Background: Surgical resection of hepatocellular carcinomas and metastases to the liver cannot always be performed, and systemic therapies for these entities are of limited value. The techniques of chemoembolization and hepatic arterial infusion have been used for patients who are not candidates for surgery.

Methods: Chemoembolization uses percutaneous intra-arterial infusion of chemotherapeutic agents and embolic material. This provides longer contact of the agents with the tumor cells and induces ischemia. Hepatic arterial chemoinfusion uses the knowledge that hepatic cancers are supplied predominantly by the hepatic artery.

Results: Chemoembolization using Lipiodol, doxorubicin, and Gelfoam has promoted necrosis of unresectable hepatocellular tumors and may have prolonged patient survival. Hepatic arterial infusion with fluorinated pyrimidines produces more objective responses than systemic chemotherapy but probably does not alter survival.

Conclusions: The nonsurgical treatments of chemoembolization and hepatic arterial infusion of chemotherapy have expanded our armamentarium to manage many primary and metastatic tumors in the liver. Additional approaches are needed.

Introduction

Advances in surgical and interventional angiographic techniques have led to increased efforts to treat primary and secondary hepatic neoplasms. These efforts include operative and percutaneous catheterization for regional perfusion or embolotherapy, and ablation by ethanol injection or cryosurgery. The historically poor response with systemic chemotherapy and the limited number of patients who are found to be resectable prior to or during operation have promoted these efforts.

Many variations in the regional treatment of hepatic neoplasms by hepatic arterial infusion (HAI) have evolved since the initial reports. Transcatheter chemoinfusion and chemoembolization are being increasingly investigated to determine if greater concentrations of chemotherapeutic agent delivered to the site of malignancy would improve response rates while decreasing systemic toxicity. The development of reliable implantable pumps has led to more effective continuous infusion, and the accuracy of targeting chemotherapeutic or embolic agents has increased with the use of microcatheters. Hepatic venous isolation techniques are being developed to increase regional drug concentration during hepatic arterial perfusion while reducing systemic exposure.

Transcatheter Therapy

The rationale for the use of intra-arterial chemotherapy to deliver a higher concentration of anticancer agent and to maximize tumor uptake is based on the physiology of hepatic and systemic circulations following HAI[1] and extensive metabolism of these agents on their first pass through the liver.[2]

Transcatheter chemoembolization (TCE) is an alternative technique for the percutaneous intra-arterial infusion of chemotherapeutic agents and embolic material. This approach is aimed at prolonging contact time of the drug and provoking ischemia. Lipiodol (Laboratories Guerbet, Aulnay-sous-Bois, France) is a lipid compound containing iodine and has been used for many years as a lymphatic contrast agent. Lipiodol has now been introduced into chemoembolization regimens as a result of its affinity to and prolonged retention in liver tumors.

Lipiodol also can be used as a carrier of anticancer agents including 5-fluorouracil and emulsified hydrophilic drugs (eg, doxorubicin, epirubicin, mitomycin C, and cisplatin).[3,4] In the treatment of hepatocellular carcinoma (HCC), the association of iodized oil and doxorubicin not only reduced the peak concentration of doxorubicin without affecting its bioavailability, but also increased intratumoral concentration and half-life, which was even more pronounced following embolization with a gelatin sponge (Gelfoam, Upjohn Company, Kalamazoo, Mich).[5]

Chemoembolization is performed percutaneously from a femoral arterial approach with selective catheterization of the right or left hepatic artery using standard 5- or 6.5-French angiographic catheters. Subselective catheterization into branch vessels that supply the tumor can be more accurately performed using a 3-French microcatheter placed coaxially through the standard catheter (Fig 1). Chemotherapeutic agents emulsified in Lipiodol are injected in small volumes of 1 to 2 mL under direct fluoroscopic visualization. This is followed by embolization with Gelfoam powder. The procedure can be repeated since vascular occlusion is temporary when Gelfoam is used.

Generally, TCE is well tolerated. However, postembolization syndrome (eg, nausea, vomiting, fever, and abdominal pain) usually occurs following the procedure, which resolves with symptomatic treatment. Severe complications such as hepatic encephalopathy and renal failure can occur in patients with impaired liver function.

