Published in final edited form as:

J Surg Oncol. 2018 April ; 117(5): 940–946. doi:10.1002/jso.24984.

Hepatic artery infusion of melphalan in patients with liver metastases from ocular melanoma

Brian A. Boone, MD¹, Samantha Perkins, MS¹, Rupal Bandi, MD¹, Ernesto Santos, MD², Kevin McCluskey, MD³, David L. Bartlett, MD¹, and James F. Pingpank, MD¹

¹Division of Surgical Oncology, Department of Surgery, University of Pittsburgh, Pittsburgh, Pennsylvania

²Department of Radiology, Memorial Sloan Kettering, New York, New York

³Department of Radiology, West Virginia University, Morgantown, West Virginia

Abstract

Background and Objectives: Ocular melanoma has a predilection for liver metastases. Systemic treatment is ineffective and the optimal regional therapy approach is poorly defined. Isolated hepatic perfusion (IHP) with melphalan has emerged as a viable treatment option, however a subset of patients are not candidates for this treatment. We therefore sought to determine if melphalan could be safely administered via the hepatic artery for these patients.

Methods: A retrospective review of patients treated with hepatic artery infusion (HAI) of melphalan was undertaken. All patients had contraindications to IHP and were without other therapy options. Melphalan infusion was repeated every four weeks with consideration for dose escalation in the absence of toxicity or significant disease progression.

Results: Fourteen patients were treated with HAI of melphalan from 2010 to 2015. All patients had hepatic dysfunction or prohibitive tumor volume precluding IHP. There were no procedure-related complications. Three patients (21%) died within 30 days and the median survival was 2.9 months. Elevated baseline bilirubin > 2.5 mg/dL was associated with worse overall survival (0.93 vs 6.3 months, $P < 0.05$).

Conclusion: HAI of melphalan is safe and feasible for patients with metastatic ocular melanoma. Further study to determine the optimal utilization of this treatment approach is warranted.

Keywords

hepatic artery infusion; isolated hepatic perfusion; melphalan; ocular melanoma

1 | INTRODUCTION

Ocular melanoma accounts for only 5% of all melanoma cases, but is the most common primary intraocular tumor in adults, arising from the melanocytes within the choroidal plexus, iris or ciliary body.¹ Ocular melanoma carries significant risk of metastatic spread, affecting approximately 35% of patients at 10 years with up to 50% lifetime risk.² The liver is the most common site of metastatic spread and is responsible for 90% of metastatic disease.³ Up to 80% of patients with ocular melanoma have liver metastasis as their only site of disease. Development of liver metastases is associated with a poor prognosis due to the lack of effective systemic treatment, with survival typically around 6 months.⁴ Surgical resection of liver metastases from ocular melanoma can result in long term survival,^{5–7} however most patients are unresectable at the time of presentation.

Because of the diffuse nature of the spread of disease in the liver and the lack of effective systemic treatments, the use of regional therapies to deliver agents to the liver has emerged as a viable treatment option for this disease.⁸ Isolated hepatic perfusion (IHP) is a surgical procedure that allows for complete isolation of the liver to allow administration of high doses of chemotherapy to be delivered directly to liver metastases while limiting systemic toxicity.⁹ Numerous studies have evaluated IHP with the drug melphalan for ocular melanoma with encouraging results^{10–19} Unfortunately, this is a complex procedure associated with significant morbidity and potential for liver toxicity. As a result, a number of patients are not candidates for the procedure due to existing hepatic dysfunction or large volume of disease, leaving them with few treatment options.

For patients who were not candidates for administration of melphalan via IHP, we hypothesized that melphalan could be administered by hepatic artery infusion. Infusion of melphalan into the hepatic artery has been evaluated in animal studies^{20,21} and used for treatment of liver metastases from ovarian and colon cancer.^{22–24} To our knowledge hepatic artery infusion of melphalan has not been described for the treatment of ocular melanoma metastases. We sought to determine the safety and feasibility of hepatic artery infusional delivery of melphalan in patients with unresectable liver metastases that had contraindications to IHP.

