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Hepatic arterial infusion of chemotherapy still plays a role in selected patients with colorectal cancer and hepatic metastases.

Hepatic Arterial Infusion of Chemotherapy for Hepatic Metastases From Colorectal Cancer

Jade Homsy, MD, and Christopher R. Garrett, MD

Background: Sixty percent of colon cancer patients develop liver metastasis. Only 25% of those have potentially resectable hepatic metastases, and approximately 58% of those patients relapse.

Methods: We review the indications and the technical aspects of hepatic artery infusion (HAI) of chemotherapy, as well as the efficacy, morbidity, and outcomes.

Results: HAI of chemotherapy has been used following hepatic metastasectomy, in patients with unresectable metastases, or in combination with other agents. Floxuridine, the chemotherapeutic agent most studied, is administered through an implantable subcutaneous infusion pump connected to a surgically placed hepatic artery catheter, which delivers the chemotherapeutic agents at a slow fixed rate. Treatment-related toxicities include chemical hepatitis, biliary sclerosis, and peptic ulceration. Some trials report a survival benefit for HAI over systemic chemotherapy with acceptable toxicity.

Conclusions: Regional perfusion chemotherapy can be logistically and technically complicated to deliver. The development of newer systemic agents with superior efficacy in the treatment of metastatic colorectal cancer will likely diminish the role of regional perfusion therapy in the future.

Introduction

In 2005, an estimated 145,000 new cases of colorectal cancer will be diagnosed in the United States, with over 54,000 deaths caused by this disease.¹ Sixty percent of patients develop liver metastasis, and for a third of those it is the sole site of disease. If untreated, the median survival is approximately 6 to 12 months, with no survivors at 5 years.² Survival rates of up to 37% at 5 years and up to 22% at 10 years were reported with hepatic resection for metastatic colorectal cancer.³ Only 25% of patients with colorectal carcinoma have potentially curative

From the Gastrointestinal Tumor Program at the H. Lee Moffitt Cancer Center & Research Institute, Tampa, Florida.

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Address correspondence to Christopher R. Garrett, MD, H. Lee Moffitt Cancer Center & Research Institute, 12902 Magnolia Drive, MCC-GIPROG, Tampa, FL 33612. E-mail: garrett@moffitt.usf.edu

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Abbreviations used in this paper: HAI = hepatic artery infusion, FUDR = floxuridine (5-fluoro-2'-deoxyuridine), 5-FU = 5-fluorouracil, LV = leucovorin.

resectable hepatic metastases, and approximately 58% of those patients relapse.⁴ To treat suspected micro-metastases in the remaining liver, prevent other metastasis, and improve survival, the use of regional chemotherapy alone (hepatic arterial infusion [HAI]) or in combination with systemic chemotherapy has been evaluated in a number of prospective randomized and nonrandomized studies. This review briefly describes the indication and technical aspects of HAI. It also reviews the data regarding the efficacy and the morbidity associated with this form of therapy when employed after hepatic metastasectomy, unresectable metastases, or in combination with other agents.

Hepatic Artery Infusion

The concept of HAI dates back to the early 1960s when it was tried in a few patients with gastrointestinal tumors metastatic to the liver and was anecdotally associated with favorable outcomes.⁵ The rationale for HAI is to expose the metastases to high chemotherapy concentrations while minimizing systemic toxicity. This can be achieved by infusing a drug into the hepatic artery that mostly supplies blood to hepatic metastases, whereas the portal vein mostly supplies normal liver cells.⁶ Multiple agents such 5-fluorouracil (5-FU), mitomycin, cisplatin, and doxorubicin have been infused, but 5-fluoro-2'-deoxyuridine (floxuridine, FUDR) has been the chemotherapeutic agent most frequently studied. FUDR has a 95% hepatic extraction when continuously infused in the hepatic artery, resulting in a 16-fold higher concentration in liver metastasis compared with venous administration.⁷

