of choice for both HILP and ILI [8,23].

Appropriate melphalan dosing balances maximal response against systemic toxicity. Historically, this calculation has been based on total body weight; however, studies have demonstrated that such calculations result in doubling the dose between two different patients with the same size extremity [8]. Because of the broad spectrum in body habitus and the variable distribution of fat, muscle and other tissues between different patients, total body weight is not an accurate metric [8,24]. Instead, limb volumetric measurements based on water displacement or circumferential measurements of the portions of the limb to be treated provides greater accuracy for dosing calculations [8,24]. The most commonly used doses of melphalan for the upper and lower extremities are 13 and 10 mg/l for HILP and 10 and 7.5 mg/l for ILI, respectively [8,12,24]. To balance against the toxicity produced from peak perfusate concentrations, melphalan is infused over 5 min for a 60-min perfusion time in HILP, and over 2 – 5 min for a 30-min of circulation time in ILI [8,12,24]. In a study of 171 patients, adjusting of ideal body weight (IBW) did not affect therapeutic response, but it did significantly reduced toxicity [25].

2.3 Tumor drug delivery

The limitations of assessing tumor drug delivery have been due to PK studies relying on plasma drug concentration, which varies in different tissues where tumor may be found [8]. Consequently, plasma concentration of melphalan does not necessarily correlate with its concentration in a tumor, tumor response or even extremity toxicity [8,26]. In contrast, microdialysis measures melphalan concentration in these sites, which has demonstrated a correlation between tumor response and melphalan subcutaneous microdialysate concentration without any correlation to extremity toxicity in ILI [8,26]. Further investigations are underway utilizing microdialysis to assess toxicity. In addition, functional imaging, such as MRI, has been applied to assess the effects of melphalan on tumor microenvironment. While studies are still underway, potential applications in the future include an assessment of the kinetics of contrast perfusion as a correlation to drug delivery and perhaps even therapeutic response [8,26].

2.4 Models for predicting outcomes

The model for understanding and studying the PK of intraarterial chemotherapy in the limb is based on a two-compartment system [8,27]. When the drug is administered into the limb, it is first distributed into the central compartment, followed by distribution into the peripheral compartment. Although compartments in the extremity are traditionally thought of along anatomic boundaries, this model instead categorizes tissues by how quickly they are perfused by the drug. That is, tissues that are perfused quickly are in the central compartment, whereas those that require more time to be perfused are in the peripheral compartment. Applying this model, the plasma melphalan concentration over time can be fitted to a biexponential equation (WinNonlin Version 2.1, Scientific Consulting, Inc.), which agreed with actually measured values in HILP and ILI [28].

Application of the two-compartment model in a study of 14 patients undergoing HILP for melanoma demonstrated differences up to fivefold in melphalan concentrations using the same dosing guidelines discussed above [8,28]. The ratio of estimated limb volume to steady-state limb drug volume of distribution (Vesti:Vss) directly correlated with toxicity. Patients with a high Vesti:Vss were more likely to have actual body weight (ABW) greater than IBW. In fact, when the melphalan dose was modified by a ratio of the IBW:ABW, there was a reduction in high-grade toxicity (15 vs 50%) without a change in the CR rate. These results were supported by further studies [8,25,28,29].

Currently, PK modeling has failed to consistently predict toxicity and clinical response to therapy – key components of the decision-making process to proceed with treatment. In fact, as many as 20% of patients present with toxicities unexplained by current models and a large percentage of patients fail to have a CR or durable response to therapy [8]. Understanding the limitations of these models will help guide efforts to better predict risks and benefits of HILP and ILI.

Because animal models demonstrate a plateau of therapeutic response independent of drug concentration, it is thought that tumor biology limits response despite any goal concentration of drug achieved [27]. For this reason, inquiry has focused on the reported mechanisms of melphalan resistance: downregulation of cellular transmembrane transporters, intracellular drug inactivation, DNA crosslinking repair and drug efflux [8,30]. Accordingly, there are studies underway to address biological mechanisms for the discrepancy between predicted and actual response to therapy. However, currently there are limits to the translation of these findings to the clinical setting. For example, although hyperthermia has been demonstrated to increase drug uptake *in vitro*, *in vivo* models have not supported increased drug uptake as the mechanism for the enhanced melphalan cytotoxicity in hyperthermia [31,32].

