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Treatment of hepatic cancer by hepatic arterial infusion chemotherapy

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Summary. A group of 213 patients with advanced primary hepatic carcinomas and 353 patients with metastatic liver cancers were treated by the prolonged intra-arterial infusion of mitomycin C and 5-fluorouracil through a surgically placed catheter over a period of time from 1966 to 1987. Regionalized chemotherapy by hepatic arterial infusion for hepatic cancer produced a greater degree and higher incidence of response than are obtainable through systemic administration. Intra-arterial infusion chemotherapy seems to offer an exciting new avenue of approach to the control of hepatic cancer.

Introduction

Chemotherapy for patients with hepatic carcinoma has resulted in subjective benefits for fewer patients, and objective responses for even fewer, and has rarely increased the survival rates of patients to any significant extent. Effective, tolerable and convenient therapies for hepatic cancers are greatly needed. The hepatic arterial infusion of mitomycin C and 5-fluorouracil is an effective treatment for primary hepatic carcinoma and for colorectal carcinoma metastatic to the liver. The increased sensitivity of liver cancer to the drugs administered intra-arterially is the result of their exposure to higher concentrations of chemotherapy. A total of 566 patients with advanced primary and metastatic cancer of the liver were treated by the prolonged intra-arterial infusion of mitomycin C and 5-fluorouracil through a surgically placed catheter over a period of time from 1966 to 1987. Regionalized chemotherapy by hepatic arterial infusion is a modality with a proven response rate and can double or triple the expected survival periods.

Materials and methods

Surgical technique. Treatment was administered by a catheter surgically placed in the hepatic artery through the gastroduodenal artery. Under open laparaotomy, the hepatic artery is exposed, and a small arteriotomy incision is made on the gastroduodenal artery. A Teflon or silicone catheter is inserted toward the hepatic artery, and secured tightly. Once the catheter is inserted into the hepatic artery, fluorescein is injected through the catheter under Wood-lamp illumination in order to ascertain the uptake of the drug in the liver parenchyma, and that there is no leakage into the stomach and duodenum.

Infusion pump and implantable drug delivery system. The catheter was introduced surgically into the hepatic artery with the consequent need for a portable infusion pump (Watkins' Chronofusor), or an implantable infusion pump (Infusaid) to maintain catheter patency, or an implantable drug delivery port (Infuse-A-Port, Port-A-Cath) for a single intermittent percutaneous bolus injection of mitomycin C and 5-fluorouracil.

Dose. 5-Fluorouracil was administered by means of continuous intrahepatic arterial infusion. The daily dose of 250 mg 5-fluorouracil was administered with the use of a Watkins' external chronometric infusion pump or an implantable Infusaid pump. While the patients were being treated with the continuous infusion of 5-fluorouracil, 2–6 mg mitomycin C was given as a bolus intrahepatic arterial injection once or twice a week.

Hyperthermia. In an attempt to treat the patients with hepatic carcinomas more effectively, in 1975 we devised an approach that combines hepatic arterial polychemotherapy with simultaneous hyperthermia. Microwave radiation was carried out in order to heat the tumors with a microwave machine operating at a frequency of 2450 MHz. Each patient received heat over the local tumors for 10–20 min. When the tumor location was heated to a peak surface temperature, mitomycin C and 5-fluorouracil were infused through the catheter.

Evaluation. Response to treatment was evaluated by the serial determination of plasma α-fetoprotein, carcinoembryonic antigen and CA19-9 and by imaging techniques consisting of computerized tomography, sonography and radionuclide scanning of the liver, as well as angiography.

Results

When cancer chemotherapeutic agents are given intravenously, the tissue concentration of the drug in the liver is quite low. Our experiment demonstrated that the tissue concentration of the drug is very high, 50 times or sometimes 100 times higher, when it is given by intra-arterial

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infusion. Of the 213 patients with primary hepatic carcinomas, the objective response occurred in 50% of the patients. The median survival period from the onset of treatment was 4.5 months. The Scintiscan, computed tomography scan, angiography, and sonography exhibit a remarkable response in half of the patients treated in this way. Biochemistry and tumor markers also produced a marked improvement in the majority of the patients.

However, most of the patients with primary liver cancer have liver cirrhosis. The patient responds well to the therapy, but the survival period is not long enough because of the cirrhosis. Many patients develop a hemorrhage of the esophageal varices and gastroduodenal ulcers, jaundice, ascites and hepatic failure. The median survival period is only 4.5 months and only 20% of the patients can survive a year or longer. The hepatic metastasis group, on the other hand, shows a very good survival rate as compared to the primary liver tumor group. The median survival period is 9.3 months, and more than 30% of the patients can survive a year or longer.

For patients with a reasonable liver function, the administration of mitomycin C and 5-fluorouracil through the hepatic artery, along with 2450-MHz microwave local hyperthermia, resulted in modest, predictable toxic effects. Acute morbidity was rarely severe and was self-limited. Symptomatic and subjective responses were observed in 60% of the patients treated in this way.

Discussion

Hepatic cancer, refractory to intravenous chemotherapy, will respond to hepatic arterial infusion chemotherapy. The rationale for hepatic arterial infusion chemotherapy is based on the observation that most antitumor agents have a steep dose-response curve: the higher the concentrations of the drug, the higher the antitumor effects observed. Since tumors in the liver derive their blood supply primarily from the hepatic artery, the administration of drugs that are metabolized by the liver by this route will result in the prolonged exposure of the tumor to high drug concentrations.

The inactivation of these drugs by the liver parenchyma subsequently occurs and blood leaving the liver through the hepatic veins contains lower drug levels, exposing normal tissues to lower drug concentrations, and thereby lessening the toxic side-effects. Since mitomycin C and 5-fluorouracil both have activity in hepatic carcinoma and are inactivated by the liver, the combination of these chemotherapeutic agents exposes the liver cancer to very high concentrations without severe side-effects. By this reasoning, hepatic arterial infusion chemotherapy was undertaken for 213 patients with primary hepatic carcinoma and 353 cases of metastatic cancer of the liver.

Embolization of the hepatic artery is an excellent roentgenographic procedure to obtain improved survival rates for patients with primary carcinomas of the liver. All hepatic neoplasms receive their blood supply almost exclusively from the hepatic artery. Embolization causes the devascularization of the tumor without any form of compromise to the normal hepatic parenchyma because of the dual portal circulation. Arterial embolization should be attempted as the primary treatment for patients with primary hepatic cancer whenever the portal vein is patent and the bilirubin count is less than 2.0 mg/100 mg. When the portal vein is occluded with a tumor embolus and the bilirubin count is less than 3.0 mg/100 mg, intra-arterial infusion chemotherapy is the method to be chosen. Regionalized chemotherapy by hepatic arterial infusion is a modality with a proven response rate, and can double or triple the expected survival periods in more than half of the patients. If the general condition of the patient is satisfactory (total bilirubin less than 3.0 mg/100 mg, no ascites), the direct surgical placement of the catheter into the hepatic artery and the placement of the implantable drug-delivery system into the subcutaneous pocket should be attempted to attain longer infusion periods. Our experience concentrated on many advanced cases, so better clinical responses might be expected in patients in better condition.

Better palliation for patients with hepatic cancer requires improved quality and period of survival with a low complication rate at an acceptable cost. Intra-arterial infusion chemotherapy with an implantable drug-delivery system is a modality yielding all of these benefits.

For patients with bilirubin counts of over 3.0 mg/100 mg and ascites, no chemotherapy should be attempted.