Hyperthermic Isolated Hepatic Perfusion Using Melphalan for Patients with Ocular Melanoma Metastatic to Liver

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ABSTRACT

Purpose: Liver metastases are the sole or life-limiting component of disease in the majority of patients with ocular melanoma who recur. Because median survival after diagnosis of liver metastases is short and no satisfactory treatment options exist, we have conducted clinical trials evaluating isolated hepatic perfusion (IHP) for patients afflicted with this condition.

Experimental Design: Twenty-nine patients (male: 14, female: 15; mean age, 49 years) with unresectable liver metastases from ocular melanoma were treated with a 60-min hyperthermic IHP using 1.5 mg/kg of melphalan (mean total dose 105 mg). Via laparotomy, perfusion inflow was established with a cannula in the gastroduodenal artery and outflow via a cannula positioned in an isolated segment of the retrohepatic inferior vena cava. Portal and infra-renal inferior vena cava blood flow was shunted externally to the auxiliary vein using a veno-veno bypass circuit. Patients were assessed for toxicity, radiographic response, and survival.

Results: There was no treatment related mortality and transient grade 3/4 hepatic toxicity was observed in 19 patients (65%). Mean length of operation and hospital stay was 8.3 h and 10 days, respectively. There were 3 (10%) complete responses (duration: 12, 14+, 15 months) and 15 partial responses (52%; mean duration: 10 months). The initial site of disease progression included liver in 17 of 25 patients (68%) who recurred. At a median follow-up of 30.7 months the median actuarial progression-free and overall survivals were 8 and 12.1 months, respectively.

Conclusions: IHP with melphalan alone results in significant regression of established liver metastases for patients with ocular melanoma. However, after IHP, disease progression is most commonly observed in the liver, and survival after disease progression is short. On the basis of a pattern of tumor progression predominantly in liver, continued clinical evaluation of hepatic directed therapy in this patient population is justified.

INTRODUCTION

There are ~54,200 new cases of malignant melanoma diagnosed annually in the United States (1), of which 3–6% are primary ocular melanoma representing up to 4,000 new cases/year (2). Metastatic disease occurs in 40–60% of patients with ocular melanoma (3), and unresectable hepatic metastases represent the life-limiting component of progressive disease in ~80% of patients with ocular melanoma in this setting (3–5). Even with aggressive treatment, the median survival after liver metastases from ocular melanoma are diagnosed is between 2 and 7 months and 1-year survival is ~10% (5). Therapeutic options are limited and none have been shown to meaningfully alter the natural history of metastatic disease (5).

A variety of chemotherapeutic agents such as dacarbazine and cisplatin or immunotherapeutic agents such as IFN, interleukin 2, or monoclonal antibodies, and the antiangiogenic agent, thalidomide, have been administered either alone or in combinations and have not been associated with remarkable antitumor efficacy (6–11). Combination regimens using chemotherapy and cytokines for patients with metastatic ocular melanoma result in response rates of no >20% (12).

Regional treatment strategies for patients with unresectable hepatic metastases from ocular melanoma have been developed because the natural history of this disease justifies measures to control tumor progression in the liver. The best results with hepatic directed therapy have been with chemoembolization, intra-arterial chemotherapy, and isolated hepatic perfusion (IHP). Chemoembolization is performed using percutaneously placed catheters to administer chemotherapy followed by infusion of absorbable or nonabsorbable particles into the hepatic artery. Mavligit et al. (13) reported results of chemoembolization using cisplatin for patients with this condition and observed a 50% response rate and a median survival time of 12 months. Leyvraz et al. (14) treated 31 patients with monthly intra-arterial fotemustine (100 mg/m2) over 4 h via the hepatic artery. The overall response rate (all partial) was 40%, the median duration of response was 11 months, and overall survival was 14 months.