2 | METHODS

2.1 | Study design

This study is a retrospective review of patients with ocular melanoma with hepatic metastases treated with hepatic artery infusion of melphalan at a single academic institution. Prior to initiation of the study, Institutional Review Board approval was obtained from the University of Pittsburgh. All patients had unresectable liver disease, contraindications to IHP, and had exhausted all liver directed and systemic therapies, including clinical trials. Treatment was carried out without a prospective protocol. Clinical data, including patient demographics, available laboratory and radiology results and clinical outcomes were retrospectively reviewed. The study was intended primarily to evaluate safety and feasibility. Treatment efficacy was secondarily evaluated using lactate dehydrogenase (LDH) response, radiographic response and overall survival.

2.2 | Patient management

While there are no consensus guidelines on which patients are most likely to benefit from treatment with IHP, our general criteria is established from clinical trials of IHP performed at our institution.^{25,26} Inclusion criteria included serum bilirubin < 2.0 mg/dL, platelet count > 150 000/L, serum creatinine < 1.5 mg/dL, and limited extrahepatic disease. Some protocols limit IHP to patients with < 50% tumor replacement in the liver.^{13,16} Our experience also dictates that the volume of hepatic disease predicts response and ability to tolerate the therapy.²⁷ Most patients thought to be potential candidates for IHP are taken to the operating room for exploration for extrahepatic disease, intraoperative biopsy to evaluate for fibrosis, steatosis, cirrhosis or sinusoid liver congestion of unaffected liver, and to grossly evaluate the color and consistency of the liver intraoperatively. Ultimately treatment decisions are made after review by a multidisciplinary tumor board that considers prior systemic treatment, cirrhosis/portal hypertension, age, performance status, intraoperative findings, and other potential therapy.

2.3 | Hepatic artery infusion procedure

Hepatic artery infusion of melphalan was performed in interventional radiology under conscious sedation. Selective catheterization of the proper hepatic artery was performed via the femoral artery. Melphalan dosing was initiated at 16 mg/m² initially with consideration for dose escalation with subsequent treatments. Studies of intravenous melphalan found a maximum tolerated dose of 30 mg/m² when administered systemically over 24 h.²⁸ Prior studies examining hepatic artery infusion of melphalan were administered at a dose of 25 mg/m² for colorectal cancer and 20 mg/m² for ovarian cancer. Melphalan was administered slowly over 30–45 min. Both vessel closure devices and manual compression were used to achieve hemostasis. Treatment was typically repeated after 4 weeks based on pharmacokinetic data of intravenous administration.²⁸ All patients received granulocyte colony stimulating factor (pegfilgrastim) for hematopoietic support and allopurinol to minimize tumor lysis syndrome given their large volume, bulky liver disease.

2.4 | Statistical analysis

Continuous variables are summarized using the mean and standard deviation or median and range. Categorical variables were reported as frequencies and percentages. Kaplan-Meier method was used to construct a survival curve. Two-sided student's *t*-test was used to compare groups to identify factors contributing to survival with *P* < 0.05 considered significant.

3 | RESULTS

3.1 | Patient characteristics

We retrospectively reviewed fourteen patients with metastatic ocular melanoma who underwent hepatic artery infusion of melphalan from May 2010 to November 2015. Patient characteristics are reported in Table 1. The median age was 63 years and 64% were male. 71% of patients had their primary ocular melanoma treated with plaque radiotherapy. Two patients (6 and 9) underwent treatment of local recurrence after two and 23 years prior to the

development of metastatic disease. The time from treatment of primary tumor to diagnosis of metastatic disease was a median of 3.5 years with a range of eight months to 27 years. The median baseline LDH was 654 IU/L. Five patients (36%) had limited extrahepatic disease. Four patients (29%) underwent prior treatment of liver metastases, including one patient who had undergone prior isolated hepatic perfusion. Isolated hepatic perfusion was contraindicated due to hyperbilirubinemia ($n = 8$, 57%), massive tumor volume/hepatomegaly ($n = 5$, 36%) and prior IHP ($n = 1$, 7%). Three patients (21%) were admitted urgently from clinic due to impending organ failure related to their volume of hepatic disease. Representative cross sectional images demonstrating tumor volume for patients included in the series are shown in Figure 1.

3.2 | Treatments and outcomes

A median of two treatments were administered, ranging from 1 to 10 infusions (Table 2). Eight patients (57%) received multiple treatments. The median dose was 32 mg of melphalan (range 12–40 mg). Of the patients treated with multiple doses, seven underwent dose escalation during the course of treatment (87%) and one had dose reduction (13%).

