Hepatic artery infusion chemotherapy for colorectal liver metastases

RUDOLPH B. RUSTIN, MD; DAVID P. VOGT, MD; RONALD M. BUKOWSKI, MD; KIRK V. SHEPARD, MD

■ Twenty-two patients with hepatic colorectal metastases had Infusaid pumps implanted for hepatic artery infusion chemotherapy, or HAIC. Prior to pump placement, 19 of the 22 patients received percutaneous HAIC with 5-fluorouracil and citrovorum factor. Floxuridine, 0.2 mg/kg/d, was administered via the Infusaid pump and was alternated with saline solution every 2 weeks. HAIC responsiveness was defined as a 50% or greater reduction in the sum of all diameters of measured lesions on computerized tomography scans and no evidence of extra-hepatic tumor. Nine patients (41%) had a favorable response to HAIC; four (18%) had a partial response to percutaneous HAIC and five (23%) were considered pump responders. All responders had pretreatment liver replacement of less than 50%. The mean survival after pump placement was 13.6 months for responders and 11.1 months for nonresponders. Although there were no operative deaths, the morbidity rate was 36%, and 31% of patients manifested significant chemotherapy toxicity. While toxicity is not insignificant and there is no survival benefit, the Infusaid pump is a reliable drug delivery system for HAIC, and may result in regression of colorectal liver metastases in patients with less than 50% hepatic replacement.

□ INDEX TERM: COLORECTAL LIVER METASTASES □ CLEVE CLIN J MED 1990; 57:692–696

OF THE 147,000 patients who will be found to have colorectal carcinoma in the United States this year, hepatic metastases will develop in 20% to 40%.[1] A maximum of 10% of these patients may undergo a potentially "curative" liver resection, with a 5-year survival rate of 25% to 30%,[2] but most patients with colorectal liver metastases must rely on other modes of therapy.

Only 20% of patients respond to conventional intravenous chemotherapy,[3] while other modalities including immunotherapy, radiation therapy, and hepatic artery ligation have been shown to offer no further survival benefit.

Hepatic artery infusion chemotherapy (HAIC) became available in the 1950s, but technical problems outweighed the relatively slight benefit.[4,5] The implantable Infusaid pump has rekindled interest in HAIC as evidenced by several encouraging reports on the use of the device.[6–8]

We report our experience with percutaneous HAIC using 5-fluorouracil (5-FU) and leucovorin and HAIC using floxuridine (FUDR) delivered via the Infusaid pump. We reviewed HAIC delivered both percutaneously and via the pump.

From the Departments of General Surgery (R.B.R., D.P.V.) and Hematology/Oncology (R.M.B.), The Cleveland Clinic Foundation; and Roxane Laboratories, Inc, Columbus, Ohio (K.V.S.).

Address reprint requests to D.P.V., The Cleveland Clinic Foundation, One Clinic Center, 9500 Euclid Avenue, Cleveland, Ohio 44195.

METHODS

Patient characteristics

Between January 1984 and November 1986, Infusaid pumps were implanted in 11 female and 11 male patients. Liver metastases were synchronous in 11 of the patients while the other 11 exhibited metachronous lesions. Five of the patients were Duke's Stage B and six were Duke's Stage C. Based upon rising carcinoembryonic antigen (CEA) levels ranging from values of less than 2.5 to 3,503, computerized tomography (CT) scans confirmed the presence of hepatic metastases in all patients, and 13 demonstrated less than 50% of the liver replaced by tumor. Three patients had received a course of intravenous 5-fluorouracil (5-FU) prior to the study.

In addition to informed consent, eligibility requirements for participation in the HAIC study included the following: (1) unresectable liver metastases as the primary factor determining survival and quality of life, (2) no pretreatment evidence of extrahepatic disease, (3) a life expectancy of at least 60 days, (4) patient fitness for surgical placement of the Infusaid pump, (5) the presence of measurable disease, (6) normal bilirubin, and (7) no evidence of ascites, cirrhosis, or uncontrolled infection.

Treatment protocol

The treatment protocol consisted of percutaneous HAIC followed by the placement of the Infusaid pump. An angiographic catheter was placed percutaneously via the femoral artery in the common hepatic artery by the Seldinger technique. Two courses of 4 days of 5-FU combined with citrovorum factor were given at 4 week intervals. The dose of citrovorum was 200 mg/m^2 given 15 to 30 minutes prior to the constant infusion of 5-FU. The infusion was administered over 24 hours at a dose of 1,200 mg/m^2. The total dose of citrovorum factor and 5-FU per course was 800 mg/m^2 and 4,800 mg/m^2 respectively.