IHP has been under clinical evaluation for ~45 years but has not gained widespread application for a number of reasons. First, it is a complex therapy to administer, and, in initial studies of IHP, there was remarkable morbidity associated with the procedure and no clearly documented efficacy (15). More recently, we and others (16, 17) have reported results of IHP using melphalan alone or in combination with tumor necrosis factor (TNF) for patients with a variety of tumor histologies. We have reported our initial results in 22 patients with IHP using melphalan with or without TNF for patients with metastatic ocular...
melanoma to the liver and observed an overall response rate of 62% with a median duration of hepatic response of 9 months (18). However, a number of treatment parameters that may have influenced outcomes were used in that series of patients, including two doses of melphalan (1.5 and 2 mg/kg), 1 mg of TNF in 11 patients, and perfusion via the hepatic artery and portal vein in 5 patients. The current article analyzes outcome of 29 consecutively treated patients using identical treatment parameters derived from previous feasibility and dose-seeking studies, which includes a 60-min hyperthermic IHP with 1.5 mg/kg melphalan alone with perfusion inflow via the hepatic artery.

**MATERIALS AND METHODS**

**Patient Population.** Twenty-nine patients with metastatic unresectable biopsy-proven ocular melanoma confined to liver underwent IHP between December 1997 and August 2002. Patients were treated on three consecutively conducted clinical research protocols that were approved by the Institutional Review Board of the National Cancer Institute. Twenty-one of the patients in this analysis underwent treatment on a Phase II study evaluating efficacy of a 60-min hyperthermic IHP using 1.5 mg/kg melphalan alone based on ideal body weight and with a minimum total dose of 90 mg and a maximum total dose of 120 mg. Eight additional patients who were enrolled and treated on a previously conducted Phase I (n = 6) or Phase II (n = 2) study and who received IHP using the same treatment parameters as the last 21 were included. Standard staging studies including computed tomography scan of the chest, abdomen, and pelvis, and who received IHP using the same treatment parameters as the last 21 were included. Standard staging studies including computed tomography scan of the chest, abdomen, and pelvis, magnetic resonance imaging (MRI) of the liver, and as clinically indicated, brain imaging or bone scan were performed. Eligibility criteria included Eastern Cooperative Oncology Group performance status of 0 or 1, a serum bilirubin < 2.0 mg/dl, a platelet count ≥ 150,000/ml, and a serum creatinine ≤ 1.5 mg/dl.

**Toxicity and Response.** All patients were evaluated 6 weeks after treatment and at 3–4 month intervals thereafter. Responses were scored by comparing gadolinium-enhanced T1- or T2-weighted images on MRI scans or contrast-enhanced computed tomography scans during follow-up with pretreatment images. A complete response was defined as the disappearance of all radiographic evidence of disease based on computed tomography scan or MRI scan. A partial response was defined as a ≥50% decrease in the sum of the products of perpendicular diameters of all measurable lesions of 1 month’s duration without progression (>25%) of any site; a minor response was defined as a 25–49% decrease in the sum of the products of the perpendicular diameters of all measurable lesions. Any patient with less than a partial response or a response of <4 weeks duration was considered a nonresponder. Appearance of new lesions or >25% increase in the products of the perpendicular of known lesions after a partial response or a complete response was scored as progressive disease. Because the therapy was limited to liver and the entry criteria limited treatment to patients with hepatic only disease, responses were assessed only on the measurable hepatic lesions. New lesions occurring outside the liver were scored separately from new lesions occurring within the liver.

The National Cancer Institute Common Toxicity Criteria version 2.0 was used for toxicity and adverse event scoring. A copy of the Common Toxicity Criteria version 2.0 is available online. Acute systemic toxicity that corrected within 24 h of IHP or hepatic toxicity that corrected within 7 days of hepatic perfusion were considered treatment related.