There were no technical complications related to the procedure, including no evidence of bleeding or hematoma. More than 90% of treatments were associated with a single night admission. Of the 39 total treatments administered, only one treatment was associated with a significant increase in bilirubin, in a patient who was urgently admitted from clinic for impending liver failure (bilirubin 11 mg/dL) and went on to develop multi-system organ failure, dying in the hospital 7 days after the procedure.

Five patients (36%) had a decrease in lactate dehydrogenase (LDH) following treatment with only one patient having an increase (7%). This patient went on to get two additional treatments and had a stable LDH thereafter. Seven patients had cross sectional imaging available for review following treatment, demonstrating one patient with partial response (7%), three patients with stable disease (21%), and three patients with progressive disease (21%).

Thirty-day mortality occurred in three patients (21%). Median survival was 2.9 months (Range: 0.2–16 months, Figure 2). There were no associations with survival and age, presence of extrahepatic disease or baseline LDH. The degree of hepatic dysfunction was associated with worse survival, with patients presenting with a bilirubin of > 2.5 mg/dL having a survival of 0.93 months versus 6.3 months in patients with bilirubin < 2.5 mg/dL ($P < 0.006$).

4 | DISCUSSION

Ocular melanoma has a predilection for liver metastases with nearly half of patients developing metastatic disease in their lifetime and a strong majority of these being liver predominant disease. The prognosis for patients with liver metastases from ocular melanoma is extremely poor, largely due to the dismal responses to systemic therapy.²⁹ Interferon has no effect on long term survival.³⁰ The progress made in immunotherapy for cutaneous melanoma has not been replicated in ocular melanoma, with studies showing minimal

response to checkpoint inhibition.³¹ This has led to the development of regional therapies to optimize delivery of agents to the liver.^{32,33} Isolated hepatic perfusion (IHP) techniques allow for complete vascular isolation of the liver so that high doses of cytotoxic agents can be delivered directly to the liver while minimizing systemic toxicity. IHP with melphalan has emerged as a viable treatment option for ocular melanoma, with up to 70% of patients demonstrating treatment response and median overall survival extending from 10 to 24 months.^{11–13,16} Minimally invasive percutaneous approaches to hepatic perfusion have also been developed to minimize perioperative morbidity with encouraging results.^{10,34–36} Percutaneous hepatic perfusion (PHP) utilizes percutaneously placed catheters to achieve vascular control of the liver and deliver the drug to the isolated liver in a similar fashion to the open approach while sparing the morbidity associated with a laparotomy and portal dissection. Unfortunately, a number of patients are not candidates for hepatic perfusion with IHP or PHP due to liver dysfunction from bulky, high volume liver disease.

Melphalan is a nitrogen mustard alkylating agent that is historically used for the treatment of multiple myeloma and has been the most frequently studied agent used in IHP for ocular melanoma. Toxicity of melphalan, primarily bone marrow suppression, precludes it from being given at high enough doses to be effective systemically. However, its short half-life and linear dose toxicity relationship make it the ideal agent for regional therapies to the liver. Given its efficacy in IHP, we sought another delivery mechanism for melphalan that may be better tolerated in patients with hepatic dysfunction due to volume of disease.

It has long been recognized that liver metastases derive blood supply from the hepatic artery, with normal hepatocytes deriving a majority of blood supply from the portal vein.³⁷ Capitalizing on this anatomy to target malignant cells and spare normal liver, hepatic artery infusion for treatment of liver tumors was first described in the 1960's.^{38–40} Administration of treatment with or without embolization to the hepatic artery has been developed as a viable method of treatment for liver metastases from ocular melanoma with various regimens delivered via hepatic artery infusion including cisplatin, vinblastine and dacarbazine,⁴¹ fotemustine,^{42–45} chemoembolization,^{46–50} yttrium-90 radioembolization,^{51–56} and immunoembolization.⁵⁷ The current study is the first to demonstrate that hepatic arterial infusion of melphalan is a safe and feasible treatment option for ocular melanoma patients with contraindication to IHP.

The procedure was associated with no procedural complications and was well tolerated. There was a single in hospital mortality in a patient admitted urgently from clinic for impending liver failure with a bilirubin of 11 mg/dL that increased to 22 mg/dL on post treatment Day 1. Unfortunately his condition continued to deteriorate after the procedure and he succumbed to liver failure. It is possible that the procedure accelerated his liver failure; however he may have also progressed to acute decompensation related to his advanced disease regardless of the intervention.

