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Intra-Arterial Hepatic Perfusion for Metastatic Melanoma of Cutaneous Origin

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Abstract

Intra-arterial Hepatic Perfusion (IHP) is a chemotherapeutic strategy that has been in use for several years. Its application in non-resectable liver metastases has gained increased acceptance following favorable results from recent clinical studies. Most of these published studies focus on outcomes of metastatic colorectal and ocular melanoma due to the high frequency of isolated liver metastases. To better understand the role of IHP in metastatic melanoma, we reviewed the pertinent literature with a focus on cutaneous melanoma. Here we present a brief report of IHP for metastatic melanoma of cutaneous origin. We have highlighted the available data on patient outcomes with attention to the unique morbidity and mortality, and future directions of IHP therapy.

Keywords: Intra-arterial hepatic perfusion; Regional therapies; Metastatic melanoma; Cutaneous melanoma

Introduction

Metastatic cutaneous melanoma portends a poor prognosis with median survival in the range of 6 to 10 months and 5-year survival less than 5% [1]. With the development of systemic immunotherapy utilizing checkpoint inhibition, long term survival has now become a possibility for selected patients with stage IV disease. In the era of improved systemic therapy, the role of regionally directed therapies remains in question. We report on the role of Intra-arterial Hepatic Perfusion (IHP) for non-resectable metastatic cutaneous melanoma to the liver.

Indication and Description of Procedure

Current clinical trials include patients with non-resectable metastatic melanoma limited to the liver. Although the vast majority of melanoma incidence is related to cutaneous disease, liver specific relapse is more commonly observed in ocular melanoma [2]. Importantly, to tolerate the extracorporeal filtration system necessary for isolated perfusion, patients must be amenable to systemic anticoagulation.

Intra-arterial hepatic perfusion *via* a percutaneous approach utilizes an extracorporeal filtration system to maximize hepatic concentration and minimize systemic exposure. Briefly, this is completed through isolating the hepatic circulation by 1) cannulating the hepatic artery *via* the femoral artery, 2) occluding the suprahepatic inferior vena cava *via* the internal jugular vein, and 3) occluding the infrahepatic IVC *via* the femoral vein. The infusate enters the hepatic circulation through the hepatic artery and is cleared by the hemofiltration system draining from the suprahepatic IVC. The liver is further excluded from systemic circulation *via* hepatic bypass from the infrahepatic IVC and return *via* the internal jugular vein cannula. CT angiography of the liver is required for pre-operative planning to ensure no inadvertent extrahepatic perfusion.

Outcomes

Of the larger studies reported, only four enrolled patients with metastatic melanoma of cutaneous origin [3-6], with a cumulative total of 18 patients treated with IHP. Of these studies, only one reports the individual outcomes for the cutaneous melanoma cohort [4]. All patients in this study experienced at least a partial response; however, in one patient, lung metastases developed, and in another, hepatic recurrence occurred within 13 months. In a large retrospective review of a prospectively collected database, 91 patients underwent IHP for liver metastases of colorectal and non-colorectal primary cancers over a ten year period [3]. Only three patients had a primary cutaneous melanoma in this study. Response rates for the colorectal, melanoma, and cholangio carcinoma cohorts were 68%, 57%, and 100%, respectively. Analysis of response rate for the subset

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Table 1: Studies of intra-arterial hepatic perfusion for metastatic cutaneous melanoma.

Study	Study Type	Number of patients (n)	Treatment Regimen	Comments
Magge [3]	Review of prospective database	3	IHP with melphalan, ± oxaliplatin ± 5-FU ± surgery	57% complete or partial response in melanoma subgroup Outcomes of cutaneous and ocular melanoma not reported separately
Vogl [4]	Retrospective review	3	IHP with melphalan, ± vemurafinib ± LITT	100% partial response Patient 1: 95% tumor volume reduction. Hepatic recurrence Patient 2: >40% tumor volume reduction. Lung metastases Patient 3: Unreported partial response
Hughes [5]	Phase III Clinical Trial	5	IHP with melphalan	Improved hepatic and overall PFS Median HPFS: IHP 7.0 months *vs.* BAC 1.6 months (p<0.0001) Median PFS: IHP 5.4 months *vs.* BAC 1.6 months (p=0.0001) Outcomes of cutaneous and ocular melanoma not reported separately
Abbott [6]	Retrospective Review	7	IHP with melphalan	Improved hepatic and overall PFS Median HPFS: PHP 361 days, CE 80 days, Y90 54 days (p=0.001) Median PFS: PHP 245 days, CE 52 days, Y90 54 days (p=0.03) Outcomes of cutaneous and ocular melanoma not reported separately Comparison of hepatic perfusion, chemoembolization, Y90. Includes patients from Hughes *et al.*.