**IHP.** The technique of IHP was performed as described previously (16, 19). Briefly, via a laparotomy the liver was extensively mobilized, the inferior vena cava was isolated, and the porta hepatis structures were completely dissected and prepared for cannulation. After heparinization, cannulae are inserted into the saphenous, portal, and axillary veins for venovenous bypass, and the hepatic perfusion circuit is connected to cannulae positioned in the gastroduodenal artery and an isolated segment of retrohepatic inferior vena cava. Melphalan was obtained from Glaxo-Wellcome (Research Triangle Park, NC), and 1.5 mg/kg were added over 3–5 min to the arterial inflow line of the perfusion circuit and IHP continued for 60 min. After IHP, the liver was flushed with crystalloid and colloid solution, and physiological blood flow was reestablished promptly to the liver.

**Statistical Analysis.** An analysis of factors relating to response and survival was performed in all patients. Patients were categorized as responders (partial or complete) or nonresponders, and continuously measured parameters were evaluated for their association with response using the Wilcoxon rank-sum test. Gender was compared with response using the χ² test. Logistic regression analysis was used to determine which factors were independently associated with response.

Survival was calculated from the on-study date until date of death or last follow-up. The on-study date represented the day on which the patient signed informed consent and was registered on the protocol, which was within 2 days of IHP. The probability of survival was calculated using the Kaplan-Meier method, and the significance of the difference between pairs of Kaplan-Meier curves was calculated using the Mantel-Haenszel procedure (20, 21). Initially, continuously measured parameters were divided into quartiles to form groups for evaluation; subsequently, data were pooled when cutoffs in the data were identified. The Cox proportional hazards model was used to identify which factors were jointly significant in association with survival (22).

All data are presented as mean and range unless otherwise specified. A comparison with a two-tailed P ≤ 0.05 was considered statistically significant, and the Ps have not been adjusted for multiple comparisons.

**RESULTS**

Demographics and tumor characteristics of the patient population are shown in Table 1. There was an equal male to female distribution and the majority had not received prior therapy for their condition. The time between initial diagnosis of the primary melanoma and IHP treatment ranged from 4 months to 10 years, which highlights the remarkable variability in the biology of this malignancy as all patients were referred within a month.
or two of diagnosis of liver metastases. Of note, the number of metastatic lesions in the liver was assessed at laparotomy, and invariably, the number of metastatic lesions was greater what was imaged on contrast-enhanced computed tomography and T-1-weighted gadolinium-enhanced MRI scans. Many metastases <5 mm in diameter and diffusely present in the hepatic parenchyma were frequently encountered, and in some circumstances, the malignancy spread as a diffusely infiltrating process throughout the hepatic parenchyma (Fig. 1). The number of metastatic lesions was counted at laparotomy, and the average number of 25 underestimates the true number because those individuals who had >50 were scored as ≥50 nodules. The diameter of the largest lesion was based on trans-axial images of the T-1-weighted gadolinium-enhanced MRI, which usually provided the most discrimination in determining tumor margin from unaffected hepatic parenchyma. Similarly, the percent hepatic replacement by tumor was estimated by viewing the sequential axial views on the MRI scan. One-third of patients had >25% hepatic replacement by tumor.

The mean total melphalan dose administered within the perfusion circuit was 105 mg based on a dosing schema of 1.5 mg/kg ideal body weight. However, the minimum and maximum total doses administered in the protocols were 90 and 120 mg, respectively. Mean flow rates during IHP were 750 ml/min and stable throughout the procedure consistent with our previous experience (23). The mean perfusion pressure of 138 mm Hg (range, 105–237 mm Hg) does not reflect the actual pressure within the hepatic artery proper but rather the pressure generated by flows through the 3-mm arterial inflow cannula positioned in the gastroduodenal artery. The hepatic artery pressure as estimated by palpation at regular intervals during treatment was usually lower and estimated to be between 80 and 100 mm Hg. The mean veno-veno bypass flow rate was 1600 ml/min, which represented significant systemic venous return back to the heart during treatment and contributed to the stable hemodynamic profile of the patients during treatment (23). Hepatic temperature was assessed with two transhepatic temperature probes placed in the left and right lobes of the liver, as well as a flexible

Table 1  Demographic and tumor characteristics of patients with hepatic metastases from ocular melanoma undergoing isolated hepatic perfusion (IHP)