While there was some subtle evidence of biochemical and radiographic treatment response, most patients died of disease progression and median survival was only 2.9 months. These unfavorable outcomes must be considered in the context of the patient population. These patients had extremely advanced disease, bringing them to the brink of liver failure with no

other viable treatment options after discussions in multi-disciplinary tumor board. Importantly, three patients had nearly 1 year survival after treatment, suggesting a potential benefit for a subset of patients studied.

Identifying patients most and least likely to benefit from a novel treatment is an important goal. Elevated bilirubin, a marker of hepatic dysfunction due to large volume disease was associated with worse survival, similar to a previous report.⁴⁷ Prior reports have also suggested that outcomes were also worse in patients with more advanced volume of disease.^{49,50} A small number of patients included in the current study had extrahepatic disease; however, consistent with prior reports, this did not appear to influence survival. These patients are more likely to succumb to their advanced liver disease,⁴⁷ justifying aggressive locoregional treatment even with limited extrahepatic disease. Further research is needed to determine the optimal utilization and patient population for treatment with hepatic artery infusion of melphalan. Because most of the patients studied had hepatic dysfunction thought to be related to bulky liver disease, this approach could be used as a bridge to IHP or PHP if liver function improved after response to treatment. While this did not occur in any of the 14 patients studied, it could warrant consideration in future patients that respond well with improvements in tumor volume or liver function. Patients with liver metastases from ocular melanoma with contraindication to IHP may not be the only patient population to potentially benefit from hepatic artery infusion of melphalan. This procedure was well tolerated and therefore could be used in combination with other treatment regimens and modalities. Furthermore, the high rate of local recurrence after liver resection and IHP supports consideration of placement of a hepatic artery infusion port after hepatectomy or IHP for adjuvant delivery of melphalan.⁶ Given the high risk of liver metastases from ocular melanoma and the poor prognosis associated with the development of hepatic metastases, adjuvant intra-arterial fotemustine to the hepatic artery after treatment of the primary lesion has been studied.⁵⁸ This approach could warrant consideration using adjuvant hepatic artery infusion of a more active regimen such as melphalan.

This study is highly limited by a number of factors. Because a retrospective review of outcomes was performed, we are unable to identify toxicities and treatment responses to the extent of a prospective trial. Additionally, patients traveled to our institution from all over the country after being told they had no additional treatment options at local hospitals and returned home after the procedure, making following post procedure laboratory values and imaging studies challenging. Because patients had primary treatment and follow up at local institutions, data on overall disease course and progression is also limited. The small number of patients limits conclusions that can be made from the study. It is also extremely difficult to determine any type of clinical response to treatment given the lack of a sufficient historical cohort that includes patients with such advanced disease.

Despite these limitations, hepatic artery infusion of melphalan is shown to be safe and feasible in patients with ocular melanoma with liver metastases. The extent of disease and resultant hepatic dysfunction at presentation dictates treatment outcome. These findings warrant consideration of placement of hepatic artery infusion ports following isolated hepatic perfusion or for adjuvant treatment of the liver in high risk patients. Further study of this approach to determine optimal utilization is warranted.

