Background: In patients with hepatic metastases from solid-organ malignancies, surgical resection may be a potentially curative option, but it is not possible in most cases. Chemosaturation with percutaneous hepatic perfusion was developed for the management of unresectable metastases to the liver.

Methods: Relevant medical literature was summarized with regard to the outcomes and limitations of chemosaturation with percutaneous hepatic perfusion.

Results: Six articles were identified that contained data on 91 individuals who received chemosaturation with percutaneous hepatic perfusion. More than 60% of these study patients were diagnosed with ocular melanoma. The overall response rate was 48% and the rate of disease control was 90%. Chemosaturation with percutaneous hepatic perfusion improved the rates of overall and hepatic progression-free survival (PFS). The data are limited but suggest that the rate of PFS was improved in study patients with isolated melanoma hepatic metastases who received chemosaturation with percutaneous hepatic perfusion compared with those assigned to standard care.

Conclusions: Our results suggest that chemosaturation with percutaneous hepatic perfusion produces favorable tumor response rates in select individuals with unresectable hepatic metastases from multiple primary cancers, particularly ocular and cutaneous melanomas. Data from a single randomized clinical trial have also shown that chemosaturation with percutaneous hepatic perfusion can affect hepatic PFS in certain patients.

Introduction

Hepatic metastases from solid-organ malignancies portend a poor prognosis in most cases and are an important determinant to survival. Complete surgical resection might represent a curative option in patients with isolated hepatic metastases, but resection is not possible in most patients because of the number, location, or size of the hepatic metastases. Likewise, poor hepatic functional reserve limits standard therapeutic options such as resection.

The liver is the predominant site of metastasis for ocular melanoma, colorectal cancer, and gastrointestinal neuroendocrine tumors. In persons with ocular melanoma, the sole site of metastatic disease in up to 50% of individuals is the liver after treatment of the primary cancer. The rate of median survival in persons with hepatic metastases from ocular melanoma is less than 9 months. Hepatic metastases will develop in 20% to 40% of individuals with colorectal cancer; the median survival rate in these cases is approximately 2 years. Neuroendocrine tumors metastasize to the liver in 25% to 90% of individuals, and the 5-year survival rate of those with liver metastases is 40% compared with a rate that exceeds 75% in those whose cancer does not metastasize to the liver. Hepatic metastases can also co-occur with many other malignancies, such as breast cancer, renal cell cancer, cutaneous melanoma, and soft-tissue sarcoma. For patients with unresectable liver-dominant disease, multiple strategies for liver-directed therapy have been developed, including hepatic artery chemomobilization, radioactive bead embolization, hepatic arterial infusion, isolated hepatic infusion, and chemosaturation with percutaneous hepatic perfusion.

In Europe, chemosaturation with percutaneous hepatic perfusion was commercially launched in 2012, and a second-generation, high-efficiency filter was approved for use in conjunction with a proprietary hepatic delivery system that same year. However, the US Food and Drug Administration has not approved chemosaturation with percutaneous hepatic perfusion for use in the United States.

Chemosaturation with percutaneous hepatic perfusion is a minimally invasive, repeatable, regional
therapy in which a high dose of melphalan is directly infused into the liver via the hepatic artery using a percutaneous approach.\textsuperscript{5,8,10} The liver is isolated from the systemic circulation by a double-balloon catheter inserted through the femoral vein. Chemotherapy-infused blood is then diverted through the arterial catheter via an extracorporeal pump circulation and is then filtered and returned to the patient via venovenous bypass and the jugular vein.

**Methods**

Authors reporting on the utility of percutaneous hepatic perfusion for any malignancy met our inclusion criteria. Only literature written in English was reviewed. If data were reported in combination with other hepatic-directed therapies, only the data reported for chemosaturation with percutaneous hepatic perfusion were included. Exclusion criteria included 5 or fewer case patients or data not evaluated in a peer-reviewed fashion.

For literature from the same institution, original deidentified data were requested to remove duplicate study patients from multiple reports. Once all study patients were determined to be unique, we analyzed the response and disease control rates. The authors of each individual report determined the response rate. We defined the disease control rate as the summation of complete response, partial response, and stable disease.