Infusing FUDR in the hepatic artery is achieved through an implantable subcutaneous infusion pump connected to a surgically placed hepatic artery catheter, which delivers the chemotherapeutic agent at a slow fixed rate, usually for 2 weeks. This method of delivery has been shown to be superior over other conventional methods in terms of complication rate and complication-free survival.⁸ Complications related to hepatic artery thrombosis, catheter displacement, hematomas, infections, and liver perfusion are all reported as pump-related complications.^{8,9} The technical complications are closely associated with surgeon experience and arterial anatomy (37% for inexperienced surgeons vs 7% for experienced surgeons).¹⁰ Treatment-related toxicities include chemical hepatitis, biliary sclerosis, and peptic ulceration. Chemical hepatitis, which is the most common (42%),¹¹ presents with elevation in liver enzymes or bilirubin. Liver function monitoring, dose reduction, or treatment cessation are recommended based on the severity of the clinical presentation. Although most cases are reversible, biliary sclerosis can develop in 3% to 26% of patients.¹¹

Palliative biliary stenting is sometimes required. This complication is usually associated with FUDR rather than 5-FU infusions. Adding dexamethasone at a total dose of 20 mg to FUDR significantly decreases hepatotoxicity. Kemeny et al¹² reported a trend toward a lower incidence of increased bilirubin levels in patients receiving dexamethasone plus FUDR when compared to those receiving FUDR alone (9% and 30%, respectively, had a 2-fold or greater increase in the bilirubin level from baseline). Response rate and survival also improve with the addition of dexamethasone.¹³

The most suitable subjects for HAI have disease confined to the liver, have undergone hepatic angiography to define their hepatic arterial anatomy, and are deemed appropriate surgical candidates for the catheter and pump placement. Contraindications include portal vein thrombosis, more than 70% liver replacement by tumor, significant impairment of liver function, or a hepatic artery anatomy that would preclude perfusion of the entire liver.¹⁴

HAI FUDR in the Treatment of Unresectable Hepatic Metastases

In the early 1980s, phase II trials first reported survival benefit in patients with unresectable colorectal metastases to the liver treated with FUDR chemotherapy using a totally implantable drug infusion pump. Radiographic response rates were reported as high as 88%; the 1-year survival rate and median survival were superior compared to historic controls (82% vs 36% and 26 months vs 8 months, respectively ($P < .0001$)).¹⁵ This study was followed by several randomized trials comparing HAI FUDR to observation, systemic FUDR, and systemic 5-FU¹⁶⁻²³ (Table). HAI of 5-FU modulated by leucovorin (LV) was also compared to systemic¹⁶⁻²³ 5-FU/LV and HAI FUDR.^{24,25} HAI FUDR and LV in addition to dexamethasone was recently compared to systemic 5-FU/LV.²⁶ All trials showed significant improvement in response (up to 62%) or time to hepatic progression for HAI compared to intravenous chemotherapy. Overall survival was significantly improved only when HAI FUDR was compared to observation and when dexamethasone and LV were added to HAI and compared to parenteral 5-FU and LV.

Two meta-analyses of earlier trials were conducted to determine if there was a survival benefit associated with HAI FUDR used in the metastatic setting.^{27,28} The first included 600 patients with unresectable liver metastases from colon cancer. A 41% response rate was seen with HAI FUDR compared to 14% with intravenous FUDR or 5-FU (odds ratio = 0.25, confidence interval [CI], 0.16-0.40; $P < 10^{-10}$). Although a 27% relative survival advantage was seen in the HAI arms ($P = .0009$) compared with the controls, the survival

advantage was 19% and no longer statistically significant ($P = .14$) when trials with best supportive care arms were excluded.²⁷ The second meta-analysis showed a modest survival benefit for HAI over systemic chemotherapy and considered quality of life rather than duration of survival as the priority when making treatment decisions. HAI FUDR was associated with a 10% ($P = .041$) and 6% ($P = .124$) increase in survival rate at 1 and 2 years, respectively.²⁸

With the emergence of cytotoxic therapies with proven efficacy in metastatic colorectal cancer, the long-term future of regional perfusion therapy in the management of this disease was questioned. Some centers have pursued phase I dose escalation studies combining these newer agents with HAI FUDR.