REFERENCES

1. Krantz BA, Dave N, Komatsubara KM, Marr BP, Carvajal RD. Uveal melanoma: epidemiology, etiology, and treatment of primary disease. *Clin Ophthalmol* 2017;11:279–289. [PubMed: 28203054]
2. Diener-West M, Reynolds SM, Agugliaro DJ, et al. Development of metastatic disease after enrollment in the COMS trials for treatment of choroidal melanoma: collaborative Ocular Melanoma Study Group Report No. 26. *Arch Ophthalmol* 2005;123:1639–1643. [PubMed: 16344433]
3. Spagnolo F, Caltabiano G, Queirolo P. Uveal melanoma. *Cancer Treat Rev* 2012;38:549–553. [PubMed: 22270078]
4. Pereira PR, Odashiro AN, Lim LA, et al. Current and emerging treatment options for uveal melanoma. *Clin Ophthalmol* 2013;7: 1669–1682. [PubMed: 24003303]
5. Caralt M, Marti J, Cortes J, et al. Outcome of patients following hepatic resection for metastatic cutaneous and ocular melanoma. *J Hepatobiliary Pancreat Sci* 2011;18:268–275. [PubMed: 21057964]
6. Pawlik TM, Zorzi D, Abdalla EK, et al. Hepatic resection for metastatic melanoma: distinct patterns of recurrence and prognosis for ocular versus cutaneous disease. *Ann Surg Oncol* 2006;13:712–720. [PubMed: 16538410]
7. Martel G, Hawel J, Rekman J, et al. Liver resection for non-colorectal, non-carcinoid, non-sarcoma metastases: a multicenter study. *PLoS ONE* 2015;10: 0120569.
8. Feldman ED, Pingpank JF, Alexander HR, Jr. Regional treatment options for patients with ocular melanoma metastatic to the liver. *Ann Surg Oncol* 2004;11:290–297. [PubMed: 14993024]
9. Boone BA, Bartlett DL, Zureikat AH. Isolated hepatic perfusion for the treatment of liver metastases. *Curr Probl Cancer* 2012;36:27–76. [PubMed: 22464447]
10. Vogl TJ, Koch SA, Lotz G, et al. Percutaneous isolated hepatic perfusion as a treatment for isolated hepatic metastases of uveal melanoma: patient outcome and safety in a multi-centre study. *Cardiovasc Intervent Radiol* 2017;40:864–872. [PubMed: 28144756]
11. de Leede EM, Burgmans MC, Kapiteijn E, et al. Isolated (hypoxic) hepatic perfusion with high-dose chemotherapy in patients with unresectable liver metastases of uveal melanoma: results from two experienced centres. *Melanoma Res* 2016;26:588–594. [PubMed: 27513071]
12. Ben-Shabat I, Belgrano V, Ny L, Nilsson J, Lindner P, Olofsson Bagge R. Long-Term follow-Up evaluation of 68 patients with uveal melanoma liver metastases treated with isolated hepatic perfusion. *Ann Surg Oncol* 2016;23:1327–1334. [PubMed: 26628434]
13. Olofsson R, Ny L, Eilard MS, et al. Isolated hepatic perfusion as a treatment for uveal melanoma liver metastases (the SCANDIUM trial): study protocol for a randomized controlled trial. *Trials* 2014;15:317. [PubMed: 25106493]
14. van Iersel LB, Hoekman EJ, Gelderblom H, et al. Isolated hepatic perfusion with 200 mg melphalan for advanced noncolorectal liver metastases. *Ann Surg Oncol* 2008;15:1891–1898. [PubMed: 18470571]
15. Noter SL, Rothbarth J, Pijl ME, et al. Isolated hepatic perfusion with high-dose melphalan for the treatment of uveal melanoma metastases confined to the liver. *Melanoma Res* 2004;14:67–72. [PubMed: 15091197]
16. van Etten B, de Wilt JH, Brunstein F, Eggermont AM, Verhoef C. Isolated hypoxic hepatic perfusion with melphalan in patients with irresectable ocular melanoma metastases. *Eur J Surg Oncol* 2009;35: 539–545. [PubMed: 18760560]
17. van Etten B, Brunstein F, Marinelli AW, et al. Isolated hypoxic hepatic perfusion with orthograde or retrograde flow in patients with irresectable liver metastases using percutaneous balloon catheter techniques: a phase I and II study. *Ann Surg Oncol* 2004; 11:598–605. [PubMed: 15172933]
18. Alexander HR, Jr., Libutti SK, Pingpank JF, et al. Hyperthermic isolated hepatic perfusion using melphalan for patients with ocular melanoma metastatic to liver. *Clin Cancer Res* 2003;9:6343–6349. [PubMed: 14695133]