HPFS: Hepatic Progression-Free Survival; PFS: Progression-Free Survival; IHP: Isolated Hepatic Perfusion; BAC: Best Available Care; PHP: Percutaneous Hepatic Perfusion; CE: Chemoembolization; Y90: Yttrium-90 Radioembolization; LITT: Laser-Induced Thermotherapy

of patients with primary cutaneous melanoma was not reported. Therefore, it remains unclear if the outcomes in metastatic ocular melanoma hold true for melanoma of cutaneous origin. A synopsis of these studies is presented in Table 1.

Morbidity and Mortality

Although introduction of the percutaneous approach abrogated the need for a laparotomy incision, significant procedural and non-procedural morbidity and mortality remain. The phase III trial by Hughes *et al.* [5] suggests that adverse events in the peri-procedural period, defined by the first 72 hrs after the procedure, are common, occurring in approximately 90% of patients. The most common adverse events in this period were thrombocytopenia and anemia. In the post-procedural time, defined as the first 30 days after the peri-procedural period, adverse events remain similar, occurring in 91% of patients in this trial. In the same trial, three deaths occurred in the treatment arm and one death occurred in the crossover arm. Of the three deaths in the treatment arm, one was attributed to neutropenia, another to sepsis, and a third to liver failure. In the crossover arm, mortality was attributed to a gastric perforation. Specific timing of mortalities was not reported in the trial.

The adverse events described by Vogl *et al.* [4] reflect a similar trend as observed by Hughes et al. However, two described events were attributed to systemic heparinization and the resultant coagulopathy with one fatal retroperitoneal hematoma at 30 hrs post-infusion. Both studies highlight a near ubiquitous rate of adverse events and a mortality rate between 4% (4/70) and 7% (1/14). There is clear potential for significant improvement with the use of newer hemofiltration systems and novel infusate regimens.

Future Directions

Melphalan has been the standard infusate for IHP in metastatic cutaneous melanoma due to its effect on dividing and resting cancer cells and the ability to achieve significantly higher maximal dosing when the liver is isolated from systemic circulation. This also holds truth for isolated limb infusion for in-transit cutaneous melanoma of the extremity. Given the parallels between the two procedures, ongoing advances in Isolated Limb Infusion (ILI) may show promise in IHP. One such advance is the addition of systemic ADH-1, a disruptor of N-cadherin adhesion complexes, to regional melphalan. Response outcomes have been mixed, but there may be a role for ADH-1 in melanoma sensitization as a component of multimodality treatment [7,8]. Lastly, the engineered oncolytic virus Talimogene Laherparepvec (T-VEC) has shown promise as intratumoral therapy. Proposed mechanism of action involves both a lytic effect on infected tumor cells and a pro-immune effect via downstream signaling [9]. Results of the OPTiM Trial comparing intralesional T-VEC *vs.* subcutaneous GM-CSF showed that patients treated with T-VEC had improved durable response (16.3% *vs.* 2.1%) and improved overall response rates (26.4% *vs.* 5.7%) [10]. Ongoing clinical trials of visceral injection of intralesional therapies are being conducted but remain in early phases.

Conclusion

The growing body of literature suggests that intra-arterial hepatic perfusion for malignant melanoma of cutaneous origin is a treatment modality with great potential. IHP improves hepatic and overall progression free survival and may be a viable option for stage IV disease limited to the liver. The encouraging outcomes for this unique cohort are limited, and ongoing accrual of cutaneous melanoma patients into clinical trials will strengthen this conclusion. Concerns regarding morbidity and mortality of IHP are well founded and any risk/benefit calculation should be carefully determined prior to offering or proceeding with such therapy. However, with improvements in technique and hemofiltration systems, hematologic complications should continue to improve. There is a growing arsenal of novel therapies and multimodality regimens, and such results offer hope for continued advancement.

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