Forty-six previously treated patients with unresectable liver metastases and no known extrahepatic disease were enrolled in a phase I study evaluating intravenous irinotecan given weekly for 3 weeks administered with concomitant HAI FUDR with dexamethasone for 14 days (cycles were 28 days in length).²⁹ The maximum tolerated dose for this combi-

nation was determined to be irinotecan 100 mg/m² and FUDR 0.16 mg/kg per day. The dose-limiting toxicities were diarrhea and myelosuppression. The radiographic response rate was 74% and the median survival was 17.2 months. Of the 16 patients who had previously received irinotecan therapy, 13 achieved radiographic partial responses. Irinotecan combined with HAI FUDR was studied in 71 patients when administered as post-operative therapy following surgical cytoreduction of unresectable hepatic metastases from colorectal cancer. The results were compared with a historical control group receiving cytoreductive surgery alone. Median survival was 30.6 vs 20 months, and the 2-year survival rate (75% vs 35%) was better in the group receiving HAI plus irinotecan.³⁰

Oxaliplatin has also been studied in combinations with HAI FUDR. A phase I study of 36 patients was performed to evaluate two treatment groups.³¹ Patients in group A were treated with HAI FUDR and systemic oxaliplatin plus irinotecan, and those in group B received systemic oxaliplatin combined with protracted venous infusion of 5-FU/LV plus HAI FUDR.

Selected Randomized Trials in Unresectable Metastases

Trial (year)	Drug	N	HAI Dose	IV Dose	Median Overall Survival (mos)
Kemeny ¹⁶ (1987)	HAI FUDR vs IV FUDR	99	0.3 mg/kg/d for 14 days/28 days	0.125 mg/kg/d (14 days every mo)	17 vs 12
Chang ¹⁷ (1987)	HAI FUDR vs IV FUDR	64	0.3 mg/kg/d for 14 days/28 days	0.125 mg/kg/d (14 days q 28 days)	17 vs 12
Hohn ¹⁸ (1989)	HAI FUDR vs IV FUDR	143	0.2-0.3 mg/kg/d for 14 days/28 days	0.075 mg/kg/d (14 days q 28 days) 0.025 increase/cycle	16.5 vs 15.8
Safi ¹⁹ (1989)	HAI FUDR vs HAI & IV FUDR	44	0.2 mg/kg/d of FUDR for 14 days/28 days	0.3 mg/kg/d for 14 days/28 days	NS
Wagman ²⁰ (1990)	HAI FUDR vs IV 5FU	41	0.1-0.5 mg/kg/d for 14 days/28 days	10-50 mg/kg weekly	13.8 vs 11.6
Martin ²¹ (1990)	HAI FUDR vs IV 5FU/LV	74	0.3 mg/kg/d for 14 days/28 days	500 mg/m ² /d (5 days q 35 days)	12.6 vs 10.5
Rougier ²² (1992)	HAI FUDR vs IV 5FU vs Observation	163	0.3 mg/kg/d for 14 days/28 days	500 mg/m ² /d (5 days q 4 weeks)	15 vs 11*
Allen-Mersh ²³ (1994)	HAI FUDR vs Observation	100	0.2 mg/kg/d for 14 days/28 days		13.5 vs 7.5*
Lorenz ²⁴ (2000)	HAI FUDR vs HAI 5FU/LV vs IV 5FU/LV	168	0.2 mg/kg/d for 14 days/28 days	800-1000 mg/m ² /d + 200 mg/m ² /d (5 days q 28 days)**	12.7 vs 18.7 vs 17.6
Kerr ²⁵ (2003)	HAI 5FU/LV vs IV 5FU/LV	290	bolus 200 + 400 mg/m ² and 22-h infusion 1600 mg/m ² , days 1 and 2 (every 14 days)	bolus 200 + 400 mg/m ² and 22-hr infusion 600 mg/m ² days 1 and 2 (q 14 days)	14.7 vs 14.8
Kemeny ²⁶ (2003)	HAI FUDR/LV/DEX vs IV 5FU/LV	135	0.18 mg/kg + 4 mg/m ² + 1 mg/m ² for 14 days/28 days	425 mg/m ² /d + 20 mg/m ² /d q 28 days	24.4 vs 20*