Because the *in vivo* system introduces microenvironment, blood flow and other factors of greater complexity than can be reproduced in a basic *in vitro* system, there are investigations to understand the implications on PK to improve models for predicting outcomes. For example, it has been shown that patients who demonstrate a partial response (PR) are more likely to have an increased disease-free survival if lesions are resected after ILI when compared to cases that do not demonstrate a PR [17]. In addition, patients with a lower overall tumor burden demonstrate improved overall response rates to ILI than those with a higher tumor burden in the affected limb [33]. Such findings are not explained by PK alone and implicate the importance of considering other potential targets for combined therapy.

2.5 Role of targeted therapy

As noted above, metastatic melanoma interacts with its surrounding microenvironment to develop aberrant blood supply, independent of the supply of normal surrounding tissue [8]. Although this difference in blood flow is most notably exploited in the approach to liver metastasis, there have been efforts in the limb to molecularly target this difference to further improve outcomes in ILI. ADH-1 induces disruption of N-cadherin complexes resulting in increased vascular permeability [8]. As a target to improve drug delivery in combination with melphalan via ILI, animal studies demonstrated decreased tumor growth and increased apoptosis compared with ILI alone [34,35]. A Phase II trial in 42 patients demonstrated that the combination of ADH-1 and ILI was well tolerated with a 16% additively increased tumor response rate and an increase in N-cadherin measured in tumors but without any difference in overall time to in-field progression of disease [29]. These findings may support the argument that improving drug delivery alone may not be sufficient to improve the completeness and duration of response to therapy [8].

A target of angiogenesis that has attracted a great deal of interest is the VEGF, which has been implicated in all aspects of vascular development, growth and permeability, in physiological and pathological states including metastatic melanoma [8]. In fact, targeted therapy utilizing the mAb to VEGF (bevacizumab) has been approved by FDA for therapy in colorectal, brain and lung cancers [8]. Of the potential applications for intraarterial chemotherapy, studies have demonstrated that bevacizumab results in changes in the tumor blood supply, similar to that found in the surrounding normal microvasculature [8,36]. This may offer a benefit in the case of regional intraarterial therapy to increase blood flow to the in-transit lesions in the limb, as the catheters are infused via the main artery and thus make use of normal channels of blood flow to the tissues in the affected extremity. This normalization of the microvasculature with increased melphalan tumor delivery and tumor response caused by bevacizumab was demonstrated in animal models [37]. However, clinical data are needed to further study the role of this pathway in this treatment modality [8].

Other important classes of targets for therapy in melanoma are linked Raf serine/threonine kinases, receptor tyrosine kinases and the RAF-MEK-MAPK signaling pathway, which are associated with both cancer proliferation and survival in metastatic melanoma [38]. Sorafenib is a multikinase inhibitor that blocks these pathways and has been found to inhibit the activity of VEGF receptor (VEGFR) tyrosine kinase [8]. Similar to the discussion above on the potential applications to enhance drug delivery in regional therapy via targeting the tumor microvasculature, results from an animal model demonstrated slow tumor growth when sorafenib was combined with ILI [34]. However, a Phase I trial of sorafenib and melphalan-based ILI combination in 20 patients resulted in increased toxicity without seeing an appreciable increase in clinical response [39]. Although patients treated with sorafenib have been reported to have reduced VEGFR2 expression, a factor reported to potentially correlate with clinical response, inhibition of the RAF-MEK-MAPK pathway has not been demonstrated in sorafenib-treated tumors [8]. There appears to be a correlation between the dose of the sorafenib and the degree of VEGFR expression (lower in 600 than 400 mg/day) [40].