**Literature Review**

We identified 6 articles from the medical literature.\textsuperscript{7,8,10-13} “The report from Abbot et al\textsuperscript{11} is an update of the study results from Forster et al,\textsuperscript{7} so these data are combined in our review. Likewise, some study patients reported in Hughes et al\textsuperscript{10} were included in Abbot et al,\textsuperscript{11} so we also omitted those case patients from inclusion in our review of the results from Abbot et al\textsuperscript{11} and Forster et al.\textsuperscript{7} No data from Pingpank et al\textsuperscript{14} were utilized because this report included preliminary results from a randomized control trial eventually published by Hughes et al.\textsuperscript{10}

**Procedural Details and Management**

Chemosaturation with percutaneous hepatic perfusion is performed in an interventional radiology suite or operating room with imaging capability under general anesthesia (Fig). A catheter is first manipulated into the hepatic artery via the femoral artery followed by catheterization of the internal jugular and femoral veins utilizing ultrasonography and fluoroscopic guidance. A multilumen, double-balloon catheter is inserted via the femoral vein into the inferior vena cava and positioned across the hepatic veins. The balloons are inflated to isolate hepatic venous outflow from the systemic circulation.

Hepatic artery angiography is obtained to confirm the absence of collateralization or extrahepatic blood flow from the proper hepatic artery. If the catheter is placed in the common hepatic artery, or there is back flow into the gastroduodenal artery, then the gastroduodenal artery is embolized to avoid the systemic circulation of chemotherapy. Likewise, unnamed collaterals or other noncritical arteries are also embolized. Identification of accessory or replaced hepatic arteries are identified (if not done so already) and used for hepatic chemoperfusion if needed.

Blood from the hepatic veins then exits the liver through a channel in the multilumen catheter and is extracorporeally filtered before it is returned to the circulation to limit systemic toxicity from chemotherapy. The second-generation extracorporeal filtration system extracts greater than 90% of melphalan before returning the filtered blood back to the patient through the internal jugular vein to minimize systemic drug delivery and the associated adverse effects.\textsuperscript{15}

The procedure is described elsewhere in detail, but high-dose melphalan 3 mg/kg is administered unless dose-limiting toxicities have been previously demonstrated.\textsuperscript{7,10} All procedures are performed under general anesthesia with heparin-induced systemic anticoagulation performed after catheterizations. Prior to introducing chemotherapy, contrast angiography is obtained of all the isolated sections to confirm the absence of leakage and to verify isolation from the systemic circulation. Melphalan is administered to the liver in a split fashion by advancing the hepatic artery catheter into the left and right hepatic arteries. Unless anatomical variations exist, 60% of the drug is given via the right hepatic artery and 40% is given via the left hepatic artery. Treatment is administered for 30 minutes, followed by an additional 30 minutes of venovenous bypass to allow for melphalan washout. During the treatment, patients undergo clinically significant changes in pulse and blood pressure that require aggressive support with intravenous fluids and vasoactive drugs such as phenylephrine, norepinephrine, and vasopressin. This is especially the case early on during the procedure when the filters are opened, and vasoactive support is weaned off as the procedure continues. After the procedure is completed, protamine is used to reverse heparin.

Catheters and intravascular sheaths are removed after baseline laboratory blood values (complete blood count, platelet count, activated clotting time, prothrombin time, and partial thromboplastin time) have normalized, with transfused fresh-frozen plasma, platelets, cryoprecipitate, and fibrinogen (blood proteins removed by the filtration system) given as needed. All patients receive 10 units of cryoprecipitate, because the real-time measuring of individual clotting proteins found in cryoprecipitate can be difficult, cumbersome, and is not routinely performed. However, platelets, red blood cells, and fresh-frozen plasma are transfused
based on postprocedure laboratory values. Pressure is held at each vascular access point for 45 minutes, and patients are then observed for 1 day in the intensive care unit. Typically, patients are discharged home on postoperative day 1, provided that laboratory values (complete blood count, renal and hepatic function tests) have returned toward baseline.

Patients are postoperatively monitored with twice-weekly laboratory studies (complete blood count, renal and hepatic function tests) for up to 4 weeks. Granulocyte-stimulating factor is used as needed for neutropenia, and, if present, anemia and thrombocytopenia are treated with transfusions. At our institution, we obtain repeat liver imaging 6 weeks following treatment with a triple-phase liver protocol for computed tomography or contrast-enhanced magnetic resonance imaging, also per the liver protocol. Positron emission tomography/computed tomography is used to evaluate disease response and for other sites of metastatic disease and functional disease burden. Magnetic resonance imaging of the brain is also obtained in cases of melanoma to rule out central nervous system metastases.