* Statically significant
 ** Same dose was given as HAI
 HAI = hepatic artery infusion, IV = intravenous, FUDR = floxuridine (5-fluoro-2'-deoxyuridine), 5-FU = 5-fluorouracil, LV = leucovorin, DEX = dexamethasone, NS = not significant

The maximum tolerated dose for group A was oxaliplatin 100 mg/m², irinotecan 150 mg/m² (administered fortnightly) and FUDR 0.12 mg/kg per day for 14 days. For group B, the maximum tolerated dose was oxaliplatin 100 mg/m², LV 400 mg/m² and 5-FU 1,400 mg/m² by continuous infusion over 46 hours (administered fortnightly) combined with FUDR 0.12 mg/kg per day for 14 days. The dose-limiting toxicities for the oxaliplatin/irinotecan/FUDR combination (group A) were fatigue, neutropenia, diarrhea and vomiting. For the oxaliplatin/5-FU/FUDR combination (group B), the dose-limiting toxicities were neutropenia, nausea and vomiting. Of interest, the majority of patients (89%) had received prior chemotherapy. The complete and partial response rates in group A and group B were 90% and 87%, respectively. Seven patients in group A were subsequently able to undergo surgical resection. These promising preliminary results suggest there may be a role for neoadjuvant regional perfusion therapy in highly selected individuals.

The recent emergence of molecularly targeted monoclonal antibody therapies,³² with proven efficacy in metastatic colorectal cancer, provides a significant improvement in the outcomes for patients, but also presenting challenges for clinicians in selecting the most appropriate combination of therapy for their patients. Future studies are needed to determine the appropriate selection of candidates with metastatic colorectal cancer for treatment with regional perfusion FUDR therapy.

HAI FUDR as Adjuvant Therapy Following Hepatic Metastasectomy

When adjuvant HAI chemotherapy following hepatic resection for metastases was compared with historical controls treated with surgery alone, a decrease in disease recurrence and an improvement in survival were reported.³³ Three major randomized trials addressed the role of adjuvant arterial infusion in this setting.³⁴⁻³⁶

The first study randomized 226 patients with colorectal liver metastases to liver resection only or to resection of the liver metastases followed by adjuvant HAI of 5-FU (1,000 mg/m² per day for 5 days as a continuous 24-hour infusion) modulated by folinic acid (200 mg/m² per day for 5 days as a short infusion) for 6 months.³⁴ Interim analysis demonstrated a median survival of 34.5 months and time to progression of 14.2 months for patients with adjuvant therapy vs 40.8 and 13.7 months, respectively, for control patients. Subject accrual was terminated early due to the lack of significant improvement in survival. Grade 3 and 4 toxicities were stomatitis (58%) and nausea (55%), which occurred in 26% of cycles and in 63% of patients.

The second study randomized 109 patients with one to three potentially resectable metastases to

receive no further therapy or postoperative hepatic arterial FUDR combined with intravenous continuous-infusion 5-FU.³⁵ The initial dose of FUDR was 0.1-0.2 mg/kg per day for 14 days to a maximum of four cycles. The 5-FU dose was 200 mg/m² per day as a continuous 14-day infusion for 4 cycles, followed by 300 mg/m² per day as a continuous 14-day infusion for an additional 8 cycles. The 4-year disease recurrence-free rate was 25% for the control group and 46% for the chemotherapy group ($P = .04$). The 4-year liver recurrence-free rate was 43% in the control group and 67% in the chemotherapy group ($P = .03$). The median survival of the 75 assessable patients was 49 months for the control arm and 63.7 months for the chemotherapy arm ($P = .60$). The median survival of all 109 patients was 47 months for the control arm compared with 34 months for the chemotherapy arm ($P = .19$). An update follow-up 5-year survival is 60% vs 45% favoring adjuvant therapy.² There were two postoperative deaths, one in each arm, due to operative complications. Nine patients had grade 3 increases of liver enzymes and 2 developed biliary sclerosis from intrahepatic therapy that required bile duct stenting.