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>29</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr, range)</td>
<td>49 (26–73)</td>
</tr>
<tr>
<td>Female:Male</td>
<td>15:14</td>
</tr>
<tr>
<td>Prior therapy for liver metastases</td>
<td>None:Interferon:Systemic chemotherapy</td>
</tr>
<tr>
<td>Prior surgery for liver metastasis</td>
<td>None:4–&gt;50</td>
</tr>
<tr>
<td>Time between initial diagnosis* and IHP (mos)</td>
<td>Median:Mean</td>
</tr>
<tr>
<td>No. of metastatic lesions</td>
<td>25:35</td>
</tr>
<tr>
<td>Diameter of the largest lesion (cm)</td>
<td>5.6 (2–14)</td>
</tr>
<tr>
<td>% liver replaced by tumor</td>
<td>&lt;25%:25–50%:50%</td>
</tr>
<tr>
<td>% liver replaced by tumor</td>
<td>20 (69%):8 (28%):1 (3%)</td>
</tr>
</tbody>
</table>

* Diagnosis of primary tumor.

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Fig. 1 Intraoperative photograph taken from a patient with metastatic ocular melanoma to liver. The right lobe is reflected anteriorly as noted by the gall bladder (GB) inferiorly. Diffuse pigmented and nonpigmented metastases and larger infiltrative lesions (arrows) in the right lobe and lateral to the falciform ligament (FL) are present.
thermister probe that was advanced into the portal venous system during treatment. Prompt and uniform increase in hepatic parenchyma temperatures reflected uniform delivery of the perfusate through the entire hepatic parenchyma. Mobilization of the liver and preparation of the vascular structures for hepatic perfusion accounted for the major portion of the operative time (mean time, 8.3 h; range, 6–10 h). The perfusion itself lasted for 60 min and the decannulation procedure was typically quite short. However, we feel that the operative preparation of the liver is important to ensure no leak of perfusate during treatment. Consistent with our previous experience the mean hospitalization was ~10 days and 19 patients (65%) had reversible grade 3 or greater hepatic toxicity.

All responses were assessed by standard radiographic criteria, and all 29 patients were assessable for response. There were three radiographic complete responses (10%; Fig. 2) and 15 partial responses (52%; Table 2, Fig. 3). Gender was not associated with response ($p_2 = 0.32$). Table 3 presents the results of analyses relating continuously measured parameters to response. As shown in the table, both lactate dehydrogenase (LDH) at baseline as well as the size of the largest metastasis were individually associated with response. Logistic regression analysis was performed and was able to demonstrate that when both factors were considered for evaluation, only baseline LDH remained as significantly associated with response. Depending on the error probabilities one is willing to accept, the LDH cutpoint of ~275 could be used to classify patients into those who were likely to respond (<275) versus those unlikely to respond. For example, of 27 patients with data, 16 of 20 (80%) with LDH < 275 responded, whereas 7 of 7 with LDH > 275 did not. Thus, baseline LDH appears to identify patients reasonably well who are likely to respond.

The actuarial median hepatic progression-free survival in 18 patients who initially had a response to treatment was 12 months. Fig. 4 shows overall survival in the cohort of 29 patients. The median time to disease progression at any site was 8 months, and the median overall survival was 12.1 months (range 3 to 39+ months). Twenty-five of 29 have had recurrence; site of first recurrence was liver in 14, systemic in 8, and both in 3.

Results of an exploratory univariate survival analysis identified several factors that appeared to be associated with survival, including baseline LDH (100–160 versus 161+), number of metastases (1–20 versus 21–60), size of largest metastasis.