A CT scan and CEA level were obtained 2 to 4 weeks after completion of the second course of percutaneous HAIC, and patients whose liver involvement had regressed or remained stable were referred for placement of an Infusaid pump.

Nineteen of the 22 patients in the study received percutaneous HAIC. Of the remaining 3 patients, 2 had replaced right hepatic arteries from the superior mesenteric artery (SMA) which precluded percutaneous perfusion of the entire liver, and 1 underwent pump placement at the time of exploration for a possible hepatic resection.

Pump placement

An exploratory laparotomy was performed through a midline incision. If the exploration failed to reveal extrahepatic disease, the gastroduodenal artery and the common and proper hepatic arteries were dissected free; the right gastric artery was ligated. The Infusaid catheter was placed into the gastroduodenal artery which was ligated distally.

The two patients with replaced right hepatic arteries from the SMA had dual catheters implanted. The second catheter was placed directly into the right hepatic artery and held in place by a purse-string suture. Pumps were located in subcutaneous pockets in the right lower quadrant; however, the gallbladder was not routinely removed. To verify perfusion of the entire liver, flow scans with technetium 99-labeled microaggregated albumin were performed through the side port of the pump between the fifth and seventh postoperative day.

Prior to hospital discharge, the pump chamber was filled with normal saline and heparin. Therapy with floxuridine (FUDR) was instituted 2 weeks later at an initial dose of 0.2 mg/kg/d for 14 days. Monthly increments or decrements in dosage of 0.1 mg/kg/d were made on the basis of toxicity. Floxuridine and saline were alternated every 2 weeks unless toxicity required cessation of the chemotherapy.

The absence of all tumor on CT scans and lack of clinical evidence of tumor for a minimum of 4 weeks was considered a complete response. A partial response was defined as 50% or greater decrease in the sum of all diameters of measured lesions on CT scans, and no evidence of extrahepatic tumor. Serial CT scans, CEA levels, and follow-up examination were obtained at 3-month intervals.

RESULTS

Twenty-two patients met the eligibility criteria. The overall response to HAIC was 41%. Of the 19 patients administered percutaneous therapy, 4 (21%) were responsive, and 5 (23%) responded to the Infusaid pump. One of the 4 patients who responded to percutaneous HAIC demonstrated a sustained response to the Infusaid pump. The remaining 3 died within a year of pump placement from progressive disease. Of the 5 responders to the pump, 4 appeared to have almost complete resolution of their hepatic disease for a mean of 6 months. Two of the four died from the recurrent hepatic disease at 11 and 15 months after pump placement. One patient is alive 21 months after pump insertion with a

sacral recurrence and stable liver disease, and CT scans of the other responder indicate the patient is disease-free 18 months after pump placement. This patient had undergone a segmental liver resection at the time of her initial colon resection for a synchronous metastasis.

Patient responses

The 9 patients who responded to either percutaneous or Infusaid HAIC were from the subset of 13 patients who demonstrated less than 50% of the liver to be replaced by tumor. None of the patients whose pretreatment scan showed more than 50% liver replacement exhibited any response to HAIC. The intravenous 5-FU treatment of the three patients prior to the study did not affect the response rate to HAIC. The mean survival for the nonresponsive patients was 11.1 months, and 13.6 months for the responders. The mean time from primary operation to pump placement was 9.3 months for patients with synchronous lesions and 32.4 months for those with metachronous metastases.

Complications

Although there were no operative deaths in this series, the morbidity rate was 36%. In three patients, seromas developed in the pump pockets; these resolved with aspiration. Pump pocket infections that were nonresponsive to drainage and systemic antibiotics eventually required the removal of two pumps, and catheter thrombosis in one patient required reinsertion of a new pump. Extravasation of chemotherapy into the subcutaneous tissue of another patient resulted in skin necrosis, necessitating relocation of the pump to the left lower quadrant. Another patient required a second operation at his local hospital approximately 2 weeks postoperatively because of catheter dislodgment and intra-abdominal hemorrhage. Although one third of the patients required additional surgery for complications, only two needed a second laparotomy.

Adverse reactions

Chemotherapy-related toxicity developed in seven patients (32%), and on three occasions floxuridine therapy was discontinued or the dose was markedly reduced because of chemical hepatitis. Gastritis or duodenitis was documented in two patients who underwent upper gastrointestinal endoscopy. Both of these patients responded to medical therapy without cessation of chemotherapy. Liver biopsy and cholangiography supported the diagnosis of biliary sclerosis in another two patients; however, one of these patients may have had asymptomatic sclerosing cholangitis prior to HAIC since her colon carcinoma was associated with a long history of mucosal ulcerative colitis. None of the patients in this study developed acute cholecystitis or myelosuppression.