Outcomes

Increased Experience

In 2004, van Etten et al. published a report of a small series of 10 study patients with colorectal and ocular melanoma hepatic metastases who underwent chemosaturation with percutaneous hepatic perfusion. Overall, these patients had a disease control rate of 80% and a 30-day mortality rate of 5%. The median number of treatments per study patient was not reported. The researchers compared chemosaturation with percutane-
ous hepatic perfusion and open isolated hepatic perfusion, which has significantly higher morbidity and mortality rates.\textsuperscript{9,12} Because open isolated hepatic perfusion has risks and, due to the development of percutaneous intravascular techniques, van Etten et al\textsuperscript{12} recommended percutaneous hepatic perfusion without abdominal incision as a potential therapeutic option for patients with unresectable hepatic malignancies.\textsuperscript{12}

Vogl et al\textsuperscript{8} published a small series in 2014 of 13 study patients who underwent chemosaturation with percutaneous hepatic perfusion for hepatic metastases predominately from melanoma. The mortality rate in this series was similar to previously reported series, and the median number of treatments per study patient was 1.\textsuperscript{8} The disease control rate for this cohort was 92%, thus demonstrating that chemosaturation with percutaneous hepatic perfusion has a significant effect.\textsuperscript{8}

Abbott et al\textsuperscript{11} built upon the data from Forster et al\textsuperscript{7}, updating it to investigate the use of chemosaturation with percutaneous hepatic perfusion in 13 individuals with ocular and cutaneous melanoma. These researchers evaluated the outcomes of chemosaturation with percutaneous hepatic perfusion at a single institution in study patients with unresectable hepatic metastases who received liver-directed therapy between 2008 and 2014. Their data suggested that chemosaturation with percutaneous hepatic perfusion was successful in this cohort.\textsuperscript{11} The researchers compared the results of chemosaturation with percutaneous hepatic perfusion against other liver-directed therapies, such as yttrium and chemoembolization, in 31 individuals. No differences were observed between the groups receiving yttrium, chemoembolization, and chemosaturation with percutaneous hepatic perfusion in regard to age, adjuvant therapy, prior regional hepatic treatment, or major complications following treatment for both melanoma and non–melanoma primary malignancies.\textsuperscript{11} Extrahepatic disease was observed to be more prevalent in the chemoembolization group compared with the groups receiving yttrium and those receiving chemosaturation with percutaneous hepatic perfusion ($P = .004$).\textsuperscript{11} The median rate of hepatic progression-free survival (PFS) was significantly longer among those who received chemosaturation with percutaneous hepatic perfusion compared with those assigned to yttrium ($P < .001$) and chemosaturation with percutaneous hepatic perfusion compared with chemoembolization ($P = .008$).\textsuperscript{11} A higher Eastern Cooperative Oncology Group (ECOG) score ($P = .01$) and a greater tumor burden also correlated with a shorter duration of hepatic PFS ($P = .03$).\textsuperscript{11}

Median overall Kaplan-Meier survival was also longer with chemosaturation with percutaneous hepatic perfusion (736 days) than with yttrium (285 days) and chemoembolization (265 days); however, on multivariate analysis, this difference was significant for chemosaturation with percutaneous hepatic perfusion compared with yttrium alone ($P = .03$) and not for chemosaturation with percutaneous hepatic perfusion compared with chemoembolization ($P = .20$).\textsuperscript{11} Neither ECOG score nor tumor burden was a significant predictor of overall survival (OS).

Because 7 study patients included in the retrospective review from Forster et al\textsuperscript{7} and Abbott et al\textsuperscript{11} were also included in clinical trial results published by Hughes et al,\textsuperscript{10} it is worth noting that these data were removed from the summary analysis and the Table that describes the unique patients.\textsuperscript{8,12,13}

Hickson et al\textsuperscript{13} described the experience of treating 18 study patients who received chemosaturation with percutaneous hepatic perfusion. The primary disease of the cohort was ocular melanoma, and the median number of treatments was 2 per study patient.\textsuperscript{13} A disease control rate of 94% was reported, confirming the work of previous groups who demonstrated significant responses to chemosaturation with percutaneous hepatic perfusion in individuals whose disease failed to respond to other treatments.\textsuperscript{13}