With the proliferation of agents targeting immunotherapy in melanoma in the past few years, there has been an interest in exploring the role of such agents as ipilimumab, the CTLA-4 mAb. In an animal model, ipilimumab alone versus ILI + ipilimumab demonstrated no increased response, but there was an increase in CD8 cells as well as antigen-specific tumor cell infiltration [41]. Clinical data are needed to understand the role of immunotherapy in ILI.

3. Percutaneous hepatic perfusion

In patients with hepatic metastases, complete surgical resection offers the best improvement in overall survival and is the only potentially curative option [42]. However, only a small minority of patients (2 – 9%) classify as a surgical candidate [42,43]. Therefore, when there is no extrahepatic disease, regional intraarterial therapies that deliver high doses of chemotherapeutic agents to tumor cells locally are the preferred method of treatment, thereby minimizing systemic side effects [1-3]. Even large tumors, covering > 50% of the liver, can be treated this way [42]. Neoadjuvant downstaging and two-stage hepatectomies may increase the number of resectable tumors in select patients.

Uveal melanoma metastatic to the liver, which is usually not amenable to surgical resection, poses a unique challenge. Despite recent successes in metastasized cutaneous melanoma and investigation of a wide range of agents, in uveal melanoma, none have shown sufficient activity to progress to a Phase III trial [42,43]. The modalities available to the locoregional treatment of unresectable metastatic cancer to the liver include ablative techniques, radiotherapy and chemoembolization. However, the effectiveness of ablation and embolization techniques is limited by the number and size of liver metastases, and radiotherapy and chemoembolization have not been proven to have an impact on survival. Because liver metastases derive the majority of their blood supply from the hepatic artery, the same principles of regional therapy have been applied to this clinical scenario in isolated hepatic perfusion (IHP) and PHP to deliver chemotherapy via the hepatic artery circulation [44,45]. IHP has demonstrated promising results, as have recent data on PHP in select patients with metastatic melanoma isolated to the liver [1].

3.1 Technique

The first treatment described for isolated treatment of liver metastasis was IHP in 1961 [46]. Although effective, IHP is a major operative procedure that requires a laparotomy with a

duration of 8 – 9 h and a prolonged hospital stay, leading to considerable morbidity and mortality. Beheshti *et al.*, therefore, developed a minimally invasive percutaneous technique in the early 1990s without the morbidity of a laparotomy [44]. This technique was further refined by Alexander, Bartlett, Pingpank *et al.* at the National Cancer Institute [47-49].

PHP is based on the principle of treating liver metastasis with a high-dose chemotherapeutic agent, while limiting systemic toxicity, by taking advantage of the unique aspects of arterial inflow and venous outflow of the liver. PHP is especially important in uveal melanoma, where 95% of patients who develop metastatic disease will have liver metastases, which in 80% of cases will be the only site of distant disease. PHP has also successfully been described in metastasized colorectal cancer, sarcoma, hepatocellular carcinoma and cutaneous melanoma [1,50].

Liver metastases obtain inflow primarily from the hepatic artery, as opposed to normal hepatocytes that derive 50% of their blood flow from the portal venous system. High doses of chemotherapeutic agents, thus, can be infused into the hepatic artery and directed right at the tumor [44,46]. Hepatic arterial infusion provides the additional advantage of a 10-fold higher intratumoral concentration of chemotherapy when compared to portal vein infusion [51]. Because venous outflow into the systemic circulation for the entire liver is via the hepatic veins into the inferior vena cava (IVC), vascular isolation of the liver can be achieved via balloon occlusion of the IVC. This also allows for filtration of the chemotherapeutic agent with a veno-venous bypass before it reaches systemic circulation in order to limit systemic toxicity.

The procedure starts by inserting the inflow catheter into the hepatic artery and embolization of any accessory arteries to prevent infusion of melphalan into any other organs outside of the liver. Vascular isolation of the liver is achieved by inserting a double-balloon catheter system (Delcath, Inc., NY, USA) into the IVC. The distal and proximal balloons are positioned superior and inferior to the hepatic veins. Balloon inflation under fluoroscopic guidance occludes the IVC. The catheter is then attached to an extracorporeal circuit. The venous outflow is circulated into the pump and subsequently into two parallel connected proprietary filtration cartridges, thus creating a veno-venous bypass with in-line hemofiltration. The filtered blood is returned to the systemic circulation veins via an introducer catheter placed in the internal jugular vein [8,50].