19. Alexander HR, Libutti SK, Bartlett DL, Puhlmann M, Fraker DL, Bachenheimer LC. A phase I-II study of isolated hepatic perfusion using melphalan with or without tumor necrosis factor for patients with ocular melanoma metastatic to liver. *Clin Cancer Res* 2000;6: 3062–3070. [PubMed: 10955785]
20. Marinelli A, van Dierendonck JH, van Brakel GM, et al. Increasing the effective concentration of melphalan in experimental rat liver tumours: comparison of isolated liver perfusion and hepatic artery infusion. *Br J Cancer* 1991;64:1069–1075. [PubMed: 1764369]
21. Rothbarth J, Woutersen RA, Sparidans RW, van de Velde CJ, Mulder GJ. Melphalan antitumor efficacy and hepatotoxicity: the effect of variable infusion duration in the hepatic artery. *J Pharmacol Exp Ther* 2003;305:1098–1103. [PubMed: 12606622]
22. Mambrini A, Caudana R, Zamagni D, et al. Intra-arterial hepatic chemotherapy in heavily pretreated patients with epithelial ovarian cancer. *Ann Oncol* 2005;16:334–335. [PubMed: 15668294]
23. Muller H, Nakchbandi V, Chatzisavvidis I, von Voigt C. Repetitive chemoembolization with melphalan plus intra-arterial immuno-chemotherapy within 5-fluorouracil and granulocyte-macrophage colony-stimulating factor (GM-CSF) as effective first- and second-line treatment of disseminated colorectal liver metastases. *Hepatogastroenterology* 2003;50:1919–1926. [PubMed: 14696433]
24. Muller H, Nakchbandi W, Chatzissavvidis I, Valek V. Intra-arterial infusion of 5-fluorouracil plus granulocyte-macrophage colony-stimulating factor (GM-CSF) and chemoembolization with melphalan in the treatment of disseminated colorectal liver metastases. *Eur J Surg Oncol* 2001;27:652–661. [PubMed: 11669594]
25. Magge D, Zureikat AH, Bartlett DL, et al. A phase I trial of isolated hepatic perfusion (IHP) using 5-FU and oxaliplatin in patients with unresectable isolated liver metastases from colorectal cancer. *Ann Surg Oncol* 2013;20:2180–2187. [PubMed: 23575907]
26. Zeh HJ, III, Brown CK, Holtzman MP, et al. A phase I study of hyperthermic isolated hepatic perfusion with oxaliplatin in the treatment of unresectable liver metastases from colorectal cancer. *Ann Surg Oncol* 2009;16:385–394. [PubMed: 19034580]
27. Magge D, Choudry HA, Zeh HJ, III, et al. Outcome analysis of a decade-long experience of isolated hepatic perfusion for unresectable liver metastases at a single institution. *Ann Surg* 2014;259: 953–959. [PubMed: 24169176]
28. Pinguet F, Culine S, Bressolle F, et al. A phase I and pharmacokinetic study of melphalan using a 24-hour continuous infusion in patients with advanced malignancies. *Clin Cancer Res* 2000;6: 57–63. [PubMed: 10656432]
29. Carvajal RD, Sosman JA, Quevedo JF, et al. Effect of selumetinib vs chemotherapy on progression-free survival in uveal melanoma: a randomized clinical trial. *JAMA* 2014;311:2397–2405. [PubMed: 24938562]
30. Lane AM, Egan KM, Harmon D, Holbrook A, Munzenrider JE, Gragoudas ES. Adjuvant interferon therapy for patients with uveal melanoma at high risk of metastasis. *Ophthalmology* 2009;116: 2206–2212. [PubMed: 19744725]
31. Komatsubara KM, Carvajal RD. Immunotherapy for the treatment of uveal melanoma: current status and emerging therapies. *Curr Oncol Rep* 2017;19:45. [PubMed: 28508938]
32. Eschelmann DJ, Gonsalves CF, Sato T. Transhepatic therapies for metastatic uveal melanoma. *Semin Intervent Radiol* 2013;30:39–48. [PubMed: 24436516]
33. Lodh S, Maher R, Guminski A. Intra-arterial infusion and chemoembolization for melanoma liver metastases. *J Surg Oncol* 2014;109: 376–382. [PubMed: 24500702]
34. Glazer ES, Zager JS. Chemosaturation with percutaneous hepatic perfusion in unresectable hepatic metastases. *Cancer Control* 2017; 24:96–101. [PubMed: 28178721]
35. de Leede EM, Burgmans MC, Martini CH, et al. Percutaneous hepatic perfusion (PHP) with melphalan as a treatment for unresectable metastases confined to the liver. *J Vis Exp* 2016 10.3791/53795
36. Hughes MS, Zager J, Faries M, et al. Results of a randomized controlled multicenter phase III trial of percutaneous hepatic perfusion compared with best available care for patients with melanoma liver metastases. *Ann Surg Oncol* 2016;23:1309–1319. [PubMed: 26597368]