Transcatheter Therapy for Hepatocellular Carcinoma
Several treatment modalities have been used in patients with HCC. Uncontrolled tumor growth in the liver remains the major cause of death in HCC, even when metastases occur. Surgical resection, a potentially curative procedure, is limited to patients with solitary or localized disease who do not have significant liver dysfunction. Orthotopic liver transplantation also is limited to patients with otherwise unresectable nonmetastatic HCC.

The most widely used treatment for unresectable HCC is systemic chemotherapy. The results have been disappointing with single-agent chemotherapy. Doxorubicin, mitomycin C, or 5-fluorouracil have not affected survival or produced consistent response rates greater than 20%.[6,7] Intra-arterial chemoinfusion using surgically implantable pumps or via a percutaneous approach has produced response rates of 50% but without longer survival.[8,9]

Chemoembolization represents another approach to the treatment of unresected HCC (Figs 2A-B). The reported cumulative survival rates in studies on hepatic chemoembolization of HCC are 56% to 69% at one year and 18% to 35% at three years[10-12] compared with 18% and 5% at one and three years, respectively, without treatment.[10] The effectiveness of Lipiodol varied in these studies. While a one-year survival rate of 86% was noted by Hatahaka et al[11] in a patient group randomized to chemoembolization with gelatin sponge and iodized oil mixed with anticancer agents, no difference was seen when compared with a group that did not receive Lipiodol. However, in a retrospective study by Nakamura et al, chemoembolization with Lipiodol and gelatin sponge resulted in longer survival than chemoembolization without Lipiodol.

An evaluation of surgical specimens following administration of doxorubicin and iodized oil demonstrated greater tumor necrosis with greater oil retention in the tumor. [13] Necrosis of the area of the largest cut surface of the tumor was 91% with Lipiodol, doxorubicin, and Gelfoam compared with 46% without Gelfoam.[14] In addition to destruction of the main tumor, embolization after Lipiodol administration destroyed small satellite tumors that may not be visible by conventional imaging and extrahepatic invasion.[14,15] Chemoembolization with Lipiodol was one of four independent variables that increased survival by multivariate analysis.[16]

The prognosis of advanced HCC is established by Okuda staging. Child class distribution, serum alpha-fetoprotein levels, bilirubin levels, anatomic patterns, and the presence of portal vein thrombosis.[10,17] The large number of variables that influence outcome probably led to the varying results from different series. The results still support the efficacy of chemoembolization compared with other forms of therapy. Chemoembolization is a valid form of nonsurgical treatment of HCC that should be performed in selected patients for whom other forms of treatment are not possible—primarily those with multifocal or infiltrating lesions or high surgical risk due to cirrhosis (Child class B or C). Chemoembolization also may be valuable as adjuvant chemotherapy in reducing intrahepatic recurrence in postoperative patients.[18]

### Regional Transcatheter Therapy for Colorectal Carcinoma

In the United States, an estimated 133,500 patients will be diagnosed with colorectal cancer in 1996, and approximately 54,900 will die of this disease.[19] Metastasis occurs most frequently in the liver and may be confined to this location for extended periods.

#### Prospective Trials of Hepatic Arterial Infusion vs Systemic Chemotherapy

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of Patients</th>
<th>Response (%)</th>
<th>P Value</th>
<th>Median Survival (mos)</th>
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<td>55</td>
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<tr>
<td>Martin et al[24]</td>
<td>33</td>
<td>39</td>
<td>0</td>
<td>20</td>
<td>15</td>
</tr>
</tbody>
</table>

* Number of patients receiving hepatic arterial infusion.
** NS = not significant
* = yes
** = no
IA = intraarterial
IV = intravenous

Prospective, randomized trials evaluating HAI versus systemic chemotherapy for hepatic metastases from colorectal carcinoma showed response rates of 42% to 62% with regional infusion compared with response rates of 9% to 21% with systemic chemotherapy using fluorouracil (FUdR) or 5-fluorouracil (Table).[20-24] Despite this improvement in tumor response, prolongation of survival could not be demonstrated in the reports of Chang et al[22] and Martin et al[24] which did not allow crossover between treatments.