The results of a phase 3 randomized trial with a cross-over design published by Hughes et al\textsuperscript{10} validated the results of previously published retrospective studies. In 44 study volunteers assigned to chemosaturation with percutaneous hepatic perfusion, the disease control rate was reported to be 89%, the mortality rate was 7%, and the complication rate was 90%, with the majority being neutropenic without significant sequelae.\textsuperscript{10} The median number of treatments was 3 per participant. Hepatic PFS and OS were significantly improved in this population. The rate of median OS improved from 46 days in the best available care group to 186 days in the chemosaturation with percutaneous hepatic perfusion group ($P < .0001$).\textsuperscript{10} Because cross-over was allowed, no difference in OS rate was observed as more than 50% of the study participants who received best available care crossed over to percutaneous hepatic perfusion. Among the study volunteers originally randomized to best available care, those who crossed over to chemosaturation with percutaneous hepatic perfusion had a median OS rate of 396 days compared with 124 days for study participants assigned to the best available care group who did not cross-over after disease progression ($P = .01$).\textsuperscript{10}

**Response Rates**

In total, 91 individuals received a total of 182 treatments of chemosaturation with percutaneous hepatic perfusion.\textsuperscript{7,8,10-15} Although it was not precisely reported in all studies, ocular melanoma was the primary malignancy in more than 60% of the cases studied (see Table).\textsuperscript{7,8,10-15} When investigating these studies, based on Response Evaluation Criteria In
Solid Tumors (when available), the complete response rate was 4%; the overall response rate was 47%; the disease control rate was 90%; the median mortality rate was 2.5% (range, 0%–7.7%); and, when reported, the median number of chemosaturation with percutaneous hepatic perfusion treatments per study patient was 3 (range, 1–3).\textsuperscript{7,8,10-13}

**Hepatic Function and Overall Survival**

As of publication, the best available data on hepatic function and OS come from Hughes et al,\textsuperscript{10} who published the results of a phase 3, randomized, cross-over trial that investigated chemosaturation with percutaneous hepatic perfusion using melphalan vs best alternative care for patients with metastatic ocular or cutaneous melanoma to the liver. Limited extrahepatic metastatic melanoma was allowed, provided that the hepatic metastases represented the life-limiting tumor burden. Patients were required to have adequate hepatic and renal function. No anatomical variations were allowed that would limit chemosaturation with percutaneous hepatic perfusion. The researchers discovered that PFS was prolonged in those receiving chemosaturation with percutaneous hepatic perfusion compared with those assigned to best alternative care (7.03 vs 1.64 months; hazard ratio 0.34; \( P < .0001 \)).\textsuperscript{10} The rate of OS was comparable among groups (9.79 vs 9.89 months for chemosaturation with percutaneous hepatic perfusion and best alternative care, respectively).\textsuperscript{10} This may be because of the design of the trial. Because it was a cross-over design, the trial allowed patients assigned to best alternative care to cross-over to chemosaturation with percutaneous hepatic perfusion after progression. The most common adverse events observed in study patients receiving chemosaturation with percutaneous hepatic perfusion with melphalan were thrombocytopenia, anemia, and neutropenia.\textsuperscript{10}

**Use in Multiple Tumor Types**

Several noncomparative studies of chemosaturation with percutaneous hepatic perfusion using melphalan for the treatment of unresectable hepatic metastases were published prior to the randomized trial conducted by Hughes et al.\textsuperscript{8,11-13} Study patients in these trials had a variety of primary tumor types, including ocu-

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**Table. — Selected Literature on Outcomes Data for Use of Chemosaturation With Percutaneous Hepatic Perfusion**