37. Breedis C, Young G. The blood supply of neoplasms in the liver. *Am J Pathol* 1954;30:969–977. [PubMed: 13197542]
38. Clarkson B, Young C, Dierick W, et al. Effects of continuous hepatic artery infusion of antimetabolites on primary and metastatic cancer of the liver. *Cancer* 1962;15:472–488. [PubMed: 13879776]
39. Brennan MJ, Talley RW, Drake EH, Vaitkevicius VK, Poznanski AK, Brush BE. 5-Fluorouracil treatment of liver metastases by continuous hepatic artery infusion via cournand catheter: results and suitability for intensive postsurgical adjuvant chemotherapy. *Ann Surg* 1963; 158:405–419. [PubMed: 14064976]
40. Sullivan RD, Norcross JW, Watkins E, Jr. Chemotherapy of metastatic liver cancer by prolonged hepatic-Artery infusion. *N Engl J Med* 1964; 270:321–327. [PubMed: 14082260]
41. Melichar B, Voboril Z, Lojik M, Krajina A. Liver metastases from uveal melanoma: clinical experience of hepatic arterial infusion of cisplatin, vinblastine and dacarbazine. *Hepatogastroenterology* 2009;56: 1157–1162. [PubMed: 19760961]
42. Egerer G, Lehnert T, Max R, Naeher H, Keilholz U, Ho AD. Pilot study of hepatic intraarterial fotemustine chemotherapy for liver metastases from uveal melanoma: a single-center experience with seven patients. *Int J Clin Oncol* 2001;6:25–28. [PubMed: 11706523]
43. Leyvraz S, Spataro V, Bauer J, et al. Treatment of ocular melanoma metastatic to the liver by hepatic arterial chemotherapy. *J Clin Oncol* 1997;15:2589–2595. [PubMed: 9215829]
44. Peters S, Voelter V, Zografos L, et al. Intra-arterial hepatic fotemustine for the treatment of liver metastases from uveal melanoma: experience in 101 patients. *Ann Oncol* 2006;17:578–583. [PubMed: 16469752]
45. Leyvraz S, Piperno-Neumann S, Suci S, et al. Hepatic intra-arterial versus intravenous fotemustine in patients with liver metastases from uveal melanoma (EORTC 18021): a multicentric randomized trial. *Ann Oncol* 2014;25:742–746. [PubMed: 24510314]
46. Agarwala SS, Panikkar R, Kirkwood JM. Phase I/II randomized trial of intrahepatic arterial infusion chemotherapy with cisplatin and chemoembolization with cisplatin and polyvinyl sponge in patients with ocular melanoma metastatic to the liver. *Melanoma Res* 2004;14: 217–222. [PubMed: 15179192]
47. Bedikian AY, Legha SS, Mavligit G, et al. Treatment of uveal melanoma metastatic to the liver: a review of the M. D. Anderson Cancer Center experience and prognostic factors. *Cancer* 1995;76: 1665–1670. [PubMed: 8635073]
48. Sharma KV, Gould JE, Harbour JW, et al. Hepatic arterial chemoembolization for management of metastatic melanoma. *AJR Am J Roentgenol* 2008;190:99–104. [PubMed: 18094299]
49. Gupta S, Bedikian AY, Ahrar J, et al. Hepatic artery chemoembolization in patients with ocular melanoma metastatic to the liver: response, survival, and prognostic factors. *Am J Clin Oncol* 2010;33:474–480. [PubMed: 19935383]
50. Fiorentini G, Aliberti C, Del Conte A, et al. Intra-arterial hepatic chemoembolization (TACE) of liver metastases from ocular melanoma with slow-release irinotecan-eluting beads. Early results of a phase II clinical study. *In Vivo* 2009;23:131–137. [PubMed: 19368137]
51. Kuei A, Saab S, Cho SK, Kee ST, Lee EW. Effects of Yttrium-90 selective internal radiation therapy on non-conventional liver tumors. *World J Gastroenterol* 2015;21:8271–8283. [PubMed: 26217079]
52. Memon K, Kuzel TM, Vouche M, Atassi R, Lewandowski RJ, Salem R. Hepatic yttrium-90 radioembolization for metastatic melanoma: a single-center experience. *Melanoma Res* 2014;24:244–251. [PubMed: 24638152]
53. Kennedy AS, Nutting C, Jakobs T, et al. A first report of radioembolization for hepatic metastases from ocular melanoma. *Cancer Invest* 2009;27:682–690. [PubMed: 19219675]
54. Eldredge-Hindy H, Ohri N, Anne PR, et al. Yttrium-90 microsphere brachytherapy for liver metastases from uveal melanoma: clinical outcomes and the predictive value of fluorodeoxyglucose positron emission tomography. *Am J Clin Oncol* 2016;39: 189–195. [PubMed: 24441583]