Because of these features, PHP provides several advantages over IHP, which include the ability to repeat treatments in the same patient with reduced toxicity and morbidity. In fact, as many as six procedures have been described in a single patient, with a median hospital stay of 3 days [2,50,51].

3.2 Outcomes in melanoma

Four trials investigating the use of PHP have been conducted in the past 20 years, which demonstrated promising results (**Table 2**). Two Phase I trials have been published by

Ravikumar *et al.* and Pingpank *et al.* The series by Ravikumar *et al.* included 23 patients with various liver tumors treating 21 of them, out of which 2 were melanoma patients, with either doxorubicin or 5-fluorouracil [52]. Two patients, one of whom was a melanoma patient, achieved a PR. This patient experienced a 50% reduction in the liver metastases after two PHP treatments with doxorubicin and a 96% reduction after four treatments. Treatment details for the second melanoma patient were not reported.

Pingpank *et al.* performed 74 PHP treatments with melphalan on 28 patients every 4 – 8 weeks [48]. A total of 27 patients were available for evaluation, among whom 10 were uveal melanoma patients and 2 were cutaneous melanoma patients. Response was seen in 50% of the uveal melanoma patients (3 PR, 2 CR) but not in cutaneous melanoma patients. Based on these data, Pingpank *et al.* completed the first, and only, Phase III trial comparing melphalan PHP to best alternative care (BAC) in 93 patients with uveal and cutaneous melanomas [47]. Up to six PHPs at 4- to 8-week intervals were given, provided the patients did not show disease progression. Patients in the BAC group were permitted to crossover to PHP on hepatic progression. Median hepatic progression-free survival was 245 days in the PHP group versus 49 days in BAC (p < 0.001) group. Overall response rate was 34.1 and 2%, respectively, indicating a benefit from PHP (p < 0.001). The study showed no benefit in overall survival, which may be due to the crossover design, as 28 BAC patients crossed over to PHP and 27 of these received PHP. For BAC, PHP and BAC-PHP crossover, median overall survival was 9.8, 4.1 and 15.3 months, respectively [53].

A single institutional experiment at Moffitt Cancer Center by Forster *et al.* reported results of PHP using melphalan in 10 patients with hepatic metastasis of cutaneous melanoma (n = 3), uveal melanoma (n = 5), melanoma of unknown primary (n = 1) and leiomyosarcoma (n = 1) [50]. Six of the patients were treatment-naïve. Patients underwent a median of 3 PHP treatments (range 1 – 4). There was a 90% disease control rate with 4 patients having stable disease and 5 having a PR. Only 1 patient with uveal melanoma progressed on initial post-procedure restaging imaging. One patient with cutaneous melanoma in the liver has not progressed after 1337 days. The median hepatic progression-free survival was 240 days after a median follow up of 11.5 months. At the time of publication, the median overall survival was 12.6 months from the time of diagnosis of hepatic metastases.

3.3 Pharmacokinetics

Although in the early Phase I trials both melphalan and doxorubicin were used for PHP, melphalan is the agent of choice after a dose–escalation study by Pingpank *et al.* [47,48]. It is a very suitable chemotherapeutic agent because of its high first-pass metabolism, high hepatic clearance rate, dose-dependent toxicity and enhancement of its effects by hyperthermia [52]. Locoregional melphalan levels decline steadily during perfusion, indicating a rapid uptake by liver tissue, with most

Table 2. PHP studies.