DISCUSSION

Interest in HAIC chemotherapy has resulted from poor response rates associated with conventional systemic chemotherapy in the treatment of colorectal liver metastases. Sullivan reported good results in 1964 with HAIC chemotherapy.[5] The theoretical advantages include higher drug delivery to the tumor, prolonged tumor exposure to the drug, and less systemic toxicity.[9] Many subsequent studies report measurable response rates to percutaneous HAIC with median survivals of 7 to 16 months.[10–13] However, therapy was discontinued in up to 35% of the patients because of complications, including arterial thrombosis, catheter dislodgment, sepsis, and a cumbersome external pump.[14]

The introduction of the totally implantable Infusaid pump has been responsible for a resurgence of interest in HAIC.[6,15] Although a major laparotomy is required for pump and catheter insertion, the reliability, ease of drug administration, and patient acceptance of the device have been quickly realized. Several reports contain encouraging results including response rates by CEA or CT criteria (50% or greater decrease in the sum of all diameters of measured lesions) ranging from 30% to 88%.[7,8,16–18] A decrease in the CEA, however, did not always correlate with a significant reduction of measurable disease on CT scans. Except for Balch's report which used historical controls,[7] none of the trials demonstrated a survival advantage of HAIC. Furthermore, none of these series was prospective or randomized.

Previous studies

Four prospective, randomized trials have failed to demonstrate that patients who receive HAIC live longer than those treated with intravenous systemic chemotherapy.[19–22] Hohn and colleagues reported response rates of 37% with HAIC and 10% with systemic therapy, but did not address survival benefits.[20] Reports by Kemeny and associates showed a 50% response with HAIC and a 20% response with systemic therapy.[21] Although the median survival was 18 months in both groups, the fact that this was a crossover trial made interpretation of the survival data difficult. In 1987 Chang and co-workers reported response rates with HAIC and systemic therapy at 62% and 17%

respectively; but the 2-year survival in these groups was not significantly different (22% *v* 15%.[22]

Implications of current study

Our study was selective rather than randomized as several criteria had to be met before the patient was accepted. Pumps were implanted in those patients whose liver involvement had not progressed after two courses of percutaneous HAIC. In fact, since none of the patients demonstrated progression of disease after percutaneous HAIC, pumps were implanted in all participants.

Overall, only nine of the 22 patients (41%) responded to HAIC, either delivered percutaneously (18%) or via the Infusaid pump (23%). The response rates were virtually equal in both the percutaneous group treated with 5-FU and leucovorin and the Infusaid group treated with floxuridine, suggesting that these two drugs have similar efficacy and that the mechanism of drug delivery into the hepatic arterial circulation also yields similar results. Continuing the percutaneous HAIC and not using the Infusaid pump may have resulted in the same overall response rate of 41%. Further analysis reveals that all nine responders, regardless of the delivery system, were patients who had less than 50% of the hepatic parenchyma replaced by tumor. In fact, most had only three or four small metastases. In spite of the selective bias of the study, no survival benefit was demonstrated in responders compared to nonresponders.

The technical problems in our study reflect the learning curve associated with a new procedure. Although only two patients had serious complications or required pump replacement, the morbidity of 36% is high. Relatively few problems were associated with the pump, yet toxicity was not insignificant (31%). The incidence of chemical hepatitis has been reported as high as 79%, although it resolves with dose reduction or cessation of floxuridine.[21,23] Shepard and colleagues suggest a trend toward a higher incidence of hepatitis in patients with a better response to chemotherapy.[24]

Gastritis develops in 20% to 48% of patients despite ulcer prophylaxis.[21,25] The most dreaded toxicity, reported in up to 20% of some series,[20,26] is biliary sclerosis, as it does not always reverse with cessation of therapy and can result in death from liver failure.

The Infusaid pump is a reliable drug delivery system. Varying response rates probably reflect different doses of drug, various response criteria, and the presence of undetected extrahepatic disease. Our series is relatively small and the patients were selected, not randomized. Nonetheless, our data suggests that HAIC has some efficacy in controlling liver metastases from colorectal carcinoma. The lack of a survival benefit from HAIC emphasizes the lack of effective systemic therapy for metastatic colorectal carcinoma.

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