Background
- The prognosis for patients with liver-dominant metastatic melanoma is dismal with a survival time of approximately 2 months.
- Recently introduced drugs are limited by toxicity, long induction periods (e.g., vemurafenib) or applicability (e.g., dabrafenib - vemurafenib is an inhibitor of BRAF mutations, but these mutations do not occur in cutaneous melanoma and are evident only in a subset of patients with cutaneous melanoma (40% to 60%).
- There are no agents meaningfully altering the natural history of metastatic melanoma.
- Regional therapies deliver high-dose chemotherapy to the whole organ while limiting untoward systemic toxicity.

Chemosaturation-PHP*
- Isolates the liver from the systemic circulation using a system of special catheters introduced percutaneously.
- Infusion via the proper hepatic artery allows perfusion of the liver without systemic administration of chemotherapy.
- The procedure allows for considerable dose escalation to the cancer-burdened organ and provides treatment for both limited extra-hepatic disease.
- Regional hepatic infusion is a double-balloon catheter positioned the extrahepatic vasculature, forced to remove chemotherapeutic agents, and then returned to the systemic circulation.

The procedure is minimally invasive and repeatable.

Study endpoints:
- Randomized, open-label, multicenter phase 3 study.
- Study endpoints primary:
  - Hepatic progression-free survival (hPFS) (RECIST)
  - Time from randomization to hepatic disease progression or death.
- Secondary:
  - Hepatic objective response rate
  - Overall survival

Patient population
- Male/female: 61/39
- Median age: 59 years (range 19-80)
- ECOG class: 0: 11/44, 1: 33/44
- Performance status: 0: 11/44, 1: 33/44
- BAC constituted: active treatment (n=39), supportive care/watchful waiting (n=10).

Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PH-P randomized (n=44)</th>
<th>BAC only (n=21)</th>
<th>BAC to PHP crossover (n=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (y)</td>
<td>59 (42-72)</td>
<td>66 (51-73)</td>
<td>62 (46-70)</td>
</tr>
<tr>
<td>Primary tumor site</td>
<td>Dural</td>
<td>89/85</td>
<td>BAC-PHP randomized (n=44)</td>
</tr>
<tr>
<td>Palmar</td>
<td>11/12</td>
<td>11/12</td>
<td>BAC only (n=21)</td>
</tr>
<tr>
<td>Cutaneous</td>
<td>86/82</td>
<td>86/82</td>
<td>BAC to PHP crossover (n=28)</td>
</tr>
<tr>
<td>Hepatic tumor burden</td>
<td>≤50%</td>
<td>77/70</td>
<td>77/70</td>
</tr>
<tr>
<td>&lt;50%</td>
<td>13/12</td>
<td>13/12</td>
<td>13/12</td>
</tr>
<tr>
<td>75%</td>
<td>5/5</td>
<td>5/5</td>
<td>5/5</td>
</tr>
<tr>
<td>100%</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>&lt;2 seconds</td>
<td>8/8</td>
<td>8/8</td>
</tr>
<tr>
<td>Efector bilirubin</td>
<td>≤3.0 mg/dL</td>
<td>21/33</td>
<td>21/33</td>
</tr>
<tr>
<td>Interior bilirubin</td>
<td>≤3.0 mg/dL</td>
<td>52/53</td>
<td>52/53</td>
</tr>
<tr>
<td>ALT increased</td>
<td>10/8</td>
<td>8/8</td>
<td>8/8</td>
</tr>
<tr>
<td>AST increased</td>
<td>30/8</td>
<td>12/12</td>
<td>12/12</td>
</tr>
<tr>
<td>Blood albumin decreased</td>
<td>8/8</td>
<td>8/8</td>
<td>8/8</td>
</tr>
<tr>
<td>Blood calcium decreased</td>
<td>10/8</td>
<td>10/8</td>
<td>10/8</td>
</tr>
<tr>
<td>Blood bilirubin increased</td>
<td>10/8</td>
<td>10/8</td>
<td>10/8</td>
</tr>
</tbody>
</table>

Melanoma-PHP
- 3.5 mg/m2 as a 30-minute intra-arterial infusion
- an additional 30 minutes of extracorporeal filtration at end of infusion (sham control)
- allowed up to 8 treatments, repeated every 4–6 weeks.
- Best alternative care (BAC): investigator’s choice of systemic, regional or other appropriate therapy.
- crossover to PHP permitted after hepatic progression (if patients still meet eligibility criteria).

Treatments

- BAC: constituted:
  - active treatment (n=39),
  - supportive care/watchful waiting (n=10).
- Active treatments:
  - Temozolomide (n=20)
  - supportive care (n=19).

BAC treatments

- BAC constituted:
  - active treatment (n=39),
  - supportive care/watchful waiting (n=10).
- Active treatments:
  - Temozolomide (n=20)
  - Chemoradiation (n=10).
- Ynithromycin (n=3)
- Systemic chemotherapy (n=6).

Conclusions

- Efficacy of melphalan PHP in BAC-PHP crossover patients was consistent with that seen in PHP randomized patients with hepatic metastases from cutaneous melanoma.
- Crossover from BAC to PHP after hepatic disease progression led to a median 14 months survival advantage vs BAC alone.
- The safety profile of melphalan PHP in BAC-PHP crossover patients was similar to that seen in PHP randomized patients.
- PHP delivery of melphalan is a new treatment option for unresectable metastatic melanoma in the liver.

Study investigators

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References


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Percutaneous Hepatic Perfusion (PHP) with Melphalan versus Best Alternative Care (BAC) in Patients with Unresectable Hepatic Metastases from Melanoma: A Post-hoc Analysis of PHP-randomized vs BAC-to-PHP versus BAC-only Patients

H. Richard Alexander, Jr. on behalf of the CS-PHP Investigators (University of Maryland School of Medicine, Baltimore, MD)