Authors	n	Treatments	No. of treatments	Perfusion time (min)	Drug	Response	hPFS	OS (months)
Ravikumar et al. [52]	2	PHP	2 (median)	15 – 30	Fluorouracil Doxorubicin	50% PR	n/a n/a	n/a n/a
Pingpank et al. [48]	12	PHP	2.5 (mean)	30	Melphalan	42% ORR	n/a	n/a
Pingpank et al. [47], Alexander [53]	93	PHP (n = 44) BAC (n = 49)* [Crossover n = 28]*	3 (median)	30	Melphalan BAC BAC/melphalan	34% ORR 2% ORR n/a	8.0 months 1.6 months 8.8 months	9.8 4.1 15.3
Forster et al. [50]	10	PHP	3 (median)	30	Melphalan	56% PR	240 days	n/a

*Patients on BAC were allowed to crossover to PHP after hepatic progression.
BAC: Best alternative care; hPFS: Hepatic progression free survival; n/a: Not reported; ORR: Objective response rate; OS: Overall survival; PHP: Percutaneous hepatic perfusion; PR: Partial response.

of it cleared within 10 min after infusion [48,54]. In PHP, isolation of the hepatic perfusion system has been shown to increase locoregional concentrations of melphalan up to 10-fold as compared to intravenous administration in an animal model. Further, during perfusion, drug concentrations in the liver are 20- to 40-fold higher than systemic concentrations, thus showing a low systemic exposure to the drug [8]. The mean filter rate extraction during the procedure is 77%. Thus, melphalan PHP provided high treatment doses to the disease in the liver with reduced systemic exposure, limiting toxicity. Melphalan is used at a dose of 3 mg/kg based on IBW, as determined in a Phase I dose–escalation study by Pingpank et al. [48].

3.4 Complications and toxicity

Although PHP has a lower risk profile than IHP, it is not without its own risks and complications. However, dose-limiting adverse events are rare. Complications can be categorized as those related to percutaneous catheterization, hepatic isolation with veno-venous bypass along with the drugs administered such as heparin and protamine sulfate and melphalan infusion. Due to the small number of patients currently reported in the literature and the fact that not all studies present a comprehensive summary of adverse events, the frequency of these events has to be interpreted with caution. Ravikumar et al. present the most comprehensive summary of side effects but did not use the current drug of choice, melphalan, in their study [52].

Percutaneous catheter placement associated complications include hepatic artery dissection, pneumothorax and hematoma at the balloon insertion site [52]. Hepatic isolation associated complications include hypoxemia, hypothermia, hemodynamic instability, heparin-induced thrombocytopenia, mild elevations in troponin and hepatic enzyme levels, protamine reactions and deep venous thrombosis [51]. Transient metabolic acidosis during the procedure is very common, as is hypotension after balloon inflation (78.5%), caused by fluid administration prior to balloon inflation and the return of hepatic venous blood via the internal jugular or subclavian veins. Hypotension also occurs after flow is diverted through the filters, as the filters remove endogenous catecholamines on top of chemotherapeutic agents, and by hemodilution caused by the veno-venous bypass system [51]. Hypotension is usually transient and is treated with pressors such as norepinephrine and vasopressin by anesthesia. The infusion of melphalan is not begun until the mean arterial pressure is > 70 mmHg and the hepatic arteries demonstrate no spasm on repeat angiogram. Spasm of the hepatic arteries can cause retrograde flow into the stomach and/or duodenum and potentially cause damage to these organs due to high concentration of melphalan directed into their feeding vessels. Spasm is relieved by nitroglycerin into the hepatic artery. The process of the PHP allows for rechecking of hepatic artery spasm after each 100 cc aliquot of chemotherapy (at 25 cc/min) is given, therefore identifying an correcting spasm if it may occur before higher doses are diverted to the stomach or duodenum. As a prophylaxis, the gastroduodenal artery and any branches off the gastric or hepatic arteries are embolized pre-perfusion to make sure that there is no collateral flow to unwanted area.

Melphalan-induced associated complications include myelosuppression and systemic toxicities due to systemic leak to surrounding organs (e.g., gastritis) [8,48,52,53]. In the Phase I trial, at the currently used dosage of melphalan (3.0 mg/kg), grade III/IV neutropenia, thrombocytopenia and anemia were noted in 73.7, 36.8, and 21.1%, respectively [48]. Postoperatively, nausea and vomiting are common (10%) [52]. It is expected that future improvements in chemofiltration will reduce bone marrow suppression and other manifestations of systemic leak.