55. Gonsalves CF, Eschelman DJ, Sullivan KL, Anne PR, Doyle L, Sato T. Radioembolization as salvage therapy for hepatic metastasis of uveal melanoma: a single-institution experience. *AJR Am J Roentgenol* 2011;196:468–473. [PubMed: 21257902]
56. Klingenstein A, Haug AR, Zech CJ, Schaller UC. Radioembolization as locoregional therapy of hepatic metastases in uveal melanoma patients. *Cardiovasc Intervent Radiol* 2013;36:158–165. [PubMed: 22526099]
57. Valsecchi ME, Terai M, Eschelman DJ, et al. Double-blinded, randomized phase II study using embolization with or without granulocyte-macrophage colony-stimulating factor in uveal melanoma with hepatic metastases. *J Vasc Interv Radiol* 2015;26: 522–532.
58. Voelter V, Schalenbourg A, Pampallona S, et al. Adjuvant intra-arterial hepatic fotemustine for high-risk uveal melanoma patients. *Melanoma Res* 2008;18:220–224. [PubMed: 18477897]

FIGURE 1.

Representative cross sectional imaging demonstrating volume of hepatic disease in patients included in the series. A, 70 year old female with innumerable, bilobar hepatic lesions typical of those seen in metastatic ocular melanoma. B, 59 year old male with diffuse hepatic tumor involving most of right lobe and extending into the left. Occlusion of the right and left portal vein and the right and middle hepatic veins were demonstrated on this scan. C, 44 year old male with massive hepatomegaly secondary to diffuse tumor infiltration

FIGURE 2.

Survival of 14 patients receiving hepatic artery infusion of melphalan for metastatic ocular melanoma. Thirty-Day mortality was 21%. Median survival was 2.9 months

Characteristics of patients treated with hepatic artery infusion of melphalan for metastatic ocular melanoma

TABLE 1

Patient #	Age	Gender	Treatment of primary	Years from primary	Extrahepatic disease	Emergent admission	Prior treatment	Baseline LDH	Contraindication to IHP
1	70	F	Plaque	4	Bone metastases		Cisplatin Chemoembolization (x 2)	463	Hyperbilirubinemia
2	67	F	Unknown	5			Ipi/Nivo, Embolization (x 2)	473	Hyperbilirubinemia
3	59	M	Plaque	3		Yes		6580	Tumor volume
4	63	M	Plaque	5	Omental deposits			644	Hyperbilirubinemia
5	76	F	Plaque	6	Bone metastases		IHP, TACE w/ cisplatin (x 4)	264	Prior IHP
6	59	M	Plaque	6		Yes		937	Hyperbilirubinemia
7	56	M	Enucleation	2				2527	Hyperbilirubinemia
8	55	F	Enucleation	1				663	Tumor volume
9	72	M	Plaque	27				1436	Hyperbilirubinemia
10	75	F	Plaque	<1	Omental deposit		Yttrium-90 spheres (x 7)	256	Hyperbilirubinemia
11	68	M	Plaque	1		Yes		3295	Hyperbilirubinemia
12	44	M	Enucleation	2				2553	Tumor volume
13	60	M	Plaque	3	Splenic mass			502	Tumor volume
14	62	M	Plaque	4				134	Tumor volume

IHP, isolated hepatic perfusion

TABLE 2

Treatment outcomes of patients treated with hepatic artery infusion of melphalan for metastatic ocular melanoma

Patient	# Melphalan treatments	Melphalan dosing (mg)	Radiographic response	Survival (months)
1	1	26	-	0.4
2	3	16, 31.5, 26	-	2.9
3	1	30	-	1.4
4	6	31, 31, 40 (x4)	PD	11.6
5	3	12, 16, 20	SD	6.3
6	1	31	-	0.2
7	1	28	SD	0.9
8	10	24, 32, 40 (x8)	PR	11.7
9	1	30	-	0.6
10	1	25	-	1.1
11	2	32, 36	PD	2.9
12	3	30, 37.5, 37.5	PD	4.8
13	4	32, 32, 40, 40	-	3.7
14	2	30, 15	PD	15.8

PD, progressive disease; SD, stable disease; PR, partial response.