One prospective trial[20] showed improved survival when HAI was used. However, half of the control group received intravenous 5-fluorouracil, and the other half did not receive any treatment. One third of the HAI group also received systemic 5-fluorouracil in a nonrandomized fashion, which invalidates direct comparison of these groups.

The clinical trials also report operative complications, catheter-related problems, and increased local/regional toxicity to increased concentrations of chemotherapeutic agents. In the evaluation of 180 patients undergoing hepatic pump or port placement, operative or early postoperative complications occurred in 5.5%, and late complications requiring removal of the device in 16 patients.[25] HAI with FUdR was associated with significant hepatic and biliary toxicity including biliary sclerosis, sclerosing cholangitis, and chemical hepatitis.[21-23] Infusion of dexamethasone with FUdR may allow higher doses of FUdR administration with less toxicity and better tumor response. Although there was a trend toward a decrease in bilirubin and a delay in the onset of sclerosing cholangitis, the frequency of sclerosing cholangitis did not improve.[26] Extrahepatic complications including gastrointestinal inflammation and ulcerations also were noted.

For treatment of unresectable liver metastases from colorectal cancer, HAI should be considered for symptomatic patients who are refractory to systemic chemotherapy. The primary role of HAI in this setting is symptom relief. Since HAI may prolong survival in certain subgroups (ie, patients with less than 50% tumor replacement at presentation),[27] asymptomatic patients should be included in clinical trials that are designed to discover more effective and less toxic HAI regimens and combined local and systemic adjuvant chemotherapy. In our institution, patients with unresectable hepatic metastases without extrahepatic disease at the time of exploration are also considered for pump placement.

The role of percutaneous therapy of colorectal metastases to the liver also is uncertain. No randomized trials are available to demonstrate increased survival for patients who receive hepatic embolization or chemoembolization over systemic chemotherapy.
In a controlled, randomized trial of 61 patients with unresectable colorectal liver metastases, Hunt et al.[27] randomized patients to receive no treatment, to receive hepatic arterial embolization with homologous dura mater and Gelfoam, or to receive chemoinfusion with 5-fluorouracil and degradable starch microspheres. No apparent survival benefit was noted in either the embolization group or the chemoinfusion group. In a study of patients with bulky hepatic metastases who failed systemic therapy, Martinelli et al.[28] concluded that embolization and chemoembolization as second-line therapy may have antitumor activity and may provide patient benefit.

**Hepatic Metastases From Neuroendocrine Tumors**

Tumors arising from neuroendocrine cells of the gastrointestinal tract, pancreas, and bronchi commonly metastasize to the liver and can cause debilitating symptoms related to the uncontrolled secretion of peptide substances. Surgical resection of localized hepatic metastases provides the best response.[29] However, only 7% of patients with metastatic disease are surgical candidates (Fig 3).[30] Systemic chemotherapy has demonstrated tumor response but is associated with morbidity and drug resistance. Alternative approaches such as surgical and transcatheter hepatic arterial occlusion have been performed.

Recent TCE studies have been conducted to evaluate doxorubicin, iodized oil, and gelatin sponge embolization for unresectable hepatic metastases. These studies are similar to regimens used with TCE for HCC. In a study of 30 patients with significant symptoms from hepatic metastasis of carcinoid and islet cell tumors, Perry et al.[31] reported a 92% response rate (complete and partial), with 79% of the patients having at least a 50% reduction in hormonal markers or tumor size. Median survival was 24 months following treatment. In a computed tomography follow-up of treated patients, tumor vascularity and distribution of metastatic lesions were not clearly correlated with outcome, whereas the presence of an unresectable primary tumor had a negative effect on survival. Using a similar treatment regimen in 23 patients, Therasse et al.[32] reported a symptom-free survival of 29 months following therapy and an average survival time of 24 months. Ryszniwski et al.[33] described 24 cases managed with TCE in conjunction with subcutaneous octreotide to prevent carcinoid crisis. Patients with carcinoid liver metastases demonstrated the best response, with a decrease in tumor size in one third of the patients and a decrease of greater than 50% in hormonal secretion in more than half of them. The response rates obtained in these studies indicate that TCE is the best overall therapeutic option for patients with symptomatic unresectable hepatic metastases from neuroendocrine tumors.