The third study randomized 156 with resection of hepatic metastases from colorectal cancer to receive six cycles of HAI FUDR and dexamethasone plus intravenous 5-FU, with or without LV, or 6 weeks of similar systemic therapy without regional perfusion therapy.³⁶ 5-FU was administered daily for 5 days as an intravenous infusion of 325-370 mg/m², preceded each day by a half-hour infusion of LV at a dose of 200 mg/m² and FUDR 0.25 mg/kg per day for 14 days in combination with dexamethasone 20 mg. The 2-year survival rate was 86% in the combined-therapy group vs 72% for systemic therapy alone ($P = .03$), with median survivals of 72.2 and 59.3 months, respectively. The 2-year hepatic progression-free survival rate was 90% for combined therapy and 60% for monotherapy ($P < .001$). At 2 years, the risk ratio for death was 2.34 among patients treated with systemic therapy alone compared with those who received combined therapy (95% CI, 1.10 to 4.98; $P = .027$), after adjusting for important variables. A survival follow-up was recently presented in which overall survival and 10-year survival was 68 months and 41% in the combined-therapy group compared with 59 months and 27% in the group receiving systemic therapy alone ($P = .1$ and $.07$, respectively).³⁷ Progression-free survival is now significantly greater in the combined-therapy group than in the monotherapy group (31.3 vs 17.2 months, $P = .02$). Grade 3 and 4 diarrhea was significantly higher in the combination arm (29% vs 15%, $P = .3$). Neutropenia, nausea, vomiting, and stomatitis were not significantly different between the two groups.

Newer agents are also being tested in the adjuvant setting. In a phase I/II study of HAI FUDR plus systemic

irinotecan as adjuvant therapy following complete hepatic resection in 96 colon cancer patients, the 2-year survival rate was 89%.³⁸

HAI of Other Cytotoxic Agents (Mitomycin C, Oxaliplatin, Pirarubicin)

Agents other than FUDR have been evaluated experimentally when administered by HAI. High-dose mitomycin C has been combined with FUDR and dexamethasone and infused by HAI in 63 patients (26 of whom were chemotherapy-naïve) with unresectable, hepatic-confined metastatic colorectal cancer.³⁹ The response rates were 73% and 70% in the chemotherapy-naïve and previously treated groups, respectively, with median survivals of 23 and 20 months. The chemical cholangitis was higher compared to that observed in trials with HAI FUDR alone. Intra-arterial hepatic infusion of oxaliplatin (100 mg/m²) combined with the conventional-dose LV5FU2 protocol as previously described, administered every 14 days (LV 200 mg/m², 5-FU 400 mg/m² IV bolus, and 5-FU 600 mg/m² 22-hour continuous infusion on days 1 and 2 every 2 weeks) was given to 28 patients with liver-confined metastatic colorectal cancer who had not previously received oxaliplatin.⁴⁰ Radiographic response rates were 64% with a median survival of 27 months. Toxicity was acceptable and the results were encouraging, even for this highly selected group of patients. The intrahepatic anthracycline pirarubicin, at a dose of 60 mg/m² administered on day 16), has been combined with systemic irinotecan (150 mg/m² on days 1 and 15, followed on days 1, 2, 15, and 16 by LV 200 mg/m², bolus 5-FU 400 mg/m² and protracted infusion 5-FU 600 mg/m² over 22 hours.⁴¹ In this study of 31 subjects, the objective response rate was 48%, with 11 patients able to undergo surgical resection following chemotherapy cytoreduction. The median overall survival was 20.5 months.

Conclusions

Regional perfusion chemotherapy can be logistically and technically complicated to deliver, but in medical centers with a high degree of proficiency in utilizing this route of chemotherapy administration, it can be accomplished with acceptable toxicity and catheter complication rates.⁴² It is not routinely recommended at centers where the placement and use of hepatic artery catheters occur infrequently. Single-arm phase II studies demonstrate impressive radiographic response rates and a surprisingly high number of patients who were able to undergo surgical resection following this approach. The significance of many of these studies is limited by the highly selected patient population being

evaluated and the paucity of controlled, randomized trials. The development of newer systemic agents with superior efficacy in the treatment of metastatic colorectal cancer, when compared to 5-FU, will likely diminish the role of fluoropyrimidine regional perfusion therapy in the future. Studies will be required to select the most appropriate patients for this form of therapy, in addition to determining the appropriate combination therapies with novel systemic agents.

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