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Study Patients</th>
<th>Type of Primary Tumor, n</th>
<th>No. of Treatments Received</th>
<th>Median No. of Treatments</th>
<th>Rate of Disease Control, %</th>
<th>Selected Outcome</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hughes\textsuperscript{10}</td>
<td>44</td>
<td>Cutaneous melanoma (5) Ocular melanoma (39)</td>
<td>120</td>
<td>3</td>
<td>89</td>
<td>CR: 0 PR: 16 SD: 23 PD: 5</td>
<td>Phase 3 randomized trial Deaths associated with treatment: 3 (7%)</td>
</tr>
<tr>
<td>van Etten\textsuperscript{12}</td>
<td>10</td>
<td>Colorectal cancer (9) Ocular melanoma (1)</td>
<td>10</td>
<td>Not reported</td>
<td>80</td>
<td>CR: 0 PR: 2 SD: 6 PD: 2</td>
<td>30-d mortality rate: 5%</td>
</tr>
<tr>
<td>Abbott\textsuperscript{11} (update of Forster\textsuperscript{14})</td>
<td>10</td>
<td>Ocular melanoma (4) Sarcoma (1) Unknown primary melanoma (1)</td>
<td>30</td>
<td>3</td>
<td>100</td>
<td>CR: 1 PR: 5 SD: 4 PD: 0</td>
<td>PFS improved with therapy compared with other treatments (( P &lt; .04 )) No reported mortalities</td>
</tr>
<tr>
<td>Hickson\textsuperscript{13}</td>
<td>18</td>
<td>Ocular melanoma (18)</td>
<td>34</td>
<td>2</td>
<td>94</td>
<td>CR: 2 PR: 13 SD: 2 PD: 1</td>
<td>2 study patients NT due to technical anatomical reasons</td>
</tr>
<tr>
<td>Vogl\textsuperscript{8}</td>
<td>13</td>
<td>Breast cancer (1) Cholangiocarcinoma (1) Cutaneous melanoma (3) Ocular melanoma (8)</td>
<td>18</td>
<td>1</td>
<td>92</td>
<td>CR: 1 PR: 6 SD: 5 NE: 1</td>
<td>1 death resulted in NE 1 study patient NT due to in- procedural bleeding</td>
</tr>
</tbody>
</table>

Disease control rates are CR + PR + SD.

\textsuperscript{7}Seven patients not listed here because they are included in Hughes et al.\textsuperscript{10}

CR = complete response, NE = not evaluable, NT = not treated, PD = progressive disease, PR = partial response, SD = stable disease.

This table describes therapy not approved by the US Food and Drug Administration.
lar melanoma, cutaneous melanoma, cholangiocarcinoma, leiomyosarcoma, and colorectal, breast, and gastric cancers.\textsuperscript{8,11,13} In these studies, rates of overall hepatic response ranged from 50% to 75%.\textsuperscript{8,11,13} Hepatic responses were seen in those with cholangiocarcinoma, colorectal cancer, ocular melanoma, cutaneous melanoma, and leiomyosarcoma. Complete responses were observed in 1 study patient with cholangiocarcinoma and 2 with ocular melanoma.\textsuperscript{8,11,13}

**Adverse Events**

Observed toxicities following chemosaturation with percutaneous hepatic perfusion are consistent among reports of the therapy used in conjunction with melphalan.\textsuperscript{7,8,10,16-18} Overall, approximately 90% of patients have experienced a treatment-related adverse event.\textsuperscript{7,8,10} Thrombocytopenia, anemia, and neutropenia are the most common adverse events of chemosaturation with percutaneous hepatic perfusion.\textsuperscript{7,8,10,14,16-18} In the majority of cases, these adverse events were managed with granulocyte colony-stimulating factor, blood-product transfusions, or both, as necessary.\textsuperscript{7,8,10,14,16-18}

Two studies with the highest toxicity rates — van Etten et al\textsuperscript{12} and Hughes et al\textsuperscript{10} — utilized the first-generation filter. A second-generation filter was utilized in the other studies, which had lower rates of grade 3 or higher toxicities.\textsuperscript{7,8,11,13} Furthermore, pharmacokinetics have shown that more than 93% of melphalan is removed by the second-generation filter, thus minimizing systemic exposure.\textsuperscript{19} Likewise, a general trend is associated with the second-generation filter that has demonstrated that the newer-generation filter is associated with a decreased rate of hematological toxicities, an increased number of treatments per patient, and a decreased rate of treatment-associated mortality (see Table).\textsuperscript{7,8,10-13}

**Conclusions**

Results from a randomized trial and several retrospective studies demonstrate that chemosaturation with percutaneous hepatic perfusion achieves good tumor response rates in patients with unresectable hepatic metastases from ocular or cutaneous melanoma, colorectal cancer, or cholangiocarcinoma.\textsuperscript{7,8,10,11,13} In 1 study, chemosaturation with percutaneous hepatic perfusion was significantly associated with prolonged rates of hepatic progression-free survival compared with 2 other regionally delivered, liver-targeted therapies.\textsuperscript{11} More randomized trials are needed to confirm these initial findings, to investigate the potential benefit in overall survival, and to study the use of chemosaturation with percutaneous hepatic perfusion in combination with current immunotherapy-based treatments for melanoma. To this end, a phase 3, multicenter, international, randomized trial without a cross-over design that is comparing percutaneous hepatic perfusion with best alternative care is now recruiting patients (NCT02678572).

**References**