Table 2  Results of treatment in patients undergoing isolated hepatic perfusion for liver metastases from ocular melanoma

<table>
<thead>
<tr>
<th>n</th>
<th>Complete response</th>
<th>Duration (mos)</th>
<th>Partial response</th>
<th>Duration (mos)</th>
<th>Follow-up status</th>
<th>Follow-up time (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>29</td>
<td>3 (10%)</td>
<td>12, 14+, 15</td>
<td>15 (52%)</td>
<td>10 (5–22)</td>
<td>AWD*</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DOD</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* AWD, alive with disease; DOD, dead of disease.
(1.5–7 versus 7.5+ cm), and percent hepatic replacement. Only those factors that were associated with a marginal statistical significance in a univariate analysis (unadjusted $P < 0.05$) were evaluated in a Cox model. Because trends in survival were not necessarily linear over the four quartiles used in the initial exploratory univariate survival analyses, for the Cox models, the data were dichotomized at the cutpoint that yielded the most significant results in the univariate analysis. As a result, the Cox model $P$-values may be biased because the cutpoints were selected based on an examination of the same data that went into the model. However, the Cox models indicated clearly that the only factor that was significantly associated with survival when all of the above factors were taken into consideration was baseline LDH (0–160 versus $>$160, Fig. 4). Having a baseline LDH $\geq$ 161 was associated with a hazard ratio of 17.1 with an associated 95% confidence interval from 2.2 to 130.9 ($P = 0.0062$).

Thus, the magnitude of the baseline LDH is very useful to identify the likely survival course of patients with ocular melanoma metastatic to the liver who are treated with IHP.

**DISCUSSION**

These data show that IHP with hyperthermia and melphalan can result in significant regression of metastatic ocular melanoma. However, only baseline LDH was found to be a significant predictor of survival when all other factors were considered.

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**Table 3** Relationship between response and continuously measured parameters in patients undergoing isolated hepatic perfusion (IHP)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>Mean</th>
<th>n</th>
<th>SE</th>
<th>Min.</th>
<th>Med.</th>
<th>Max.</th>
<th>$P_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline lactate dehydrogenase</td>
<td>Nonresp.</td>
<td>548.0</td>
<td>11</td>
<td>167.2</td>
<td>154</td>
<td>335.0</td>
<td>1993</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Resp.</td>
<td>173.0</td>
<td>16</td>
<td>10.9</td>
<td>101</td>
<td>159.5</td>
<td>275</td>
<td>0.0009</td>
</tr>
<tr>
<td>No. of metastases</td>
<td>Nonresp.</td>
<td>28.7</td>
<td>11</td>
<td>5.8</td>
<td>4</td>
<td>25</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Resp.</td>
<td>28.4</td>
<td>16</td>
<td>4.0</td>
<td>2</td>
<td>25</td>
<td>55</td>
<td>0.87</td>
</tr>
<tr>
<td>Size of largest metastases</td>
<td>Nonresp.</td>
<td>8.3</td>
<td>11</td>
<td>0.7</td>
<td>4</td>
<td>6</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Resp.</td>
<td>5.1</td>
<td>18</td>
<td>0.6</td>
<td>1.5</td>
<td>4.4</td>
<td>12</td>
<td>0.0048</td>
</tr>
<tr>
<td>Percentage of hepatic replacement</td>
<td>Nonresp.</td>
<td>22.7</td>
<td>11</td>
<td>4.9</td>
<td>5</td>
<td>20</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Resp.</td>
<td>15.5</td>
<td>18</td>
<td>2.2</td>
<td>5</td>
<td>15</td>
<td>40</td>
<td>0.25</td>
</tr>
<tr>
<td>Melphalan dose</td>
<td>Nonresp.</td>
<td>98.2</td>
<td>11</td>
<td>3.4</td>
<td>81</td>
<td>95</td>
<td>120</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Resp.</td>
<td>105.7</td>
<td>18</td>
<td>2.8</td>
<td>90</td>
<td>106.5</td>
<td>135</td>
<td>0.11</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>Nonresp.</td>
<td>49.5</td>
<td>11</td>
<td>4.0</td>
<td>26</td>
<td>47</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Resp.</td>
<td>47.1</td>
<td>18</td>
<td>2.2</td>
<td>27</td>
<td>46.5</td>
<td>64</td>
<td>0.65</td>
</tr>
<tr>
<td>Months from diagnosis to IHP</td>
<td>Nonresp.</td>
<td>48.2</td>
<td>10</td>
<td>11.1</td>
<td>7</td>
<td>42.5</td>
<td>125</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Resp.</td>
<td>28.2</td>
<td>18</td>
<td>4.2</td>
<td>4</td>
<td>23.5</td>
<td>70</td>
<td>0.13</td>
</tr>
</tbody>
</table>

*a* Upper limit of normal: 226 units per liter.