**Hepatic Metastases From Other Primary Sites**

The effectiveness of regional therapy for hepatic metastases from less common primary tumors is also promising. In particular, hepatic metastasis from ocular melanoma, which is associated with a poor prognosis, appears to be palliated more effectively by chemoembolization. In a nonrandomized study of 30 patients, Mavligit et al.[34] showed tumor regression equal to or greater than 50% in almost half of the patients. A median survival of 11 months for the entire patient population was noted following chemoembolization with cisplatin and polyvinyl sponge particles (Ivalon), whereas the historical median survival is two to six months with conventional systemic therapy.[35,36]

Regional treatment for hepatic metastases from gastrointestinal leiomyosarcoma, also highly resistant to systemic chemotherapy, also may be beneficial.[37] However, randomized trials with longer follow-up are necessary to assess whether the demonstrated tumor regression will translate to prolonged survival.

**Hepatic Arterial Perfusion With Hepatic Venous Isolation and Extracorporeal Chemofiltration**

Intra-arterial chemoinfusion has been used to increase regional exposure of the drug and to reduce systemic toxicity. Fluoropyrimidines such as FUDr and 5-fluorouracil have high first-pass hepatic extraction, and the dose-limiting factor has been hepatic toxicity. However, doxorubicin, which has demonstrated tumor response in both primary and metastatic hepatic malignancies, has a low hepatic extraction rate. Systemic toxicity as the dose-limiting factor prevents dose escalation and therefore may limit therapeutic effect. To reduce this systemic toxicity, HAI with complete hepatic venous isolation and extracorporeal chemofiltration has been developed.[38,39] This approach described by Curley et al.[38] entails percutaneous selective catheterization of the proper hepatic artery for chemoinfusion with a transfemoral, dual-balloon, vena cava catheter positioned within the inferior vena cava to obtain complete hepatic venous isolation. Hepatic venous blood is directed to carbon filters for hemofiltration prior to return to the circulation via the internal jugular vein.

The results of a preclinical evaluation showed that extracorporeal chemofiltration reduced postfilter and systemic levels of doxorubicin by more than 90% compared with prefilter levels.[40] In a phase I study,[38] the average peak systemic levels of doxorubicin were 85.6% lower than peak prefilter levels during infusions lasting 20 minutes with a maximum tolerated dose of 120 mg/m². This study was conducted to determine systemic exposure and the hepatic maximum tolerated dose of doxorubicin. However, follow-up of those treated patients with HCC suggests that doxorubicin may induce tumor cytoreduction, thus allowing surgical resection (which was possible in two of 10 patients enrolled in this study). Randomized, prospective trials are required to determine survival benefits using this mode of treatment.

Another area of research in the use of HAI with hepatic venous isolation involves tumor resistance to chemotherapeutic agents. Normal liver cells and liver tumors can express P-glycoprotein, which is a transmembrane efflux pump for lipophilic toxins that may be inducible by treatment with chemotherapeutic drugs.[41] Pharmacologic blockade of this pump is possible with several drugs (eg, verapamil). However, the high dose required to block this protein is associated with systemic toxicity. By using HAI with hepatic venous isolation in animal models, Fuhrman et al.[42] demonstrated significant reduction in systemic exposure when high doses of verapamil with doxorubicin were administered. However, this combination of drugs caused significant elevation in liver enzymes with histologic evidence for liver damage, which may not be tolerated by patients with limited hepatic reserve. Further investigation with different drug combinations is warranted to discover treatment approaches that increase antitumor response and prolong survival.

**Conclusions**

Transcatheter hepatic arterial therapy has evolved into formal treatment protocols with a valid role in the treatment of primary and secondary hepatic neoplasms. Hepatic arterial chemoinfusion can induce tumor regression in patients with metastases from colon cancer. Tumor response and prolongation of survival has been documented following chemoembolization of HCC and other metastatic tumors to the liver. Research is ongoing to develop more effective combinations of chemotherapeutic agents and to determine the effectiveness of concurrent systemic adjuvant chemotherapy. Novel approaches to increase the delivery of drugs to the liver while reducing systemic toxicity may enhance the use of transcatheter arterial therapy in the treatment of hepatic neoplasms.

**References**