As of the publication date of this article, the FDA in the USA has not approved the PHP for use. It is currently being used on an expanded access protocol as well as compassionate use cases. The device is available for commercial use in the EU (CE Mark approved). Further Phase II and Phase III protocols are being planned.

4. Conclusion

Unresectable melanoma to the liver and unresectable intransit disease in the limb pose a clinical challenge with

limited options for treatment; however, ILI and PHP provide the opportunity to treat with high-dose chemotherapy utilizing minimally invasive techniques with minimal morbidity and is associated with minimal systemic toxicity. Further, these regional therapies have demonstrated improved response rates when compared to the results of standard systemic therapy in select patients.

5. Expert opinion

When the metastatic melanoma is limited to the limb or liver, regional therapy is an important option to consider, especially the minimally invasive ILI and PHP techniques. The benefits they provide include a percutaneous approach that avoids the morbidity of open and complex surgical procedures, for the ability to perform multiple treatments as well as use other agents in the setting of clinical trials. Further, ILI and PHP have demonstrated efficacy in achieving control of disease confined to the limb or liver. These two features are important to consider in a patient population whose goals of therapy are to control their disease which oftentimes is symptomatic and to develop new treatment options to improve disease-specific survival. In addition, because control of locoregional disease in select cases has demonstrated durable improvements in survival, further studies to guide patient selection offer the potential to further improve outcomes.

ILI and PHP also provide a unique opportunity to evaluate novel therapeutic agents without any added risk to the procedure. Readily available tumor for biopsy in the field of an ILI as well as a closed circuit makes in ILI and PHP attractive procedures to perform real-time tumor biopsy to assess treatment affect and PK studies on the effluent with the chemotherapy in the closed circuit. Such features are important to consider because further studies are necessary to predict which patients will benefit from these interventions to improve outcomes. *In vivo* systems introduce microenvironment, blood flow and other factors of greater complexity for investigation, factors which cannot be reproduced in a basic *in vitro* system. Even assessing tumor drug delivery itself has been limited by reliance on plasma drug concentration, for the actual concentration of drug delivered varies in different tissues within the limb or liver perfused. Because of this variable distribution, plasma concentration has not reliably predicted response or toxicity. Although preliminary findings in the role of targeted therapy, especially in the exciting era of immunotherapy, are promising, further development of these models for understanding and predicting response to regional therapy will be critical for translating such preliminary findings into clinical application.

The question remains what applicability these animal models truly have in predicting outcome. Although they do offer advantages over the *in vitro* systems by providing a more complex system for experimentation, their limitations are important to consider, especially in regional therapy. ILI and PHP rely on human patients responding to a treatment by immunologically destroying human cancer cells. This system may be too complex to reliably test in animal models and may explain some of the discrepancies between the results of animal studies and preliminary clinical data. These challenges underscore the importance of well-designed clinical trials that assess outcomes and address biological mechanism.

Because of the easily accessible bypass circuit, real-time PK data can be readily obtained. ILI has the added feature of providing access to tumor tissue in the treated field during the entire time course of treatment via tumor biopsy of subcutaneous lesions with minimal morbidity. Although PHP may not offer access to tumor tissue as in ILI, the imaging modalities available to assess the tumors, including angiography during the procedure itself, does offer areas for investigation to address the questions of tumor blood flow. Utilizing these features in clinical trials may be of particular applicability in assessing the role of targeted therapies, especially in the field of angiogenesis. Therefore, clinical trials addressing the factors discussed above offer the opportunity to understand how these factors impact treatment response and toxicity with tremendous implications on PK to improve models for predicting outcomes. Further, with the rapid proliferation of novel agents for systemic therapy in melanoma over the past few years, the potential to combine these novel systemic and regional therapies in prospective trials is critical for patients with advanced melanoma.

Declaration of interest

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