*b* nonresp., nonresponders; resp., responders.
melanoma to the liver in the majority of patients treated. However, the duration of response is variable and time to disease progression at any site was relatively short (8 months). Of note, hepatic recurrence was observed in two-thirds of patients who did recur and tended to be at new sites of disease rather than regrowth of established lesions. These data are consistent with the observation that in individuals with in-transit extremity melanoma who have experienced a complete response to isolated limb perfusion using melphalan, with or without TNF, recurrences in the extremity are most commonly at new site of disease (24). Taken together, these data suggest that microscopic tumor deposits that do not have a well-established neovascularature may be somewhat resistant to isolation perfusion in general.

In this cohort, there was no treatment-related mortality, although the toxicity associated with IHP can be substantial. Overall the treatment related mortality in recently reported series of patients undergoing IHP is <5% (15). We have previously shown that the use of TNF in IHP is associated with some additional regional and systemic toxicity compared with IHP with melphalan alone, but the toxicities are transient and clinically straightforward to manage (25). The systemic toxicities may be because of the production of proinflammatory cytokines such as interleukin 6 and interleukin 8 in the liver as a consequence of high-dose TNF administration that result in a transient hyperdynamic cardiovascular profile for the first 12–24 h after treatment. The greater question as to the role of TNF in isolated organ perfusion for in-transit extremity melanoma or unresectable hepatic metastases has not been defined in random assignment trials. We have reported initial results in 22 patients with IHP using melphalan with or without TNF for patients with metastatic ocular melanoma to the liver and observed an overall response rate of 62% with a median duration of hepatic response of 9 months (18). However, various treatment parameters, as dictated by the Phase I trial design, were used in that series of patients, including two doses of melphalan (1.5 and 2 mg/kg), 1 mg of TNF in 11 patients, and perfusion via the hepatic artery and portal vein in 5 patients. Outcomes from 6 patients in that series are included in this study.

IHP with melphalan alone appears to have comparable outcome with respect to response and survival with other reported regional treatment strategies for patients with unresectable metastases from ocular melanoma. Mavligit et al. (13) reported an objective response rate of 50% and an overall survival of 1 year using chemoembolization, and Leyvraz et al. (14) reported a 40% response rate and 11-month overall survival using intra-arterial fotemustine (13, 14). Although all these strategies can result in regression of hepatic metastases, additional treatment must be integrated to prolong duration of response and prevent progression of occult systemic disease. To that end, options are somewhat limited. Combination chemotherapy with cytokine administration results in a 20% partial response rate for patients with this condition (12).

Our data are consistent with others who have shown that baseline LDH is a significant independent prognostic factor with respect to survival (14, 26). Our data confirm that observation and also demonstrate that baseline LDH is independently associated with response. We noted that baseline LDH values < 275 were associated with an 80% response rate, whereas all 7 individuals with baseline LDH values ≥ 275 did not have any response to therapy. In the Cox proportional hazards model, we found that a baseline LDH of ≤ 160 was associated with a significantly better survival than in individuals with baseline LDH values > 160. Therefore, baseline LDH appears to be a very useful tool to identify the likely response or survival outcome for patients with ocular melanoma metastatic to liver who are treated with IHP.

In conclusion, IHP with melphalan appears to warrant continued clinical evaluation for patients with hepatic metastases for ocular melanoma. The role of TNF in IHP for this
condition has not been definitively established. Additional agents administered via the perfusate or systemically after hepatic perfusion are required to meaningfully improve the outlook for patients afflicted with this condition.

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